DISEASES OF
THE BREAST

Diagnosis · Pathology · Treatment

By

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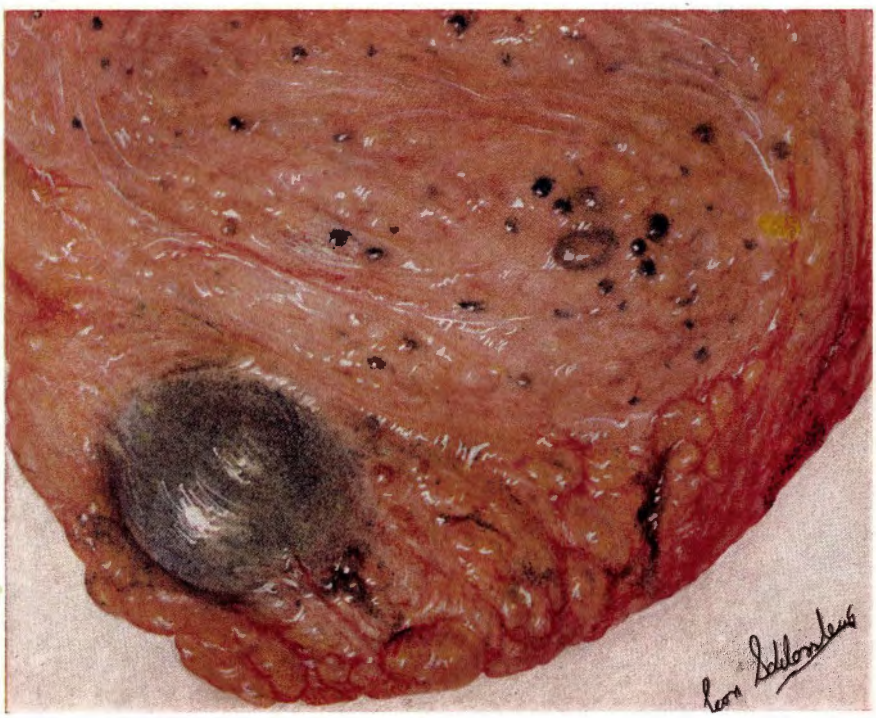

FIG. 196. The blue dome cyst of Bloodgood. (See also pages 225-226.)

THIS BOOK
IS GRATEFULLY DEDICATED TO
THE MEMORY OF
BLANCHE AND FRANK WOLF

Preface to the Second Edition

The Second Edition of this work has afforded an opportunity to make a number of revisions and additions. The orientations to the seven major divisions of the book have been enlarged and rewritten so that they more fully summarize the salient features included in the individual chapters. Chapter 17, which reviews the present-day knowledge in regard to mammary carcinoma, has been enlarged, while Chapter 35, The Mechanism of Tumor Formation, has been entirely rewritten.

New material has been added on parasitic infestations; cosmetic considerations concerning underdeveloped and pendulous breasts; penicillin therapy for infectious mastitis; the criteria of operability and inoperability of mammary carcinoma; the relative merits of surgery and irradiation for this condition; the endocrine therapy of chronic cystic mastitis and on the etiology of mammary carcinoma. A number of new black and white text illustrations as well as two colored plates are included. The bibliographies have been brought up to date.

It is a source of satisfaction to the author that the major conclusions set forth in the first edition have received reiteration and additional support from work recently reported. The importance of radical mastectomy as the primary treatment for operable mammary carcinoma and of post-operative irradiation as a routine adjunct for cases in the operable group which have extended beyond the confines of the breast has been confirmed by the results reported from a number of large clinics. The incidence of carcinoma in chronic cystic mastitis (less than three per cent) has been supported by additional statistics and the importance of endocrine factors in the etiology of benign and malignant mammary neoplasms has been extensively confirmed.

C. F. G.

Preface to the First Edition

In recent years contributions to the etiology, the diagnosis and the treatment of mammary diseases have accumulated rapidly. Much of the progress made can be attributed to the different groups of specialists interested in these problems. The specialties concerned include surgery, radiology, obstetrics and gynecology, pathology, endocrinology and laboratory technology. In bringing together in this volume the work done in these diverse fields, the usefulness of this information to the general practitioner as well as to the specialties enumerated has been foremost in mind.

A comprehensive and critical treatment of the subject necessitates the analysis of an adequate amount of original material. In addition to the patients seen in practice and on the surgical wards of Doctor Dean Lewis at the Johns Hopkins Hospital a study has been made of the case histories, specimens, and follow-up studies recorded in the Surgical Pathological Laboratory of Johns Hopkins. This library of data to which Doctor Bloodgood and his predecessors, Doctors Halsted and Welch, so largely contributed has been analyzed and presented in tabular form. In this way it is possible for the reader, to a great extent, to form his personal judgments concerning the conclusions and recommendations made.

It is now established that childbearing and nursing, as well as ovarian function, play a role in the development of mammary cancer, in the formation of benign tumors and in the diseases collectively known as chronic cystic mastitis. The influence of the sex hormones in the production of these conditions has been demonstrated experimentally. It is hoped that the increased interest in the mammary gland on the part of the obstetrician, the gynecologist, and the endocrinologist that has resulted, will be stimulated further by the parts of this book dealing with this aspect of the subject.

The increasing importance which has been placed upon microscopic pathology in the diagnosis and treatment of lesions of the breast has led to the inclusion in each chapter, of a section devoted to this important phase of the subject, and to separate chapters dealing with the pathology of forms of mammary cancer and with their differential diagnosis by means of the microscope.

The controversial points in the treatment of mammary disease, including bleeding from the nipple, the relation of chronic cystic

mastitis and benign tumors to cancer, and the relative merits of radical surgery, irradiation, or a combination of both forms of therapy, have been dealt with on the basis of the end-results achieved in a large series of cases. In presenting the data on these problems an attempt has been made to place on a more secure footing the choice of treatment by the clinician.

In experimental studies conducted in the author's laboratory over a period of years on the relation of endocrines to mammary pathology, the forms of cystic mastitis and practically all varieties of benign and malignant mammary tumors have been produced in the rat and the rabbit. The importance of these experiments for the interpretation of etiologic factors and inter-relationships among mammary diseases has led to the inclusion of a section summarizing these investigations.

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Acknowledgments

It is a pleasure for the author to acknowledge the contributions and assistance of his colleagues in the Surgical Pathological Laboratory where the material for this book has been accumulated.

I wish to thank Doctors George A. Stewart, L. Clarence Cohn and Murray M. Copeland, associates in the Surgical Pathological Laboratory, and Doctors Edwin B. Astwood, Robert L. Oliver, Robert C. Major, John G. Menville, Saul L. Fox, Clarence S. Moran, T. Robert White, Elizabeth W. Byrnes, G. Seegar Jones, Nancy L. Bucher, and also the members of the American Association for the Study of Neoplastic Diseases who contributed interesting and unusual cases of mammary diseases and neoplasms.

I am indebted to Mr. Edward P. Walker for his painstaking care in furnishing the photographs used to illustrate the text, to Miss Leoda Danner for the microscopic preparations used, to Miss Nell Starkey for her assistance in conducting the experiments herein reported, and to Mildred Clark Geschickter for aid in preparing the index. I also wish to express to the publishers my appreciation of their consideration and efforts in completing this volume.

The investigations of the author herein reported were aided by grants from the Francis P. Garvan Cancer Research Fund, the Blanche and Frank Wolf Foundation, the Doctor Simon Baruch Foundation, and the Geschickter Fund for Medical Research.

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THE AUTHOR

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PART I

MAMMARY DEVELOPMENT, PHYSIOLOGY AND HYPERTROPHY—METHODS OF EXAMINATION AND DIAGNOSIS

1. Normal Development and Functional Changes in the Mammary Gland
2. Endocrine Physiology of the Breast
3. Examination and Diagnosis
4. Mammary Hypertrophy

ORIENTATION

The breast does not achieve full development until sexual maturity. During the childbearing period new structures are added and their form and function repeatedly altered. At the menopause and extending through senescence, involutional changes occur. Because of these variations, the anatomy of the breast must be correlated with the period of life, by successive studies in the embryo, at birth, during childhood, at puberty, during the menstrual cycle, pregnancy, lactation and the menopause. The hormonal secretions of the ovary, the pituitary gland and the placenta control, for the most part, these successive stages.

Part I deals with these phases of mammary development, with their physiologic mechanisms and their abnormal variations. A chapter has been added on methods of examination and diagnosis.

The estrogenic or ovarian follicular hormone in the presence of an intact pituitary gland is responsible for adolescent development, but this stimulus alone does not give the mammary gland its mature form. In part the response is predetermined at birth. Thus, the male gland in experimental animals can not be made to equal in size that of the female, regardless of the intensity or duration of the estrogenic stimulus applied. In childhood, adolescence or pregnancy, overdevelopment of the breasts may occur, so-called infantile, virginal or gravid hypertrophy. Again, the tremendous overdevelopment of the gland seen in virginal hypertrophy is the result of increased sensitivity of the end-organ and endocrine stimulation alone will not produce such giant size. Hormonal factors are responsible for infantile hypertrophy.

Virginal hypertrophy in the female and gynecomastia in the male breast are of concern chiefly from the cosmetic standpoint, but there is a slightly greater predisposition to carcinoma in later years in such cases. In 2 per cent of the cases of gynecomastia, there may be an associated malignant tumor of the testis, and in infantile hypertrophy of the breasts in girls the possibility of a malignant ovarian or adrenal tumor must be borne in mind.

Ovulation adds to estrogenic stimulation the influence of the corpus luteum hormone, progesterone. In pregnancy this influence is intensified, the placenta acting as an additional source. In the absence of normal luteal influence to balance the effects of estrogen, mammary lobular development is abnormal and premature involutional changes occur. These involutional effects of estrogenic overstimulation, which are discussed in more detail in Part III, are concerned in the production of the pathologic changes observed in cystic mastitis, fibroadenomas and in certain cases of mammary carcinoma.

1

Normal Development and Functional Changes in the Mammary Gland

A number of developmental stages, extending from embryonic life to womanhood and through parturition, are necessary before the breast reaches the functional state of lactation. Before birth a series of temporary structures precede the permanent system of mammary tubules, and throughout childhood these permanent tubules remain rudimentary in both sexes. It is only after puberty and pregnancy have exerted their influence that the milk-secreting lobules of the female breast are formed. A knowledge of the earlier stages of development is necessary in order to understand the anomalies of growth and the variety of tumors possible in the adult organ. The structures in the embryo may be more clearly described by a review of the origin of the mammary apparatus as it appears in the different orders of mammals.

EVOLUTION OF THE MAMMARY GLAND

In the lowest order of mammals—the monotremes—Bresslau derives the mammary gland from the brood organ of a mammalian ancestor. The brood organ, as found in birds, is an altered region of skin free from cutaneous muscle and rich in blood vessels; it furnishes extra warmth to the egg. The vascularity found in this organ is characteristic of the stroma of the human breast in the active stages of development and function.

Comparative Anatomy

The mammary gland of the monotremes consists of 100 to 150 separate tubules which terminate independently on a flat skin surface without a nipple. They are bilateral and occur in both sexes. The glands arise in connection with the hair follicles after the manner of sweat glands. At first a streak of thickened epidermis appears; it extends the length of the trunk in a region rich in blood vessels and free from cutaneous muscle. This corresponds to the brood organ and also appears as the milk streak in the initial stage of human mammary development. This thickening disappears, a new thickening forms and columns of basal cells sprout from the lower edge. A rapid growth of hair (mammary hair) develops from these sprouts. Primitive mammary tubules form from the germinal buds of these hair follicles. They develop from larger and more active buds in the embryonic hair than are observed in the sweat glands of the surrounding skin. (Fig. $1a_1$-d_1.)

In the marsupials, the next order of mammals, the mammary glands are within the brood pouch. They differ from the glands of the monotremes in having well-formed nipples into which several ducts discharge; also in the absence of mammary hairs in the adult.

The marsupial mammary rudiment is first found as a region of thickened epidermis, as in the monotremes. This regresses and special thickenings mark the sites where the glands will appear. These special thickenings again regress and small knobs of basal cells form beneath, the beginnings of the individual nipples. (Fig. $1a_2$-c_2.) These nipple buds[1] remain inactive until after birth. Later, while the brood pouch is forming, these buds enlarge and are hollowed out to form nipple pouches by differentiation, cornification and atrophy of the central cells. The nipple pouches (Fig. $1d_2$) may be looked upon as

[1] The term "nipple bud" has been used here, although this germinal center is also known as the mammary bud. This term distinguishes it from the germinal buds (or true mammary buds) which give rise to the permanent mammary tubules and which are sometimes called the primary mammary sprouts.

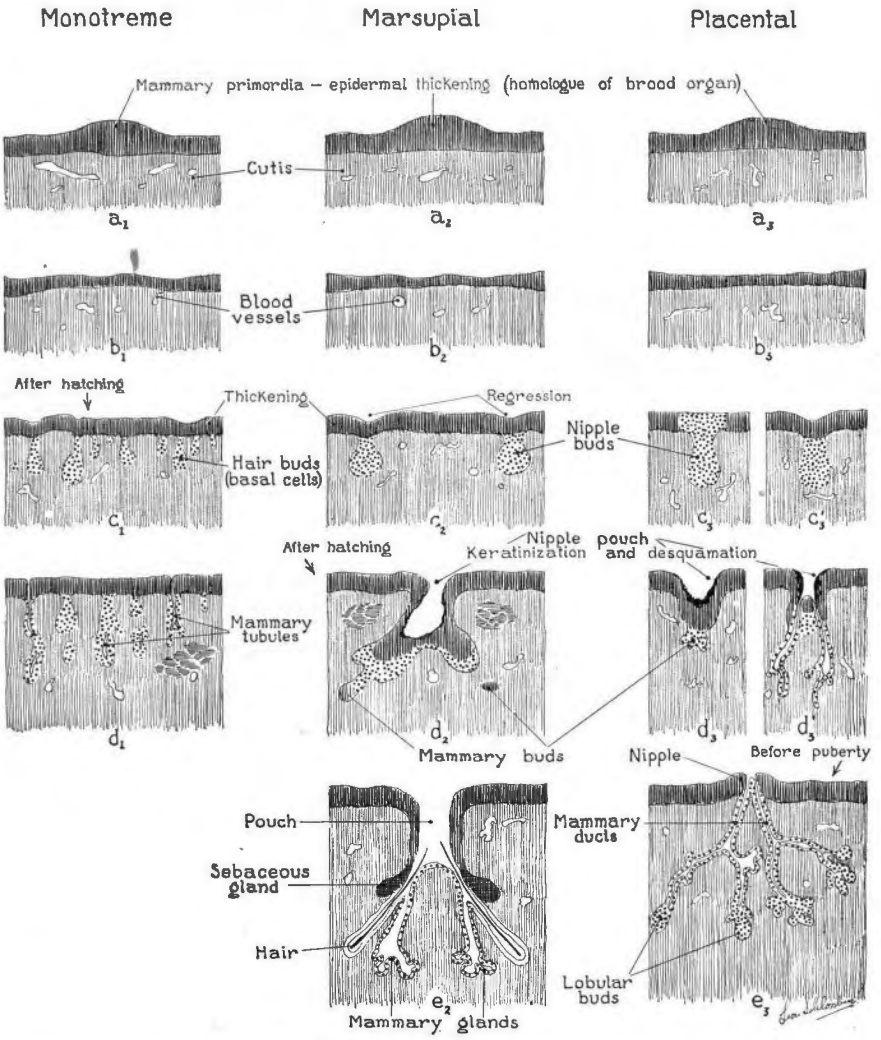


FIG. 1. The Evolution of the Mammary Gland.

MONOTREMES (a_1) Epidermal thickening, the homologue of the brood organ overlies a vascular mesenchyme (b_1) Regression of this epidermal thickening occurs (c_1) This is followed by a downgrowth of basal cells, the mammary hair buds (d_1) From the hair buds the mammary tubules develop.

MARSUPIALS (a_2) Epidermal thickening appears and (b_2) Regresses as in the monotremes (c_2) Circumscribed downgrowths of basal cells, the nipple buds, appear (d_2) Masses of keratinized and desquamating squamous cells invade the nipple buds to form the nipple pouch and at the lower margin of the nipple pouch the mammary buds arise (e_2) From the mammary buds the mammary tubules arise and also sprouts which form the mammary hairs and sebaceous glands.

PLACENTALS (a_3) Epidermal thickening appears (b_3) Regresses and ($c_3.c'_3$) the nipple bud and the invagination of the nipple pouch appear, ($d_3.d'_3$). The mammary pouch enlarges and at its base the mammary buds and the primary sprouts of the mammary tubules form (e_3) The nipple is everted and lobular buds appear at the ends of the mammary tubules.

Note: The downgrowth of basal cells designated above "the nipple bud" is sometimes termed "the mammary bud" and the term "primary mammary sprouts" is also used for the downgrowth of basal cells designated above as "the mammary bud."

the dilated remnants of the mammary-hair apparatus of the monotremes. They occur also during human mammary development.

At the base of the nipple pouch a new bud of basal cells appears. This is the true mammary bud. From it grow epithelial sprouts which separate into three groups (Fig. $1e_2$); the first provides for mammary hairs which soon atrophy, the second for the milk ducts which at first resemble sweat glands and the third for the sebaceous glands. The milk ducts open into the nipple pouch and form an elevated zone, which is the true nipple. With pregnancy it is everted from its pouch to permit being grasped in the mouth of the young.

In the placental mammals both the brood organ (milk streak) and the nipple pouch appear and are replaced. (Fig. $1a_3$-d_3.) The mammary bud appears at the base of the nipple pouch, but the pouch remains rudimentary. A portion of the permanent nipple and the milk ducts are formed from the mammary bud (with the exception of the squirrel, the development of mammary hairs is repressed). Solid buds of basal cells, the lobular buds, appear at the end of the milk ducts. These make their appearance at variable periods before adolescence, depending on the species. They continue to form after maturity (Fig. $1e_3$) and mammary lobules with acini are developed from them during pregnancy.

Thus, in all mammals there is a temporary homologue of the brood organ represented by the milk streak. Then appear the nipple buds from which mammary hairs and altered sweat glands develop. In the lowest order, the monotremes, these form the permanent mammary gland, in the marsupials they form the nipple pouch, and in the placentates only the shallow, cornified and temporary nipple pouch appears. The true mammary buds which form the permanent mammary tubules in the marsupials are added to, in the placentates, by buds which appear at the end of the milk ducts to form mammary lobules. (Fig. $1a_3$-e_3.)

An important mechanism of development is apparent in a review of the evolution of the mammary gland. The final form is achieved by the repeated replacement of temporary structures. In this replacement, the earlier structure matures and undergoes regression, and during this regression immature cells multiply to form the bud of the subsequent organ. The new is not made from the old, but is elaborated from the immature cells which formed the old and which have taken on renewed proliferative activity and a new pathway of differentiation. Apparently the biologic purpose of the temporary and obsolete structure is not to recapitulate the history of development but through aging and regression to stimulate the proliferation of immature cells which form the starting point for

the new structure which replaces the older. There is a definite overlap between old and new during which the old cells undergoing atrophy and young cells undergoing multiplication exist side by side.

This process by which the adult state of an organ is reached, not by progressive ripening of a single group of cells (monoplastic differentiation) but by maturation which passes from one group of cells to another, with an intervening stage of proliferation (duo-plastic differentiation), is characteristic of the growth and development of the breast throughout life. Growth of the duct tree represents one line of differentiation and lobule-alveolar development represents another. As we shall see in the next chapter each has its own hormonal control. Ripening of the duct epithelium stimulates proliferation of the lobular buds in anticipation of lobular development. When this ripening in the duct tree is pathologically intensified or prolonged (so-called hyperdifferentiation) cell multiplication in the lobular buds is likewise excessive (hyperplasia or neoplasia occurs). When the experimental production of cancer is discussed in Chap. 34, it will be seen that hyperdifferentiation followed by involution and degeneration stimulates the proliferation of foci of new cells from which malignant tumors may form.

DEVELOPMENT OF THE HUMAN BREAST

Embryonic Development

The human mammary gland repeats its phylogenetic history before birth. The mammary epithelial structures pass through four stages of development:

1. Ectodermal thickening of the milk streak and milk line.
2. Knob-like downgrowth of ectoderm forming the nipple bud.
3. Formation of the nipple pouch and the mammary buds which give rise to the mammary ducts.
4. Formation of the lobular buds at the end of the mammary tubules.

The following description of the embryology of the human mammary gland is based on a study of material in the Department of Embryology of the Carnegie Institution of Washington at the Johns Hopkins School of Medicine, and was made available through the courtesy of Dr. George L. Streeter, Director.

1. In the first stage of human mammary development an altered area of skin—the milk streak—can be found on either side of the trunk in embryos at the sixth week (11.5 mm.). A ridge of epidermis

containing four or five layers of transitional cells, the milk line, forms in this zone; it migrates ventrally in embryos about 21 mm. (Figs. 2, 3). There is increased cellularity in the underlying mesenchyme.

2. In the second stage, the milk line atrophies except in the pectoral region (embryos of 26 mm., 9th week), while the cells of the milk line all but disappear, and there is a proliferation of a mass of basal cells forming the nipple bud, separated by a membrane from the underlying cellular and vascular mesenchyme (Figs. 4, 5). In embryos from 32 to 36 mm., the epidermal cells overlying the nipple

FIG. 2

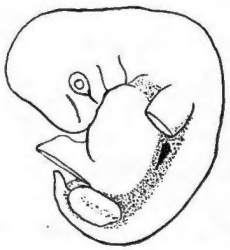


FIG. 3

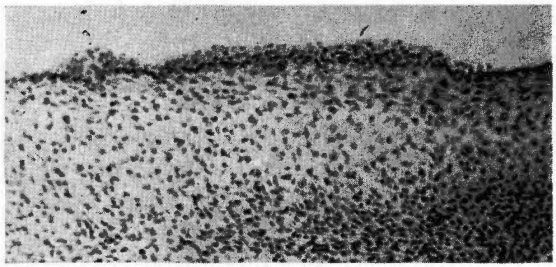


FIG. 2. Human embryo of 11½ mm. showing the milk streak and the elevated region which forms the milk line (after Schmitt).
FIG. 3. Photomicrograph of the cross section of the epidermal thickening which forms the milk line (human embryo of 21 mm.).

bud differentiate and increase in number. Some of the uppermost cells are desquamated, others approach squamous cells in their appearance. The surrounding mesenchyme continues to proliferate. This elevates the epidermis on either side suggesting the nipple pouch seen in marsupials (Fig. 6).

3. The third stage of development recalls the formation of the nipple pouch in the marsupials. In embryos toward the end of the third month (54 to 78 mm.) the squamous cells on the surface invade the nipple bud (Fig. 7), forming a progressively larger core. Following this, in 78 to 98 mm. embryos, the basal cells surrounding the core form a series of downgrowing sprouts, the mammary buds (Fig. 8). These give rise to the permanent mammary ducts. The invasion of the nipple area by squamous cells and the growth of the mammary sprouts to form the primary ducts continue in embryos of 98 to 270 mm. (Figs. 9-11). The nipple pouch is formed by keratinization of squamous cells which are desquamated to form a hollow. The buds of the mammary ducts progressively invade the underlying connective tissue and are canalized to form milk channels (Fig. 12). The mouths of these channels open into the mass of

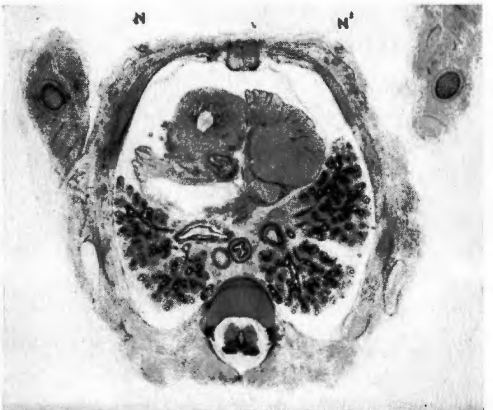


FIG. 4

FIG. 5

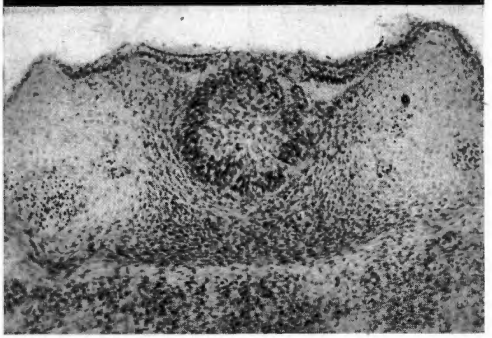


FIG. 6

FIG. 4. The nipple bud in the human embryo. Cross section of 35 mm. embryo showing the position of the nipple buds (N,N') on the anterior thoracic wall.

FIG. 5. Photomicrograph of the nipple bud in a 26 mm. embryo. The proliferation of basal cells is sharply demarcated from the vascular and cellular mesenchyme which surrounds it. × 25.

FIG. 6. Depression of the nipple bud and early differentiation in the overlying epidermis (35 mm. embryo). × 25.

FIG. 7

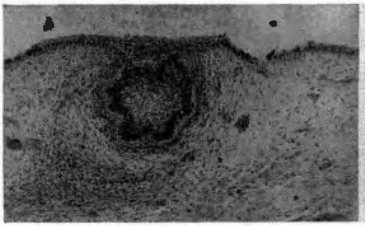


FIG. 8

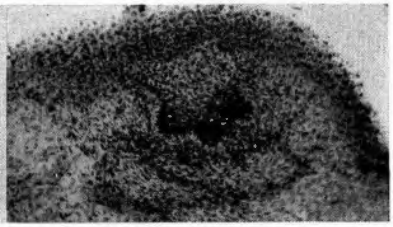


FIG. 9

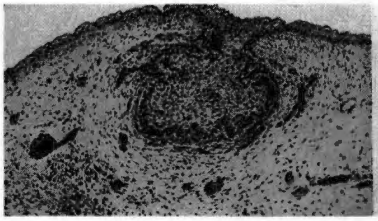


FIG. 10

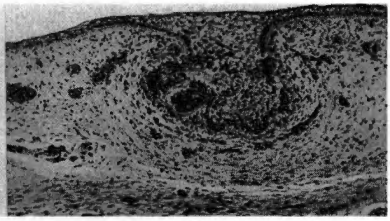


FIG. 11

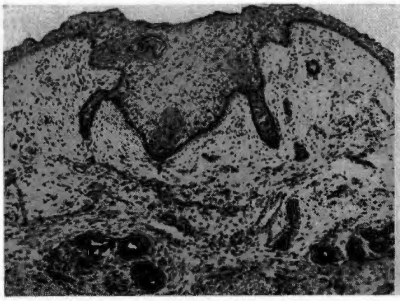
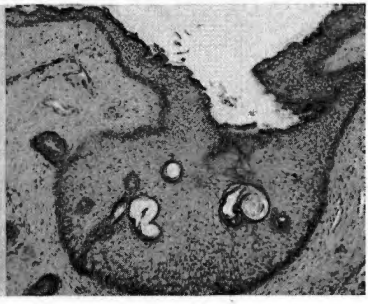


FIG. 12



Growth of the Nipple Pouch and Mammary Buds in the Human Embryo.

FIG. 7. The nipple bud is invaded from above by squamous cells (54 mm. embryo). × 25.

FIG. 8. Downgrowth from the lower margin of the nipple bud forms the primary mammary sprouts or mammary bud (78 mm. embryo). × 25.

FIG. 9. The nipple bud is replaced by squamous and transitional cells. The mammary sprouts have invaded the underlying mesenchyme (98 mm. embryo). × 25.

FIG. 10. A stage in the development similar to that in Fig. 9. The junction of the mammary buds with the squamous cells of the nipple bud is shown (132 mm. embryo). × 25.

FIG. 11. Desquamation and keratinization of squamous cells to form the nipple pouch. The downgrowing mammary sprouts have formed tubules (226 mm. embryo).

FIG. 12. Formation of the nipple pouch showing the exits of the mammary tubules (268 mm. embryo). × 50.

degenerating squamous cells. Their opposite, sprouting ends are surrounded by loose vascular mesenchyme.

4. **In the last stages** of embryonic mammary development (335 mm. embryo—Fig. 13), the milk ducts form a series of branching channels with a definite lumen lined by two to three layers of cells. On their ends are found small plugs of basal cells, the future buds of the mammary lobules. The nipple is gradually everted by the growth of subepidermal connective tissue. Its covering is formed

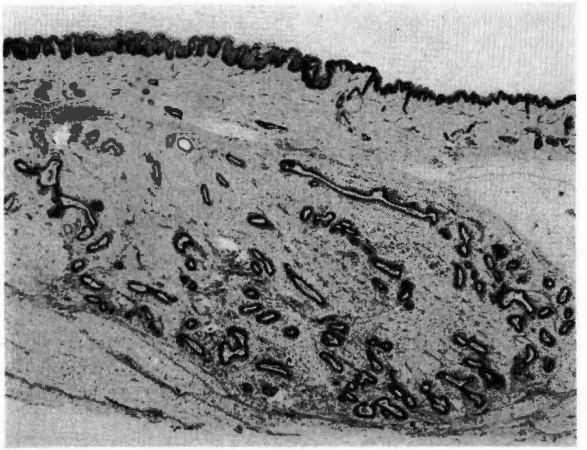


FIG. 13. The mammary gland shortly before birth. The ends of the mammary tubules contain undifferentiated basal cells from which the lobular buds will develop. × 15.

by a thickened epidermis which is continuous with the growth of the duct epithelium which meets the surface. Remnants of the nipple pouch persist. The lobular buds from which clusters of acini form after sexual maturity do not develop until puberty. They undergo atrophy after castration and enlarge following injections of ovarian hormones.

Developmental Anomalies

Polythelia, Polymastia and Amastia. The wide region of the body wall over which the milk line extends in the embryo accounts for a variety of congenital anomalies. Supernumerary nipples or breasts (polythelia and polymastia) are relatively common malformations. Deaver and McFarland estimated that upward of 10,000 cases of polymastia were recorded in the literature prior to 1917. The locations vary anywhere from the region of the neck and axilla to the inguinal region or the thigh. According to Bresslau, statistics based upon a study of the Japanese show that 1.5 per cent of males

and approximately 5 per cent of females possess accessory nipples. Guest found only 80 cases of extra nipples in 20,000 English school children.

Speert, in 1942, reviewed the literature and concluded that the incidence of polythelia is about 1 per cent. He called attention, however, to the difficulty in reconciling the various estimates of incidence because of the different criteria used for the diagnosis of hyperthelia. Thus Kajava et al. classified supernumerary breasts

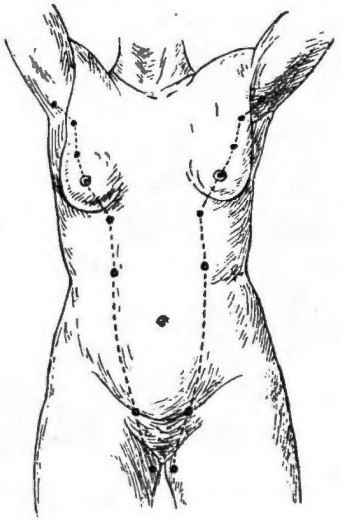


FIG. 14. Diagram illustrating the locations for supernumerary breasts and nipples and the course of the milk lines of the embryo (from Merkel). (From Henke, F., and Lubarsch, O., System of Special Pathological Anatomy and Histology; Vol. 7: P. 57, Julius Springer, Berlin, 1933.)

into eight groups, depending upon the presence or absence of the nipples, areola, hairs, and mammary parenchyma. Twenty-six such breasts were subjected to histologic examination and were found to show all gradations from a structure barely suggestive of mammary tissue to that of a "typical" breast. Hoepfner who examined nine male accessory nipples histologically found a normal nipple structure, usually associated with only rudimentary mammary glandular tissue or sweat glands.

Most authors have found the majority of the accessory mammae below the normally situated pair and Kajava et al., in their extensive study of the Finnish population, found 98.7 per cent of all accessory glands below the normal breasts. Iwai, however, in 511 Japanese polymastics, found 88 per cent of the supernumerary breasts above the normal ones, thereby emphasizing the importance

of the racial factor. He also found the incidence among females to be three times as great as among males, in contrast to the statistics of European authors which indicate a preponderance of supernumeraries among males. In general, if a supernumerary gland is situated laterally it is well formed, of considerable size and can lactate; if medial, it is usually small, imperfectly developed, and incapable of lactation. Single accessories occur with the greatest frequency, and the incidence decreases inversely to the number

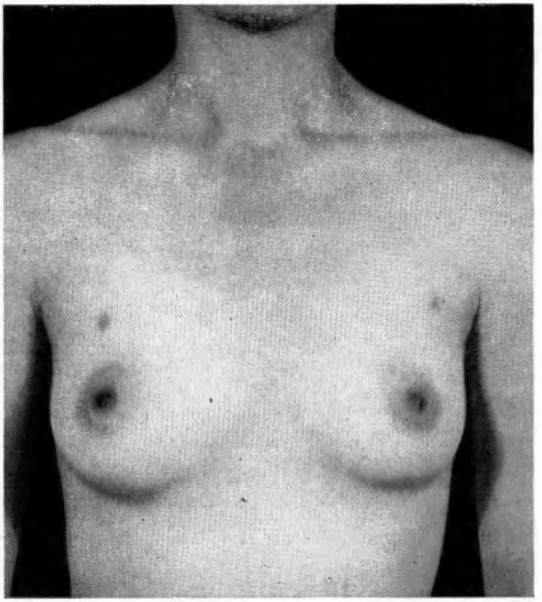


FIG. 15. Patient with supernumerary nipples.

of mammae. Accessory mammary glands or nipples occurring in the vicinity of the primitive milk lines are perhaps adequately explained on an embryonic basis. Axillary, thoracic, abdominal, inguinal, and possibly vulvar mammae fall into this category. The literature contains numerous case reports, apparently well authenticated, however, of accessory mammae occurring in bizarre locations such as on the face, ear, neck, arm, thigh and buttocks. No satisfactory explanation has been advanced for the development of these ectopic breasts, and they are simply referred to as freaks of nature. The supernumerary nipples occur in the same locations as supernumerary breasts (Figs. 14-16). In rare instances atrophy of the milk line in the embryo may extend to the pectoral region and the mammary gland may fail to develop on this side—a condition known as amastia.

Congenital anomalies of the breast are usually of academic rather than therapeutic interest. When in unusual locations, as in the neck or groin, excision is necessary to confirm diagnosis and for cosmetic reasons. Aberrant mammary tissue, usually in the axillae, is more commonly a cause of trouble during lactation, and the accessory mammary tissue may be the seat of benign and malignant tumors. The clinical aspects of these complications are discussed in later chapters (Chaps. 5, 25).

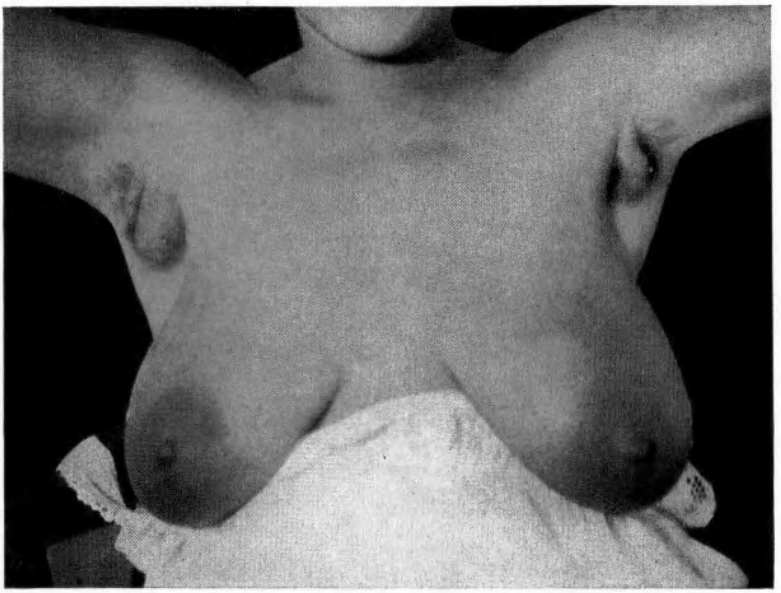


FIG. 16. Patient with axillary breasts.

Remnants of the Nipple Pouch. Transitional and squamous cells found during prenatal development in the nipple pouch may be observed in the region of the large ducts as late as puberty. Remnants of the embryonic nipple bud from which these cells are derived may explain epidermoid cysts of the breast and cancer cysts lined by similar cells. Such remnants may also be important in the interpretation of Paget's cancer of the ducts and nipple. The formation of the nipple pouch as a primary stage of nipple development accounts for the cases of congenitally retracted nipple observed in adults.

Remnants of the Mammary Buds. The series of sprouts of basal cell, which are found beneath the nipple pouch in the embryo and which form the mammary buds, may leave remnants which persist into adult life. These may be involved in the formation of be

nign and malignant papillary intraductal tumors which occur in adults in the region of the nipple. Since the mammary ducts and tubules represent modified sweat glands developed from a circumscribed area of the skin lying beneath the milk line, there is a tendency for the duct epithelium during involution and pathologic changes to resemble that found in the apocrine sweat glands. This does not mean, however, that the changes observed occur in sweat glands rather than in the mammary tubules.

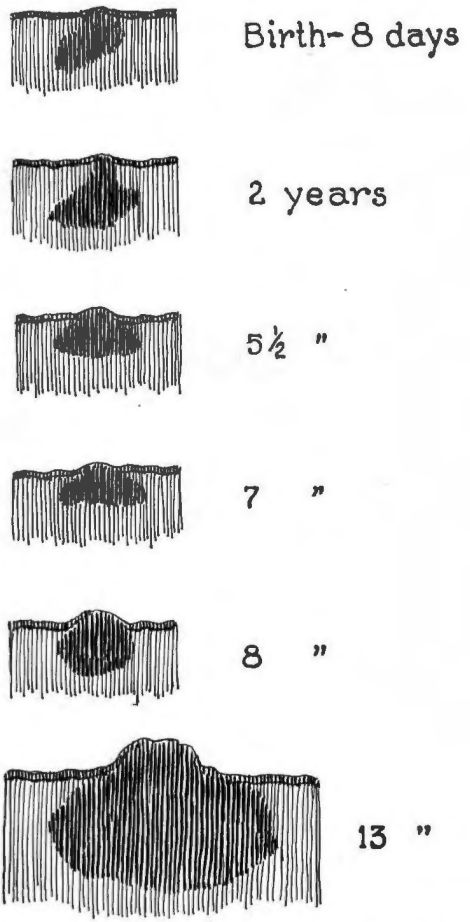


FIG. 17. The size of the mammary gland from birth to puberty. The heavy lines in the diagram indicate the area of the mammary gland as measured in paraffin sections which pass through the maximum diameter of the breast. × 1.

Mammary Development from Birth to Puberty

In the embryo the mammary gland develops early and in advance of other skin appendages. After birth, epithelial activity continues for several weeks or months, but thereafter the gland remains quiescent until puberty. The female breast scarcely maintains its size over this period of years while the male breast definitely regresses. Because of the increase in size and the physiologic activity which occur shortly after birth and the subsequent regression and inactivity, it is evident that the growth of the breast in childhood does not keep pace with general bodily growth (Fig. 17).

Neonatal Changes. Both male and female breasts show physiologic activity during the first or second week after birth. The size of the

organ is temporarily increased. According to Fabris, glandular tissue ranging from one to several centimeters in diameter is palpable beneath both nipples in about 60 per cent of the newborn, and an equal percentage of infants have a milk-like secretion which appears on the third or fourth day and lasts from one to three weeks. A visible swelling beneath the nipple accompanied by secretion of witch's milk is observed in about every tenth child, according to Williams.

In microscopic preparations, the major findings are the hypertrophy and secretory activity of the duct system and the active vascu-

FIG. 18 FIG. 19

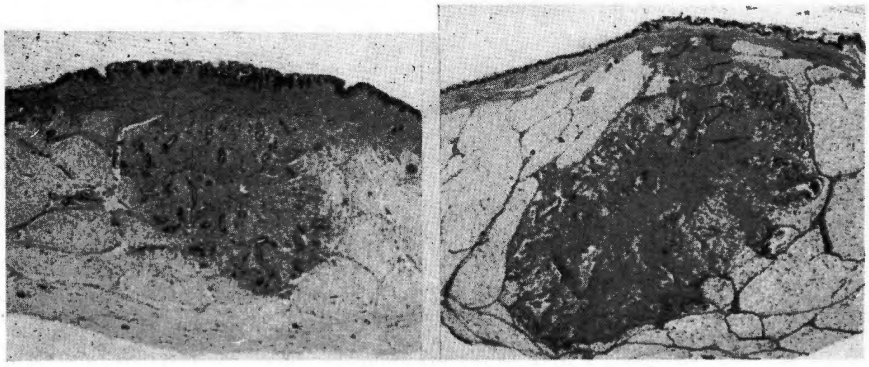


FIG. 18. A cross section of the mammary gland before birth. × 8.
FIG. 19. Postnatal hypertrophy of the mammary gland. Cross section eight days after birth. × 8.

lar stroma (Figs. 18-20). The ducts are dilated and contain varying amounts of secretion. They are lined by two layers of epithelium, the central cells being large and columnar with an irregular secretory border. The basal cells beneath are flattened and have dark staining nuclei. The epithelial buds at the end of the ducts show occasional solid sprouts, but are more often dilated and resemble acini. The ducts are surrounded by a narrow rim of loose connective tissue with many capillaries. The dilated openings of the larger ducts near the nipple are lined by keratinized squamous cells. This is a persistence of the nipple pouch of the embryo.

Later Involutional Changes. This postnatal activity is followed by involutional changes. These have been variously described as occurring from four to eight months after birth in nursing infants (Dietrich). In the specimens studied, involutional changes in the first eight months of life were more marked in male than in female infants. In males more than six months of age, microscopic studies

show shrinkage of the duct epithelium with desquamation of lining cells. The lumen of the ducts becomes narrow or collapsed and the periductal connective tissue becomes collagenous and hyalin-

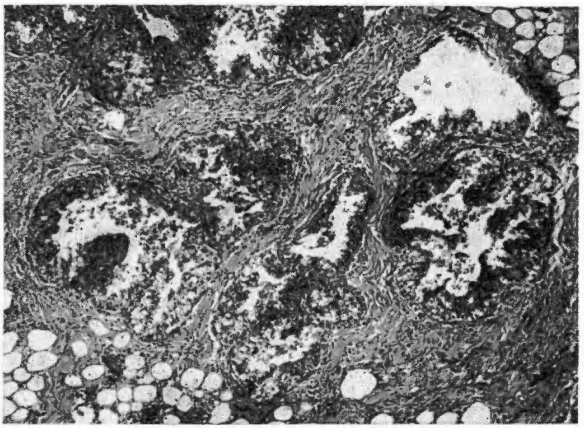


FIG. 20. High power photomicrograph of the section shown in Fig. 19. The mammary tubules are dilated and lined with two or more rows of desquamating columnar epithelium. There is round cell infiltration in the stroma.

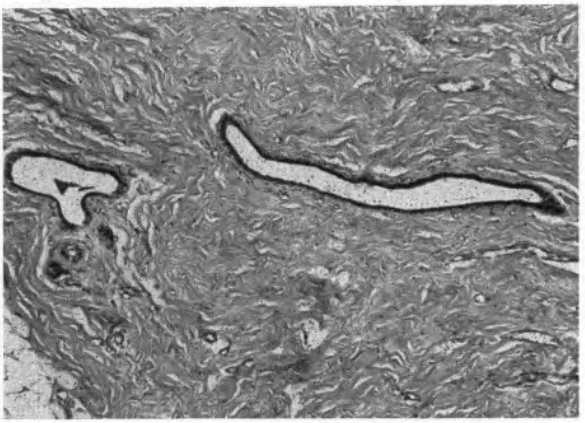


FIG. 21. Quiescent mammary gland during childhood. Photomicrograph of the breast of a female infant of ten months. The mammary tubules are narrow and lined with a single row of flattened epithelium. The surrounding connective tissue is collagenous.

ized. Wandering cells infiltrate about the tubules. Following this the male breast remains quiescent until puberty.

In female infants, the regressive changes in the breast parallel those in the male. After the sixth month the mammary tubules narrow and the lining cells shrink. However, slight residual activity in the mammary epithelium with the persistence of wandering

cells in the stroma may be found in occasional specimens from 15 to 18 months of age. Again there is a quiescent period until puberty (Fig. 21).

Pathologic changes related to postnatal physiologic activity in the mammary gland are rare. The dilated ducts containing inspissated secretion may become infected. Such infection must not be confused with the normal postnatal mammary enlargement, formerly considered a mastitis (mastitis neonatorum) and sometimes converted into such by attempts to control this normal process with massage and liniments. Widening of the duct lumen, described by Dietrich as a microscopic cyst, must also be looked upon as a normal postnatal change.

Breast Changes During Adolescence

The adolescent period begins with the first signs of sexual change at puberty and terminates with sexual maturity (Hartman). Its duration is roughly three to five years. In girls of the white race in this country, puberty changes in the breast that can be seen under the microscope begin between the ninth and the thirteenth years. In colored girls the average onset is a year earlier. According to the studies of Stratz and Weissenbérg on Europeans (cited by Taylor), "There are slight indications (in the gross) of breast growth in the tenth year . . . by the fifteenth year when practically all girls have well-developed breasts, still one-third have not menstruated." In the white male breast, puberty changes appear between the twelfth and fourteenth years (Jung and Shafton).

Male Breast. Adolescent alterations in the male breast appear later than in the female, extend over a briefer period and are followed by involutional changes. The mammary response is less intense and more irregular but in about 70 per cent of boys a palpable, button-shaped node, "the puberty node," is found beneath the nipple by the end of the first year of adolescence. Enlargement of the male breast beyond this size may be considered pathologic and persistence of the enlargement beyond a year to 18 months is abnormal. The nipple may be sensitive during this period of enlargement, particularly in cold weather, but the term "adolescent mastitis" applied to this physiologic condition is hardly justified (Jung and Shafton).

Microscopically, adolescent changes in the male breast resemble those found shortly after birth. There is moderate lengthening of the mammary tubules with widening of the lumen. The lining cells increase in height, become cuboidal in shape and rest upon a flattened layer of basal epithelium. Small amounts of secretion

are seen in some of the widened tubules. The periductal connective tissue is increased and takes only a pale stain. An increased number of patent capillaries are seen in this tissue (Fig. 22).

Involutional changes appear in the sixteenth or seventeenth year. The duct epithelium shrinks, the tubules narrow or collapse and the surrounding connective tissue condenses (Fig. 23).

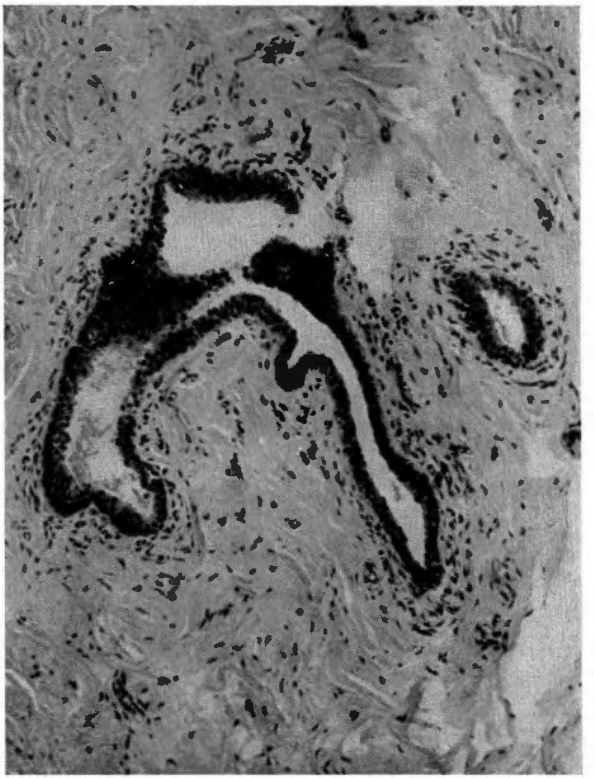


FIG. 22. The male mammary gland during adolescence. Photomicrograph showing hyperplasia in the tubules and in the periductal stroma (from a boy aged 12).

The female breast, nipple and areola enlarge gradually during adolescence. By the end of the first year a disk-shaped mass may be felt beneath the nipple and the nipple and areola increase in size and take on a deeper tint (Figs. 24, 25). The mammary gland then bulges beneath the overlying skin and creates a firm dome-like swelling which is smooth in contour. Usually, proportional growth is seen in the nipple and areola. The size of the areola is more closely correlated with mammary development, however, than is the size of the nipple. Histologically, the increase in size is due

mainly to increase in fibrous stroma and deposition of fat. There is also elongation, branching and dilatation of the duct tree. Mean-

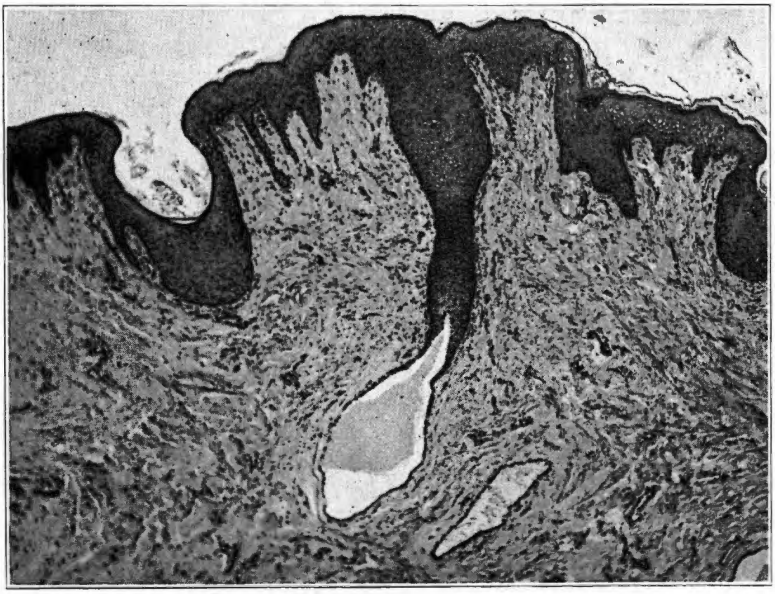


FIG. 23. The male mammary gland after adolescence. Photomicrograph of a normal male breast from a man aged 35 showing dilatation of the tubules and atrophy of the lining cells.

FIG. 24 FIG. 25

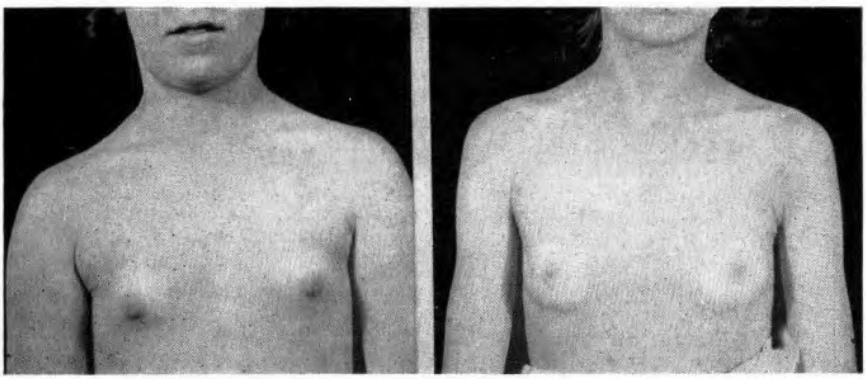


FIG. 24. The normal female breast at adolescence. Incipient mammary development in a girl aged 11.

FIG. 25. A later stage of adolescent mammary development in a girl of 14.

while, the lining cells of the ducts are increased and knobs of basal cells (lobular buds) appear at their ends (Figs. 26-28).

Branching and lengthening of the duct tree accompanied by further dilatation and secretion occur later. The lining cells enlarge and stand out individually; the connective tissue undergoes

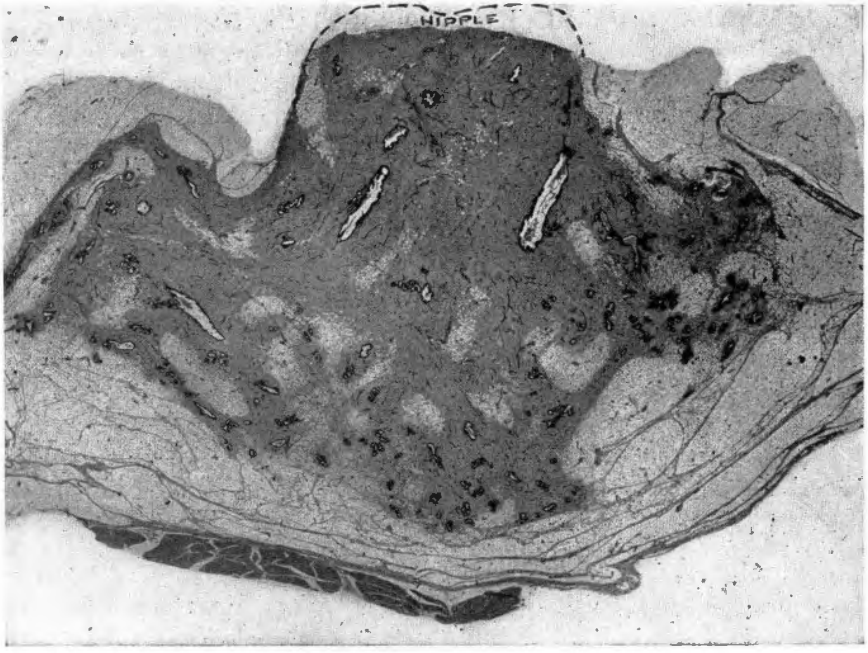


FIG. 26. Cross section of female mammary gland of adolescence showing increase in fatty and fibrous stroma and ramifications of the mammary tubules.

further growth. Adipose tissue accumulates within the stroma of the breast. The pectoral muscle and skin are separated from the

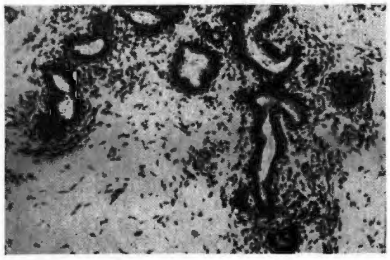


FIG. 27. High-power photomicrograph of the section in Fig. 26 showing proliferation of basal cells forming lobular buds at the end of the terminal tubules. The periductal connective tissue is increased.

breast by an increased amount of fat. This stage extends up to menstruation and ovulation.

Onset of Maturity

The first menstrual periods are usually not accompanied by marked changes in the mammary gland. Three specimens were studied within a period of six months of the first menstruation. One to four periods had occurred in subjects from 13 to 14 years old. Lobule formation had not occurred. The development in the duct tree and in the stroma represented a continuation of adolescent

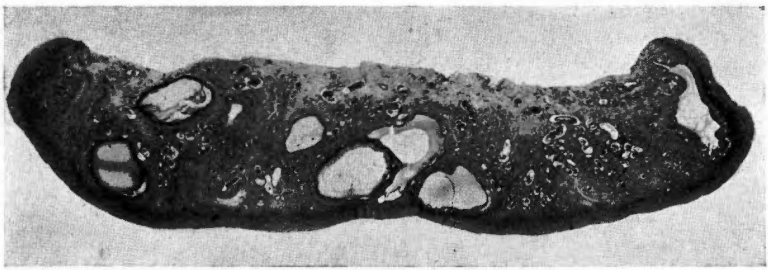


FIG. 28. Cross section of the ovary of adolescence from the same patient. Note: The specimens (Figs. 26-28) were taken at autopsy from a colored girl who had not yet menstruated. Death was due to tuberculous meningitis.

growth observed before the onset of the first period. The dilatation and amount of secretion in the larger ducts were somewhat increased, and the epithelial buds were more conspicuous (Fig. 29). The number of capillaries in the stroma was increased and a narrow, pale zone of young connective tissue surrounded the ducts and tubules.

Apparently lobule formation in the human breast occurs within one to two years after the onset of the first menstrual period provided pregnancy does not supervene. We have observed it from 12 to 18 months after the first period but not within one to six months following the first menstruation.

Histologically, the period of adolescent mammary development may be defined as beginning with epithelial and fibrous proliferation after the quiescent period of childhood and terminating with the onset of lobule formation some months after the onset of menstruation or following pregnancy. The adolescent changes are:

1. Increase in the fibrous and fatty stroma of the breast.
2. Formation of a pale-staining and vascular periductal zone of connective tissue.
3. Lengthening and branching of the mammary ducts without lobule formation.

4. Rapid increase in cells in the basal layer of the ducts (with occasional papillary projections) and increase in the cells of the terminal tubules which form sprouts and lobular buds.
5. Increased size and secretory activity in the lining cells of the larger ducts with moderate dilatation of the ducts.

Variations in the time of onset, in the intensity of the physiologic stimuli, and in the response of the breast to such stimuli during adolescence may result in mammary hypertrophy. Similar variations confined to an individual portion of the mammary tissue rather than to the breast as a whole account for the appearance of fibroadenomas during this period. The rate of development rather than the normal pattern of growth, however, is altered in these pathologic conditions. On the whole, the fundamental pattern of mammary development from birth through adolescence is remarkably stable. Cancer is practically unknown.

Menstrual Changes

The breast in normal cyclic women undergoes changes both before and after menstruation. Before the onset of the period the mammary gland is larger, more tense and firm and may be finely nodular to palpation. Pain or tenderness is often experienced at this time. Following menstruation the breasts are softer and somewhat smaller. If pain and tenderness were present before the period, they diminish or are absent.

The volume changes of the breast during the menstrual cycle have not been adequately studied. Reimann and Seabold attempted to measure these changes by radiographic studies. "The sizes of the breast tissues were determined by passing a planimeter around the edges of the x-ray shadows of the breast (taken by soft-tissue technic) thus determining the area enclosed." However, only one breast was followed through the menstrual cycle by radiographs taken in the lateral view, and a single example of pregnancy similarly studied. The percentage of increase (44 per cent) during the cycle and that from the fourth to the eighth month of pregnancy (22 per cent) indicate that the method is not sufficiently accurate.

The author attempted to measure the volume of the breast one week before the onset of the period and immediately after the cessation of menstruation. A glass funnel of special design, enclosing the breast, was applied to the chest wall and the amount of water necessary to fill the funnel to a given point when so applied was determined. The volume of the right and left breast immediately before and just after menstruation was thus determined and the

difference between these two times in the cycle was found to average 15 cc. in one normal case and 45 cc. in a case of painful breasts.

Microscopic Findings. There is little agreement on the microscopic findings which accompany these gross changes before and after the menstrual period. Rosenburg, in 1922, described a premenstrual response in the breast, characterized by new off-shoots from the lacteal ducts and a loosely arranged, reticulated stroma about the epithelial channels. He also described involutional changes and a resting stage, but his descriptions of these have not been corroborated. Following the work of Rosenburg a series of studies were made by Polano, Dieckmann, Luchsinger y Centano and others. These studies were reviewed and original observations added by Lewis and Geschickter in 1934. Taylor and Friedman are among those observers who doubt significant changes in the breast during the menstrual cycle.

Despite differences of opinion most of the observers cited agree on a definite cycle of histologic changes in the stroma and epithelial structures. Lack of agreement can be ascribed to two factors. First, there are marked variations in different portions of the same breast. Some lobules remain quiescent throughout the cycle and other hyperplastic lobules may fail to regress. This variation is accentuated by the difficulty of obtaining normal human material. Studies have been made in most instances on tissue other than tumor removed at operations for fibro-adenoma or cancer. The second factor that has introduced confusion relates to time. Perfect regularity in the menstrual cycle is probably rare in the cases studied. The changes described as occurring in the premenstruum have been placed by some observers close to the time of ovulation, by others just before the onset of menstruation. In a like manner the alterations of menstruation are sometimes described as beginning shortly before or shortly after the onset of the period. The studies described below indicate that these discrepancies are probably inherent in the response of the mammary tissue.

Because of the variations just referred to, changes in the mammary gland during the menstrual cycle are best described in two stages—a regressive and a proliferative stage. The regressive stage begins shortly before or with the onset of menstruation and is characterized by shrinkage or desquamation of mammary epithelium in the terminal tubules and lobules. The lumen of these structures is diminished, the fibrous stroma condenses and a few wandering cells may be present (Fig. 32). The proliferative stage has its onset in most instances a few days after the cessation of menstruation and continues through ovulation and the premenstruum. This stage is

characterized by expansion of the duct system, and increase in the size or amount of the epithelium in the terminal tubules and

FIG. 29

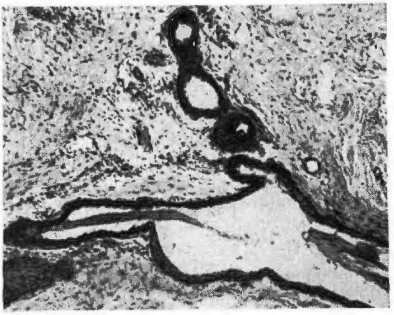


FIG. 30

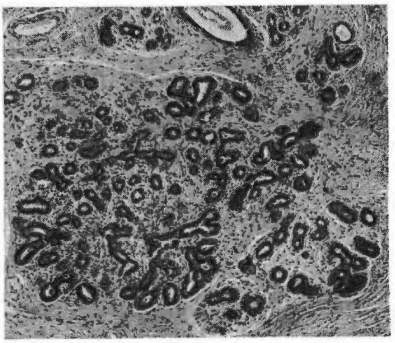


FIG. 29. Growth of the mammary tubules at the end of adolescence. Photomicrograph showing continued branching and budding of the terminal tubules. The tissue was removed from a girl of 14 whose first menstrual period was three weeks previously. Operation was performed for a benign fibro-adenoma.

FIG. 30. Mammary changes in the menstrual cycle. Low power photomicrograph showing the mammary lobules in the premenstruum. The tubules are dilated, contain small amounts of secretion and are lined by well-nourished epithelium. The connective tissue is cellular and contains wandering cells.

FIG. 31

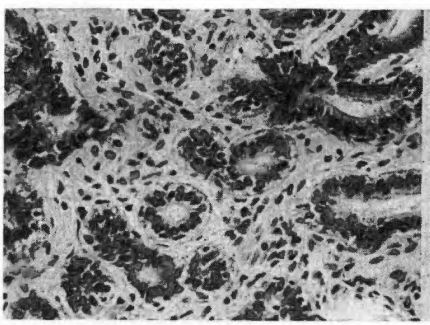


FIG. 32

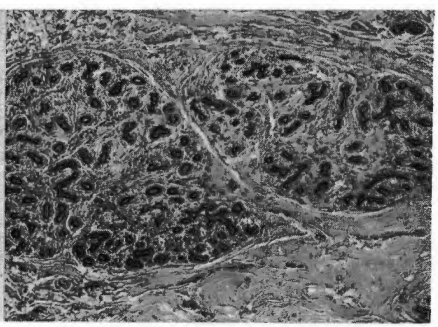


FIG. 31. High power photomicrograph of Fig. 30, showing the mammary lobules in the premenstruum. The tubules are dilated, contain small amounts of secretion and are lined by well-nourished epithelium. The connective tissue is cellular and contains wandering cells.

FIG. 32. Photomicrograph of mammary lobules on the fifth day at the end of menstruation. The tubules are collapsed, their lining cells shrunken, and the connective tissue is condensed. (Note: Figs. 30, 31, 32 are from patients with regular 28-day cycles.)

lobules. The connective tissue immediately surrounding the epithelial structures appears more edematous, stains palely and shows an increased number of young fibroblasts and lymphocytes (Figs. 30, 31).

More than 100 cases in which mammary tissue had been excised at autopsy or at operation for benign or malignant tumors and in which the time of the menstrual cycle was definitely known were available for study. The majority of these were portions of apparently normal breast obtained at operations which had been performed for mammary fibro-adenoma or carcinoma. Where possible the tissue furthest from the lesion was selected. In 22 cases the material was taken at autopsy. Cases with chronic cystic mastitis were excluded because the pathologic changes are diffuse in this disease.

REGRESSIVE CHANGES. An analysis of this material shows that the regressive changes appear about the onset of menstruation and continue to the seventh or eighth day. The intralobular stroma becomes infiltrated with round cells and then condensed and hyalinized. During this regressive period, secretion and lobular epithelium diminish, the terminal tubules collapse and many of the epithelial cells show shrinkage and desquamation. This description applies to the glandular tissue which reacts to cyclic changes. There are always portions of the breast which do not respond. Apparently, resorption of fluid takes place both from the mammary tubules and from the edematous intralobular connective tissue. As a result the breast appears smaller and softer on gross examination.

PROLIFERATIVE CHANGES follow the inactivity seen at the end of the regressive period and continue through the premenstruum. The duct system expands by the formation of new epithelial sprouts, by dilatation of the channels, and by differentiation and enlargement of the lining cells. Similar changes are seen in the lobules. Toward the end of the cycle there is an accumulation of secretion within the ducts and lobules. At the same time the connective tissue immediately surrounding these epithelial channels proliferates and becomes edematous. At the height of these proliferative changes in the premenstruum, the breast increases in volume and on gross examination is apparently more granular or finely nodular to palpation.

Speert and Hartman have recently studied the menstrual cycle in the mammary gland of the monkey. They found enlargement of the lobules and their acini in the premenstruum (see Figs. 67, 68). In the majority of women, changes in the premenstruum are sufficiently intense to maintain large numbers of well-developed lobules; in others, these structures remain more or less rudimentary until pregnancy. Hormonal irregularities during the cycle are relatively common in women in their thirties or forties who have borne few or no children; these result in corresponding irregularities in

lobule formation. The degree of irregularity thus produced is variable and inconstant. The more striking abnormalities are usually referred to as forms of chronic cystic mastitis (mammary dysplasia).

Pregnancy Changes

Enlargement of the breasts is noticeable five to six weeks after the onset of pregnancy. Increase in size is most rapid from this

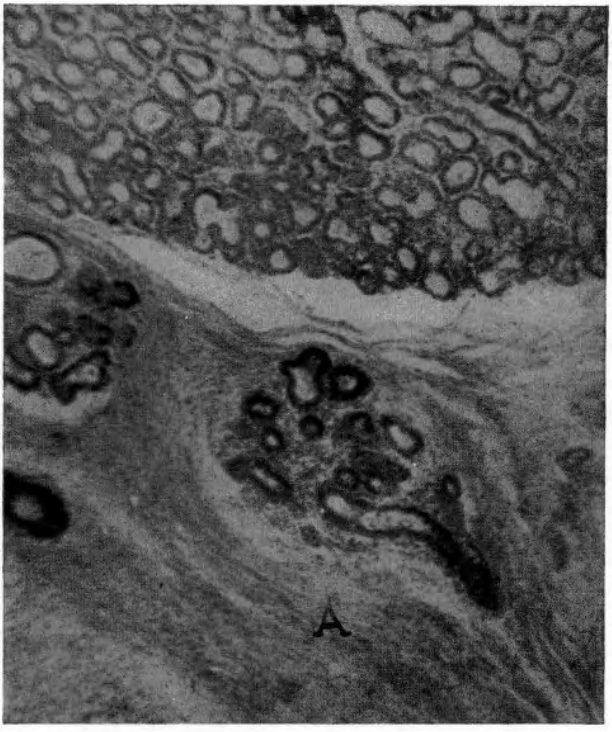


FIG. 33. Low-power photomicrograph showing irregularity in the physiologic changes during mid-pregnancy. Above is a well developed lobule, and at *A*, an undeveloped lobule.

time to midpregnancy. The superficial veins become dilated and white striae sometimes appear in the skin when the size of the gland is markedly increased. Changes in and about the nipple are conspicuous. The nipple enlarges and its epidermal covering becomes thickened; the diameter of the areola is increased and its color darkened, while the glands of Montgomery become more prominent. In some cases colostrum may be expressed after the third month. (See Fig. 133, p. 136.)

Twenty-five cases in which the breasts were removed for cancer

or portions excised for fibro-adenoma during the various stages of pregnancy have been studied histologically (Geschickter and Lewis). In this material every month of gestation except the first was represented. New epithelial elements were being added throughout the greater part of pregnancy. There was increasing differentiation in the new acini with evidence of secretion in the latter months. During this time portions of the stroma are resorbed or

FIG. 34 FIG. 35

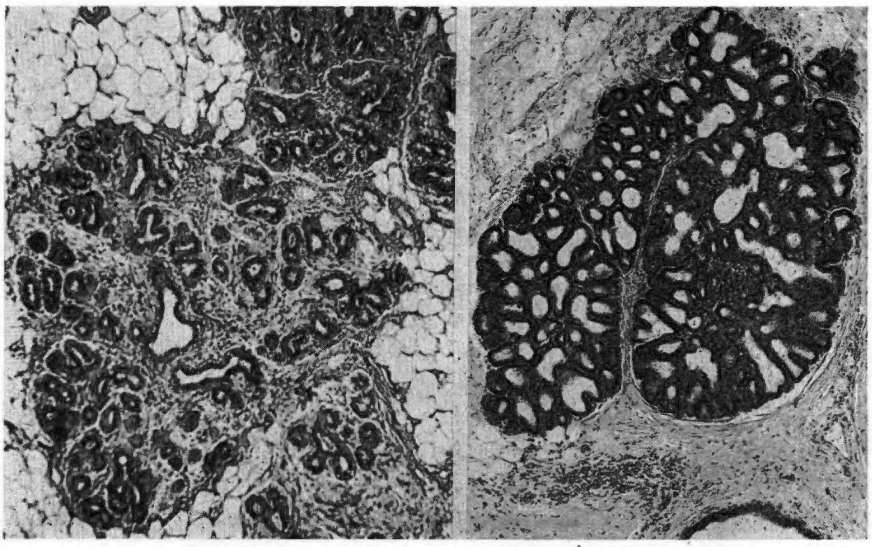


FIG. 34. The human breast in the first third of pregnancy. Epithelial and connective tissue proliferation occur from the fifth to twelfth week of pregnancy.
FIG. 35. The human breast in the mid third of pregnancy. The number of lobular alveoli has increased while the periductal connective tissue has practically disappeared.

compressed. These changes may show marked irregularity. Until lactation made its appearance, many of the large lobules were still undergoing epithelial proliferation, while small virginal lobules remained unaffected by pregnancy and lactation (Fig. 33).

Changes in the breast during pregnancy may be conveniently divided into those of the first, of the mid, and of the third trimesters.

During the first trimester sprouting and epithelial proliferation occur in the terminal tubules; wandering cells and young fibroblasts appear in the adjacent connective tissue. Some of the new tubules extend into the adjacent fat. The epithelium lining the ducts consists of small oval cells, many of which are undergoing mitosis. In places, these proliferating cells are without basement membrane or obliterate the lumen of the ducts (Fig. 34).

In the mid trimester the reduplicated terminal tubules are grouped together to form large lobules. Their lumens are dilated, form acini lined by cuboidal epithelium with intracellular fat droplets; the acini may contain small amounts of secretion. The surrounding connective tissue remains loose and contains aggregates of lymphocytes (Fig. 35).

In the last third of pregnancy the acini formed in the mid trimester are progressively dilated and show increasing amounts of

FIG. 36 FIG. 37

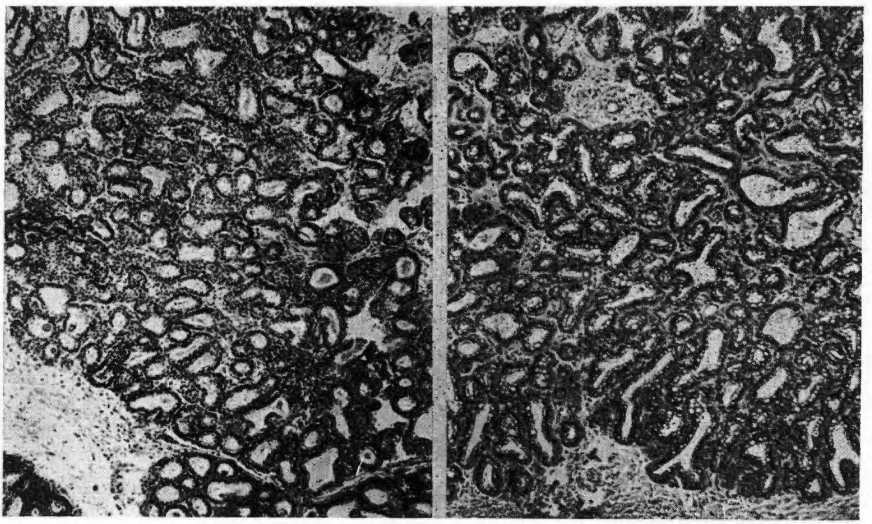


FIG. 36. The human breast in the last third of pregnancy. The increased size of the lobule and its acini are shown in the seventh month of pregnancy.
FIG. 37. Further increase in the size of the lobule; dilatation of the acini and the appearance of secretory vacuoles, in the eighth month of pregnancy.

secretion. The interlobular connective tissue is compressed and becomes increasingly vascular. There is expansion of both the duct and lobular systems. Much of the periductal fibrous tissue has disappeared and there are numerous capillaries engorged with blood. Many acini are lined by a single row of low cuboidal cells with secretory vacuoles. A few small nests of proliferating epithelial cells may still be seen and also an occasional duct plugged with epithelial cells. Some acini are greatly dilated, suggesting the beginning of lactation (Figs. 36, 37).

Lactation Changes

Although colostrum may be expressed from the nipple after mid-pregnancy, true lactation does not appear until three or four days

after childbirth. Following delivery and before the appearance of milk, the breasts become increasingly tense and painful. Distention may be sufficiently acute to arouse fear of "caked" breasts. These sensations are relieved with suckling. The quantity of secretion varies widely in individual cases; also, milk may be ample in one breast and insufficient in the other.

During lactation, the lobules and their afferent ducts serve two functions: the secretion and storage of milk. Secretion takes place

FIG. 38 FIG. 39

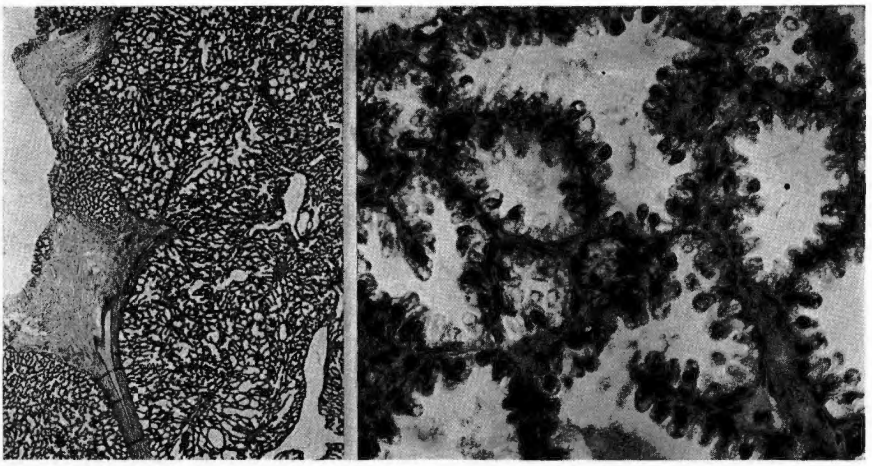


FIG. 38. Lactation. Low-power photomicrograph showing the acinar structure and secretory changes at the height of lactation.
FIG. 39. High-power photomicrograph of Fig. 38.

in the epithelial lining of the dilated acini. These acini which are grouped together to form immense lobules are lined by a single layer of secretory epithelium. The cells are of various shapes, cuboidal to columnar (Figs. 38, 39), with nuclei at the base or the tip. The cytoplasm is pale, granular and refractile, but secretory bodies occupy the major portion. The epithelium rests upon a narrow band of connective tissue which encloses thin-walled capillaries. The lobules are separated by strands of dense connective tissue in which the larger vessels are embedded. Secretory globules and desquamated cells distend the acini and their afferent channels. When lactation is at its height these secretory products may comprise from one-fifth to one-third of the breast volume, the expanding duct system acting as a reservoir.

Lobules which have failed to respond to the influence of pregnancy may also fail to lactate. Deaver and McFarland suggest that

such lobules may account for the variations in the volume of milk observed in different women. Langer found that the number of inactive lobules was relatively smaller in women who had had repeated pregnancies.

Postlactation Changes

Changes following the cessation of lactation are subject to many irregularities. If the child is not nursed, involutional changes make their appearance within a few days. The extent to which lactation may be prolonged by suckling varies greatly but usually secretion diminishes after the ninth or tenth month.

FIG. 40 FIG. 41

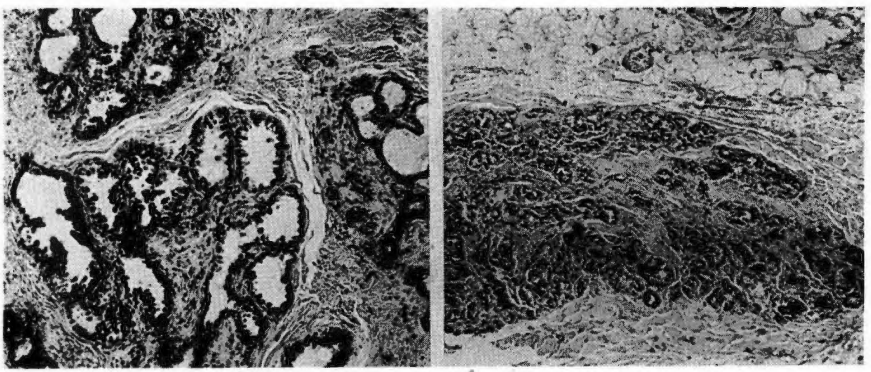


FIG. 40. Post-lactation changes. Photomicrograph showing irregular size of the acini and involution of secreting epithelium, six weeks after weaning.
FIG. 41. Atrophic changes in the mammary lobules six months after weaning.

Regressive Changes. The order of the regressive changes in the postlactation period is: disruption of the acini; collapse of these structures and narrowing of the tubules; the appearance of round-cell infiltration and phagocytes in and about the disintegrating lobules; and, finally, regeneration of the periductal and perilobular connective tissue with renewed budding and proliferation in the terminal tubules. The postlactation breast is often pendulous or flabby because this fibrous regeneration is insufficient to replace the amount of stroma absorbed during lactation.

Disruption of the acini usually follows within several days after cessation of lactation. Secretory granules disappear from the epithelium and the basement membrane is interrupted. Disruption of the acinar wall results in the formation of large and irregular acinar spaces (Fig. 40). Scattered and disintegrating epithelial cells are seen in the region of the collapsing lobules (Fig. 41). Round

cells infiltrate the surrounding connective tissue. Wandering cells loaded with fat can be seen in the various lymphatic channels and in the regional lymph nodes. This stage of epithelial disintegration and resorption is followed by gradual increase in the adjacent connective tissue and eventually by signs of budding and regeneration in the terminal tubules.

The time required for these involutional changes varies. Usually the breast returns to a nonpregnant state within a few months. Residual lactation has been observed in isolated portions of the breast many years after lactation, however. Moran reported such findings in a case of fibro-adenoma which was excised eight years after lactation and Cohn reported a case of residual lactation mastitis in which similar changes were found 14 years after the last lactation.

Pathologic Changes. Both benign and malignant lesions of the breast may respond to the physiologic changes of pregnancy and lactation. Chronic cystic mastitis may disappear during the course of pregnancy or during the postlactation period. The growth of benign fibro-adenomas may be markedly accelerated and a similar influence may be exerted on mammary carcinoma. Residual lactation may be the seat of chronic inflammation; so-called residual lactation mastitis, a condition which may be difficult to distinguish from cancer both clinically and pathologically.

Involution and Senile Changes

Involution. In women near the menopause, regressive changes appear both in the epithelial structures and in the stroma of the breast. Although the breast may enlarge through a deposition of fat, the amount of the glandular tissue decreases and the fibrous tissue becomes increasingly dense and hyalinized. The ducts and their major branches remain but the lobules shrink and collapse although occasionally acinar-like structures persist.

First Stage. The mammary lobules and acini which are the last structures to appear with sexual maturity are the first to regress. Repeated pregnancies serve to extend lobular development, but in the absence of childbearing their size and number decline and irregularities appear. Lobular irregularities were found microscopically in 33 per cent of the cases of mammary tissue removed at autopsy from women between the ages of 30 and 40 years who had clinically normal breasts. These irregularities consisted of nonencapsulated areas of epithelial proliferation in the region of the terminal tubules, cystic dilatation of acinar-like structures and

metaplasia of the duct epithelium into the so-called sweat gland type (Figs. 42, 43). The average age of the autopsied cases showing such changes was 38 years. These lobular irregularities were the earliest form of involutional changes observed.

FIG. 42 FIG. 43

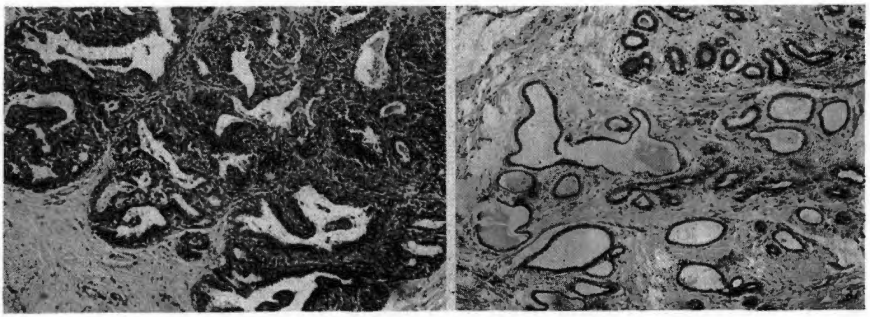


FIG. 42. Lobular irregularities occurring in normal cyclic women between thirty and forty years. Epithelial proliferation from a clinically normal breast obtained at autopsy from a woman aged 32, dying of strangulated hernia.
FIG. 43. Cystic changes in the mammary lobules found in a clinically normal breast in a woman aged 36 dying of lobar pneumonia.

THE NEXT STAGE of mammary involution is characterized by shrinkage and disappearance of the lobular elements, and narrowing of the epithelial channels. This collapse of lobular and tubular structures is accompanied by increased density in the surrounding

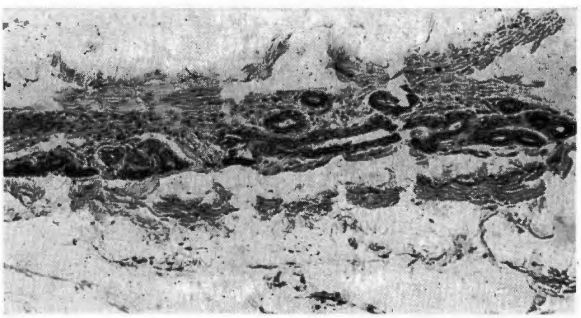


FIG. 44. Involutional changes occurring at the menopause. Lobular atrophy and collapse of the terminal tubules in a woman 44 years old.

stroma. The average age of autopsied cases studied which showed this stage of involution was 44.6 years (Fig. 44). The number of children borne and the time of the menopause condition the age at which these changes appear. This phase of mammary involution,

characterized by collapse of the epithelial structures, is first to appear in young patients castrated by surgery or x-rays.

IN A LATER STAGE of involution in women of more than 45 years there is flattening of the duct epithelium and cystic dilatation of these channels (Fig. 45). The majority of these women are at or past the menopause. Lobular remnants are usually absent but a few may remain. The stroma is hyalinized and contains increased amounts of fat.

FIG. 45

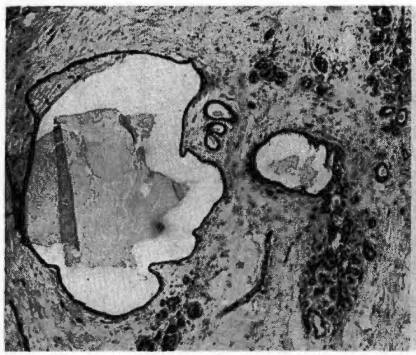


FIG. 46

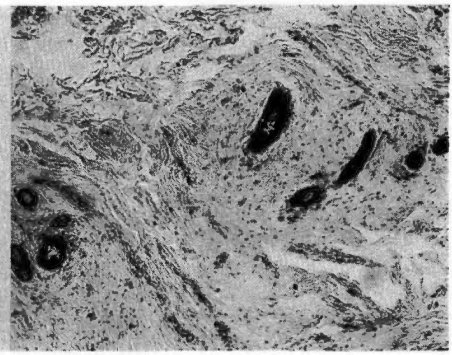


FIG. 45. Cystic involution occurring in a woman aged 52, the patient was still having irregular menstrual periods.

FIG. 46. Remnants of the mammary apparatus and sclerosis of connective tissue in a woman aged 65.

Note: The specimens illustrated in Figs. 42 to 46 were taken at autopsy from women with clinically normal breasts and with negative findings in the reproductive organs. (Courtesy of Dr. L. A. Keasbey, Lancaster, Pa.)

Tietze, Askanazy, Borchardt and Jaffe, Lindgren and other investigators estimate that 25 to 93 per cent of the breasts of women more than 40 years old, when examined at autopsy, show senile changes simulating chronic cystic mastitis without having clinical evidence of the disease. In the author's study of 100 autopsied cases, in which tissue was removed from clinically negative breasts of adult women, microscopic changes resembling those seen in chronic cystic mastitis occurred in 55 per cent. These changes include both the lobular irregularities which comprise the earliest form of involution and cystic dilatation of the ducts which appears at a later stage.

Senile Changes. In the last stages of mammary atrophy in women more than 50 years of age, the stroma becomes increasingly dense and sclerotic (Fig. 46). The smaller mammary ducts and blood vessels may be obliterated by hyalinized connective tissue which

occasionally shows calcification. Riedel noted marked hyperplasia of the elastic tissue about the vessels and ducts in this stage.

These stages of mammary involution may be summarized as follows:

1. Lobular irregularity (35 to 40 years).
2. Shrinkage and collapse of epithelial structures (40 to 45 years).
3. Cystic dilatation of the ducts (46 to 50 years).
4. Sclerosis and obliteration of smaller ducts and vessels (over 50 years).

Pathologic Changes. The involutional changes of the mammary gland are associated with the most common abnormalities of this organ—chronic cystic mastitis and mammary carcinoma. The various forms of chronic cystic mastitis may be looked upon as exaggeration of the irregularities in the lobular epithelium found in the earlier stages of involution. Mammary carcinoma frequently is associated with the late stages of mammary involution and atrophy, and often makes its appearance when the mammary epithelium has been largely replaced by fat and fibrous tissue.

Summary of Mammary Development

The mammary gland is an epidermal appendage. It arises from the basal cells of the ectoderm in relation to thickening and hyperdifferentiation of the epidermis. Remnants of such hyperdifferentiation derived from the embryonic nipple pouch may be found in the human adult.

Prepubertal Development. The primary human mammary epithelium is found in the duct system, a series of 15 to 25 branching epithelial channels which find exit at the nipple. The beginning of the duct system appears in the embryo beneath the nipple pouch at the end of the third month. The duct system continues to extend and branch until birth. Following birth there is temporary expansion and secretion in the duct system which regresses in infants between the fourth and eighth months. Childhood is a period of quiescence in both sexes.

At puberty there is renewed growth and extension of the duct tree. This is followed by quiescence and involution in male adults. In females, the growth of the duct tree, which is accompanied by marked increase in the surrounding fibrous and fatty tissue, is greatly accelerated during adolescence and continues into sexual maturity and through the first third of pregnancy.

During adolescence a second system of mammary epithelial structures is developed. The beginning of this system takes the form of buds of undifferentiated basal cells at the end of the mammary tubules. These are the buds of the lobular system. Increase in the size and sprouting of the lobular buds occurs throughout adolescence. With the onset of sexual maturity, acinar-like structures are differentiated from the lobular buds—the true mammary lobules. These reach their maximum development during pregnancy and lactation.

During the menstrual cycles, alternating periods of regressive and proliferative changes, small and variable in extent, occur in the ducts and periductal fibrous tissue and in the lobular epithelium.

Menopausal and Postmenopausal Changes. Involutional changes make their appearance in the mammary gland in women approaching the menopause. The earliest changes in women younger than 40 years, who have borne few or no children, consist of epithelial irregularities in the mammary lobules. Next shrinkage and collapse of the lobular elements and their afferent tubules occur. Disappearance of the lobular epithelium and cystic dilatation of ducts with condensation and hyalinization of the surrounding stroma follow the menopause. Sclerosis in the mammary stroma with obliteration of the smaller ducts and blood vessels are late senile changes.

ANATOMY OF THE ADULT BREAST

The greatest number of lesions requiring surgical interference occur in the adult breast and hence anatomic interest centers on the structure of the fully developed gland.

Position. The adult female breast extends from the second to the sixth rib and from the sternum to the anterior axillary line, lying directly over the pectoralis major muscle. The size of the breast, however, is variable and may extend below over the rectus abdominus and serratus anterior muscles, or laterally, to the mid axillary line. Most of the outer and upper quadrant extends posteriorly and laterally beyond the outer border of the pectoralis major.

Epithelial Structures. Except for the region of areola, the breast tissue is separated from the overlying skin by a layer of adipose tissue and from the pectoralis fascia by a similar layer of fat. The mammary tissue, however, is nonencapsulated and minute lobules have been found in the pectoralis fascia, and in cases of hypertrophy the breast tissue may be found directly beneath the epidermis. For the most part, the mammary ducts and lobules spread radially

from the nipple which, before puberty, is usually in the fourth inner space about an inch lateral to the cartilages of the fourth and fifth ribs. Fifteen to 25 ducts open into the nipple and dilate to form the ampullae immediately beneath. The course of these ducts and the number of lobules that sprout from them vary greatly in different individuals and at different times during life. The glands of the areola are the glands of Montgomery.

Fatty Stroma. Except for the region of the areola the entire mammary gland is encased in fat, sometimes referred to as capsula adiposa mammae. Connective tissue strands extend through this to the skin, particularly on the upper hemisphere, and are known as the suspensory ligaments of Cooper. The attachment of the gland posteriorly to the sheath of the rectus major is extremely loose. The free spaces are sometimes called the retromammary bursae.

Fibrous Tissues. Four forms of fibrous tissue are recognized in the breast. Two of these are fascial in type. One, the enveloping fascia,

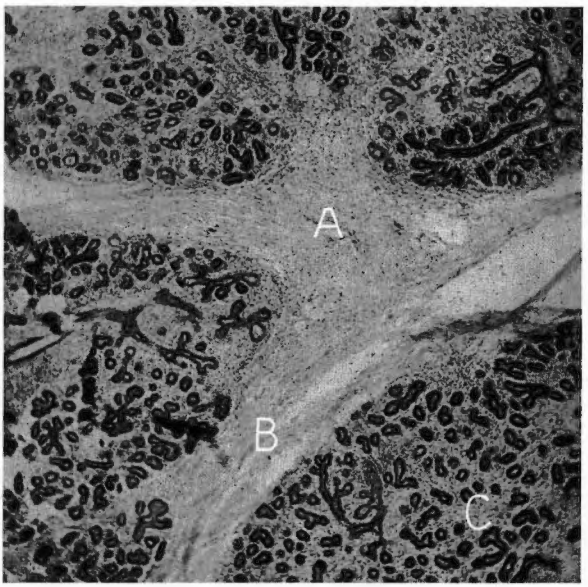


FIG. 47. The fascia and stroma of the breast. The fascia surrounding the breast is not shown. A—Interlobular connective tissue, B—Perilobular connective tissue, and C—Periductal and periacinar connective tissue.

surrounds the entire breast and is known as the interlobar connective tissue. The second, or subdividing, fascia separates the gland into lobules, and is known as the interlobular connective tissue. These fascial structures are continuous with the fascia over the

pectoral muscles and carry the lymphatics of the deep fascial plexus. The third and fourth forms of fibrous tissue constitute the true stroma of the breast. One of these surrounds the ducts and acini in concentric fashion and is known as the perilobular connective tissue. The other immediately surrounds the ducts and potential acini and is referred to as periductal or periacinar. (Fig. 47.)

Vascular Supply. The mammary gland receives its vascular supply from small aortic vessels, from the internal mammary artery and from branches of the axillary artery. The intercostal branches from the aorta are in the second, third, fourth and fifth interspaces. Similar intercostal branches arise from the internal mammary artery, several small branches being given off in each interspace. The lateral thoracic artery and sometimes an external mammary artery, both arising from the axillary artery, supply the outer portion of the gland. (Fig. 48.)

The internal mammary artery arises from the subclavian artery opposite the inferior thyroid and superficial cervical arteries. The thoracic portion of the mammary artery lies behind cartilages of the six upper ribs and the intercostal muscles. Behind is the pleura. The intercostal branches run laterally and anastomose with the corresponding branches of the aortic intercostals. The lateral thoracic artery arises from the axillary artery and extends along the lower border of the pectoralis minor muscle under cover of the pectoralis major. It sends branches around the border of the pectoralis major to the mammary gland. It also anastomoses with the aortic intercostals and internal mammary artery. The veins follow the course of the arteries (Maliniak).

The nerves that supply the breast are the anterior cutaneous branches of the second, third, fourth and fifth intercostal nerves and the lateral branches of the last three. Diffusion of pain along the intercostal trunks is felt around the chest and toward the back. along the medial side of the arm, along the intercostal brachial nerve, and sometimes up into the neck or over the scapula.

The mammary lymphatics are extremely numerous. There is a rich plexus around the areola and nipple which empties into the subareolar plexus. There is also a deep plexus arising from vessels around the individual alveoli and lobules which converge toward the subareolar plexus, usually through large lymph vessels which run parallel to the lacteal ducts. Some of the drainage of the deep plexus is toward the periphery of the breast and this is called the deep fascial plexus. From the subareolar plexus, two large lymphatic vessels usually pass toward the axilla. These two main vessels

pass to the anterior pectoral group of the axillary nodes and thence to the central axillary and subclavian nodes. One or two vessels pass to the nodes along the axillary border of the pectoralis major and sometimes a vessel passes directly to the subclavian nodes.

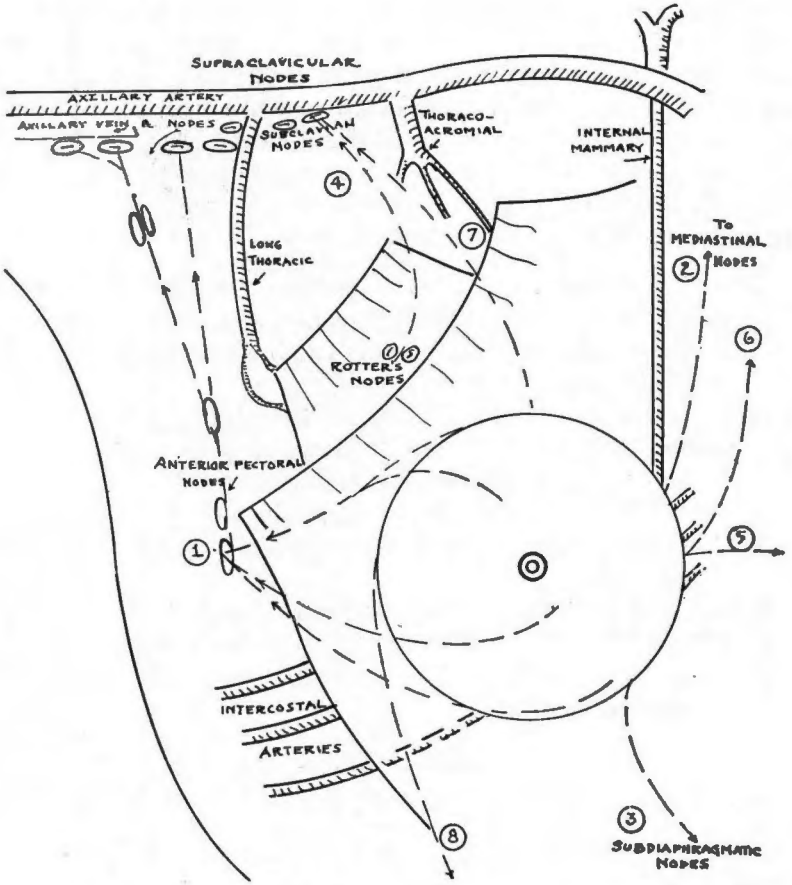


FIG. 48. The blood supply and lymphatic drainage of the breast. In the diagram the lymphatic pathways are: (1) Axillary route, to anterior pectoral nodes (low), central axillary nodes (mid), to subclavian nodes (high or apex). (2) Internal mammary route along the internal mammary artery to mediastinal nodes. (3) Paramammary route of Gerota, through the abdominal lymphatics to the subdiaphragmatic nodes. (4) Groszman's path from lymphatics beneath the breast perforating the pectoral major muscle to Rotter's nodes, thence to subclavian nodes. (5) Cross mammary pathway via superficial lymphatics to the opposite breast. (6) Substernal pathway to the mediastinal nodes. (7) Subclavian pathway direct to the subclavian nodes. (8) Lower superficial pathway to the lymphatics of the abdominal network.

Three main groups of lymph nodes draining the breast are in the axilla. The first or lowest is the anterior pectoral group. The

next is the central axillary group which is along the axillary vein in the mid axilla and the last is the subclavian group at the apex of the axilla where the subclavian and axillary veins join.

On the medial side of the breast, lymphatic vessels follow the branches of the internal mammary artery to the mediastinal nodes. In addition, there are crossed anastomoses with the lymphatics of the opposite breast and also with the abdominal network. Lymphatic vessels in the lower medial portion of the gland drain into fascial lymphatics. Some of these drain beneath the sternum to the mediastinum. Others pass through the abdominal wall under the xiphoid process of the sternum to join the lymphatics of the diaphragmatic region (Fig. 48).

The various lymphatic pathways are:

1. Axillary route, to anterior pectoral nodes (low), central axillary nodes (mid), to subclavian nodes (high or apex).
2. Internal mammary route along the internal mammary artery to mediastinal nodes.
3. Paramammary route of Gerota, through the abdominal lymphatics to the liver or subdiaphragmatic nodes.
4. Groszman's path through lymphatics perforating the pectoral muscle to Rotter's nodes, beneath the pectoralis major.
5. Cross mammary pathway via superficial lymphatics to the opposite breast.
6. Substernal pathway to the mediastinal nodes.
7. Subclavian pathway directly to subclavian nodes.
8. Lower superficial pathway to the lymphatics of the abdominal network.

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2

Endocrine Physiology of the Breast

Endocrine studies emphasize the dependence of postnatal mammary development upon ovarian function. The estrogen secretion of the ovarian follicle plays a major role in adolescent development and, with sexual maturity, both estrogenic and luteal hormones combine to produce physiologic changes. The hormones of the anterior pituitary gland are important not only to stimulate and maintain ovarian function but to activate lactation. Moreover they seem to be essential for the response of the mammary gland to the ovarian hormones. Testicular and adrenal cortical influences may also induce changes in the mammary gland.

Changes produced by endocrine and other physiologic influences are not uniform throughout the breast. Marked differences may be found in different lobes of the same breast (which are independent anatomic units). Response at puberty may differ from that in adulthood, and there are differences between male and female breasts.

POSTNATAL HYPERTROPHY

The early development of the mammary gland in the embryo is apparently uninfluenced by sex hormones. It is possible that the

adrenal acts as a primitive sex gland but there is no experimental evidence to confirm this. Development is the same in both male and female. In marsupials, where the young are born before development is complete, mammary growth proceeds without interruption in the absence of maternal or placental hormones (Bresslau, Hartman). In the rat, where the young are born in a very immature state, mammary growth proceeds through the sixth week at approximately the same rate in males and females in spite of castration performed before the fourth week (Astwood, Geschickter, Rausch).

Infancy. Superimposed upon the embryologic development of the human mammary gland there is an additional growth, occurring about the time of birth[1] which surpasses that seen during childhood. In some infants there is a palpable enlargement of the gland (incorrectly termed "mastitis neonatorum") and after a few days there may be a milk-like secretion microscopically. Such hypertrophy, characterized by expansion of the duct tree and by increased amounts of periductal stroma is assumed to be stimulated by the sex hormones of late pregnancy, maternal and placental in origin.[2] This supposition is based upon the fact that these hypertrophic changes are seen in both boys and girls at a period when both the ovaries and testes are quiescent. Philipp and Brill, independently, found estrogen in the urine of the newborn, Philipp reporting that the hormone rapidly decreased by the fourth day and disappeared by the sixth day. The disappearance of estrogen is followed by secretory changes in the mammary gland, by dilatation of the ducts and by vascular engorgement. The hormonal basis of witch's milk, the secretion of the mammary gland of the newborn, has been discussed by Lyons. He was able to detect pituitary lactogenic hormone in the urine of four newborn babies. One of the babies, a boy who was lactating, had the largest amount of hormone. He concludes that since estrogen has been found in the blood and in the urine in babies for about five days after birth, witch's milk is formed in the infantile breast after successive stimulation by estrogen and lactogenic hormone.

Childhood. The period of quiescence in mammary development during childhood parallels a similar quiescent period in the gonads.

[1] It has not yet been demonstrated whether the hypertrophy of the human mammary gland at birth has its onset during the last few weeks of fetal life, at the time when development is sufficient for the structures to respond to maternal and placental hormones, or whether the hypertrophy begins immediately after birth upon the withdrawal of a preceding and unidentified inhibitory substance.

[2] A review of the hormonal functions of the placenta is given by Newton. Catchpole and Cole, and also Parker and Tenney believe that the estrogens of late pregnancy may be of other than placental origin. However, evidence is overwhelmingly in favor of the placenta as the chief endocrine organ of this period. The ovary of the female infant is quiescent while the uterus and breast show activity.

GROWTH DURING ADOLESCENCE

Adolescent Female Breast and Estrogen Effects

As previously described adolescent growth of the breast in the human being and in laboratory animals is characterized by extension and branching of the mammary ducts, hypertrophy of their lining cells, increase in the size of the lobular buds, and proliferation of the supporting stroma of fat and fibrous tissue. The nipple is enlarged and its epidermal covering thickened. Apparently this adolescent growth is stimulated by ovarian estrogenic hormones.

In girls, a constant and increasingly intense estrogenic stimulus is present throughout adolescence as a result of the ripening of ovarian follicles. This is attested by assays of the urine. While these assays for estrogenic substance show increasing amounts, they probably do not provide a true index of the intensity of stimulation to which the mammary gland is subjected. Mammary growth is rapid in adolescent girls and is definite even in boys at this period. The urine assays for estrogenic substance, however, yield lower values for girls of this age than for normal adult men in whom no mammary growth occurs and are less than those found in the urine of mature cyclic women. Unfortunately, reliable determinations of the estrogen values in the blood or tissues are not available. Recent animal experimentation (Mixner, Lewis and Turner) suggests that a mammogenic factor of the anterior pituitary may play a role in adolescent development.

Estrogen Excretion. Frank gives the following figures for estrogen excreted in the urine of girls before puberty:

> Two international units of estrogen in 500 cc. of urine at 4 years.
> Two international units of estrogen in 250 cc. of urine at 9 years.
> Two international units of estrogen in 30 cc. of urine at 12½ years (one-half adult amount).

Oesting and Webster did not find mensurable quantities of estrogen in urine of girls (or boys) before 10 years but found from 10 to 80 international units per 24 hours in girls between 10 and 15 years, an average of 40 international units in 9 girls. In boys of corresponding ages the values were 10 to 60, averaging 25 international units per 24 hours. Dorfman and Greulich obtained similar values in 18 boys and 5 girls between the ages of 6 and 16.

The adolescent breast of girls responds to estrogen with a growth of both ducts and periductal stroma, but the growth of stroma predominates. The author has never observed lobule formation in the

normal adolescent female breast and is of the opinion that this does not occur before ovulation or pregnancy, that is, prior to the advent of the corpus luteum. The marked stromal growth and absence of lobule formation in adolescence are distinguishing features of the human breast.

Clinical Evidence of Estrogen Effects. Mammary hypertrophy occurring in immature girls having granulosa-cell tumors of the ovary, with estrogen secretion, demonstrates the effect of estrogen on the

FIG. 49 FIG. 50

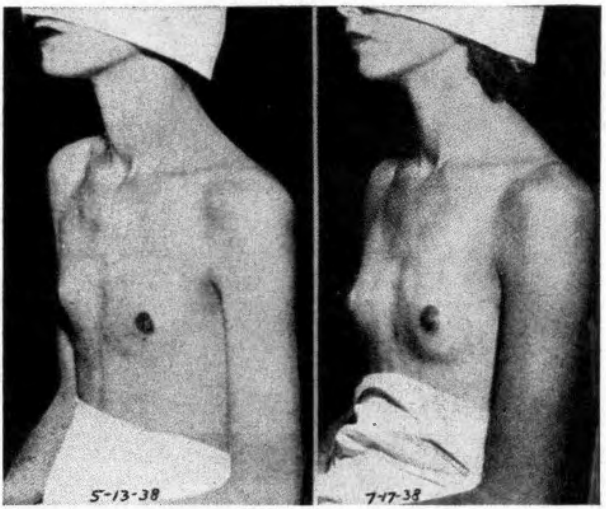


FIG. 49. The effect of estrogen on the human breast (after MacBryde). Patient with hypogonadism before treatment with estrogen ointment applied daily to the mammary region.
FIG. 50. The same patient after eight weeks' treatment with estrogen ointment locally.

development of the human breast. (Chap. 4.) In a case previously reported by the author, infantile hypertrophy in a girl of five followed the administration of 6 mg. estrone over a period of six weeks for the treatment of gonorrheal vaginitis. Kurzrok, Wilson, and Cassidy noted enlargement of hypodeveloped breasts in girls treated with estrogen for primary amenorrhea. MacBryde treated with estrogen three women who lacked mammary development and exhibited other signs of hypogonadism. He was able to demonstrate that active mammary growth could be produced in these patients by the injection of from 150,000 to 350,000 international units of estrone or of estradiol benzoate per week. The mammary enlargement subsided when injections were stopped. It returned when these patients were treated with an estrogen-containing ointment rubbed in for five

minutes each night. (Figs. 49, 50.) The author has obtained similar results in his own patients.

Experimental Evidence. Biopsies of the breast of five adult cyclic women have been studied following the injections of 25,000 to 100,000 international units of estrone over a period of one to two months. Extension of the ducts, increase in the number of their lining cells and proliferation of periductal stroma in these specimens duplicate the histology seen in the normal adolescent female breast. (Fig. 51.)

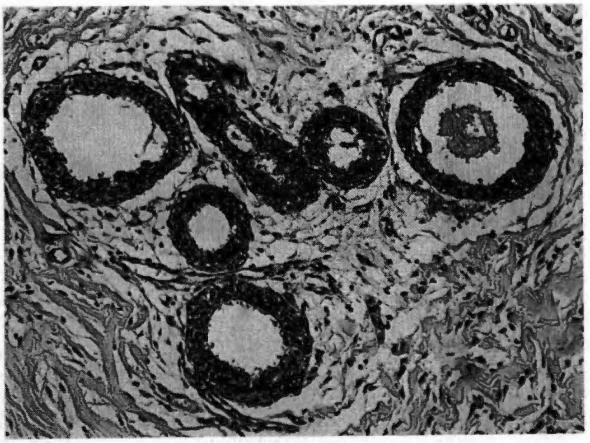


FIG. 51. Mammary response to estrogen. Photomicrograph showing hypertrophy of the duct epithelium and hyperplasia of periductal connective tissue following the injections of 75,000 I. U. of estrone in a woman 42 years old.

Extension of the duct tree during adolescence and in response to estrogen has been demonstrated in monkeys. (Fig. 52.) There is less response in the stroma than is seen in the human breast and lobule formation may occur. Aberle found that the ovary and the mammary gland in the macaque monkey showed a parallel and rapid increase in size during adolescence.

The studies of Gardner and Van Wagenen on prepubertal, spayed female monkeys show that the mammary growth described by Aberle can be produced experimentally with estrogen stimulation. The size of the mammary gland (measured by whole mounts) doubles with estrogenic injections over a period of two to five months. These authors observed lobule formation in response to injections of estrogen. Hartman, Speert, and Geschickter have also reported lobular growth of the monkey breast in response to estrogen. Speert has shown that the growth of the mammary gland in the monkey may be stimulated directly and that the estrogens do not necessarily

stimulate growth through the mediation of the pituitary. He applied the estrogen directly to one breast and not to the other, and obtained

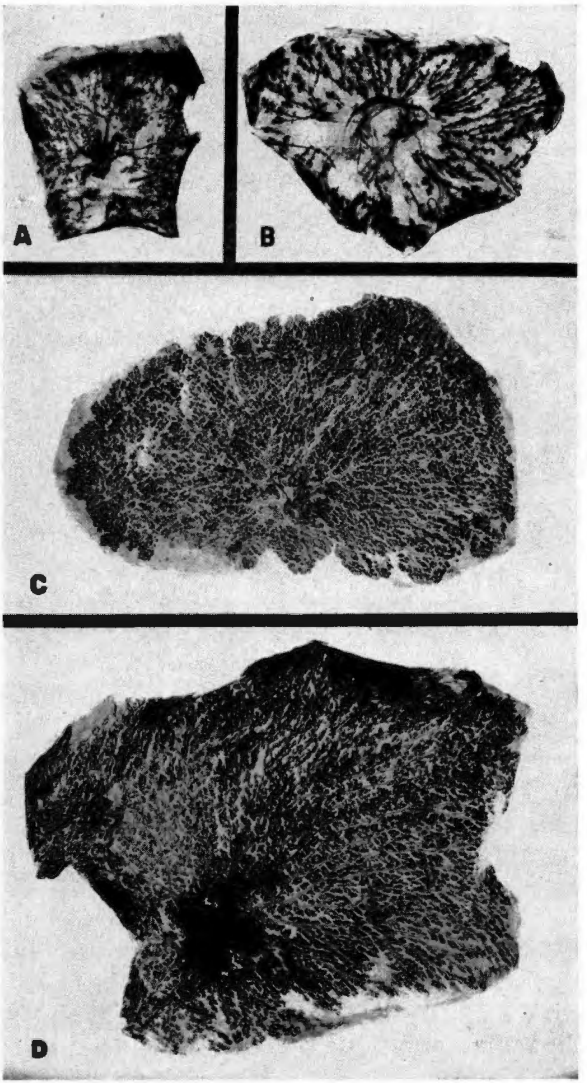
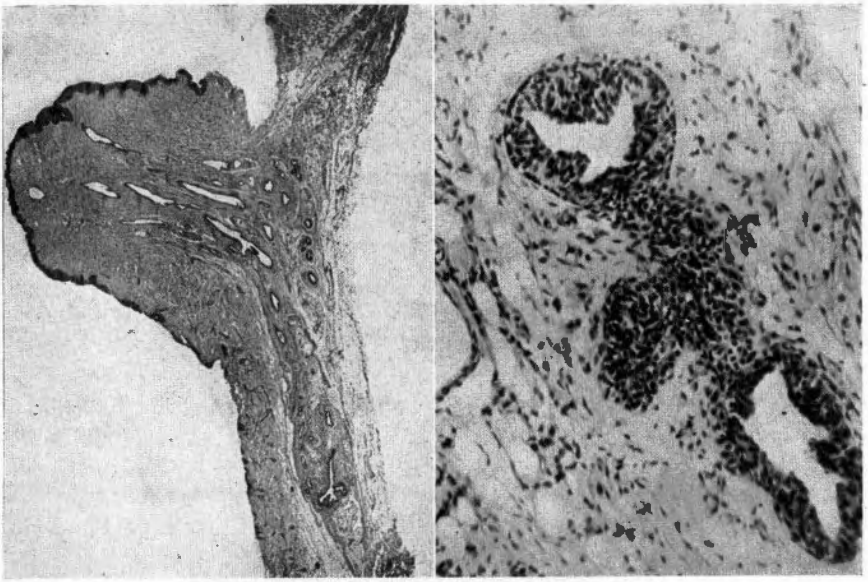


FIG. 52. Growth of the mammary gland of the monkey from puberty to maturity. Whole mounts of the mammary gland of the monkey, showing normal growth. Glands removed at prepuberty (A), puberty (B), toward the end of adolescence (C) and at full maturity (D).

growth only in the treated breast. The author has noted a similar inequality in breast development in a patient who applied estrogen percutaneously in greater amount to one breast than the other.

In the rat, growth of the duct tree is identical in males and females until puberty (sixth week). Castration at three weeks of age does not prevent prepubertal duct growth in either sex, but does inhibit the adolescent growth and causes atrophy of the lobular buds.

FIG. 53 FIG. 54



The Effect of Moderate Doses of Estrogen on the Mammary Gland of the Monkey. There Is Extension of the Duct Tree, Hypertrophy of the Lining Cells and Proliferation of Periductal Connective Tissue.

FIG. 53. Whole section through prepuberty male monkey after 20,000 I. U. of estrone over a period of six weeks. The size of the breast and nipple has doubled. Note the thickening of the epithelium overlying the nipple.

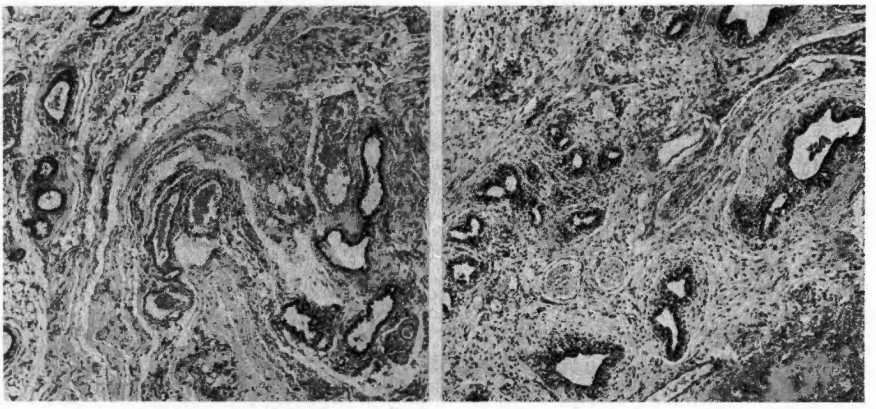
FIG. 54. Photomicrograph of the breast shown in Fig. 53. Hypertrophy of the duct epithelium and increase in periductal fibrous tissue have occurred.

In female rats, castrated at three weeks of age, daily injections of 2 gamma[1] of estrone in oil for three weeks result in an increase of the diameter of the gland from 6 to 13 mm. With 5 gamma of estrone daily over the same period, the maximum diameter measures about 25 mm. (Figs. 57-59). Thus, in castrate female rats, growth of the duct tree may be stimulated at the normal rate or beyond by increasing the intensity of estrogenic stimulation. The physiologic limit of size, however, is reached sooner if larger doses of estrone (5 gamma and over) are given. There is an optimal dosage (less than 10 gamma of estrone daily in the rat) and a period in adolescent

[1] Gamma (γ) or microgram (μgm.) equals one thousandth of a milligram or 10 international units of estrone. It is equivalent to one rat unit or about five mouse units.

mammary development when the gland is most responsive. Estrogenic stimulation beyond physiologic limits (more than 10 gamma) does not result in similar extension of the duct tree but in an abnormal and stunted gland. Premature, enlarged and irregular lobular buds appear at the ends of the mammary tubules with doses of 25 or more gamma of estrone.

FIG. 55 FIG. 56



The Effect of 70,000 I. U. of Estrogen on the Mammary Gland of an Adult Female Monkey. The Monkey Was Castrated Two Years Prior to the Experiment and the Estrogen Given Over a Period of Two Months.
FIG. 55. Microscopic appearance of the gland before estrogen.
FIG. 56. Same gland after estrone injections.

Physiologic Limits. Although estrogen stimulates mammary growth, there is a limit to the amount of growth that can be obtained. The maximum extent of the duct tree is achieved after the end of adolescence. The rate of growth during adolescence is proportional to the intensity of the hormonal stimulus (within physiologic limits), but the maximum extent of growth is controlled by inherent factors. Prolonged estrogenic stimulation after sexual maturity or intense stimulation during pregnancy fails to produce proportional growth in the duct tree after the adult size has been reached. Estrogenic stimulation beyond physiologic limits in adolescence produces stunted growth in the gland and abnormal epithelial changes in the lobular buds. These facts in regard to mammary development stimulated by estrogen have been demonstrated experimentally in the rat (Geschickter and Astwood). For a discussion of these pathologic changes with overdosage of estrogen see Chap. 11.

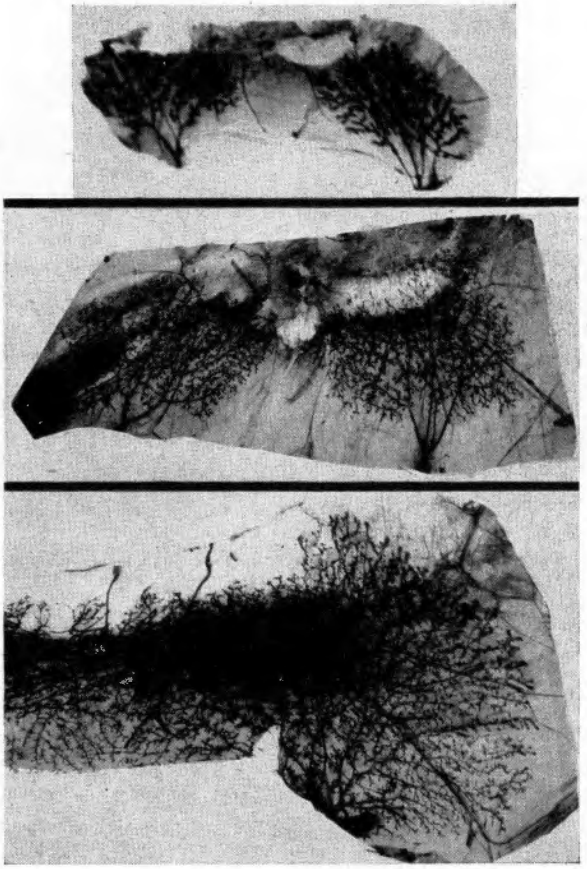
A knowledge of the effects of estrogen on the growth of mammary tissue is important from a clinical standpoint. Estrogenic effects are

responsible for infantile hypertrophy in young girls with granulosa-cell tumors or other estrogen-secreting ovarian tumors, and account for gynecomastia in males with chorio-epithelioma of the testicle. The growth of pre-existing fibro-adenomas during pregnancy is the

FIG. 57

FIG. 58

FIG. 59



Growth of the Female Rat Breast in Response to Estrogen.
FIG. 57. Whole mount of the mammary glands of a normal female rat at 21 days. (× 4).
FIG. 58. Whole mount of the mammary glands of a castrated female rat at 42 days. Animal in Fig. 58 is a litter mate of one in Fig. 57 and was castrated at 21 days. (× 4).
FIG. 59. Whole mount of the mammary glands of a female rat, castrated at 21 days and treated for 20 days with 50 I. U. of estrone daily. (× 4).

result of stimulation by estrogens. Estrogen has been used clinically to promote the growth of the undeveloped breast in cases of hypogonadism. The mammary hypertrophy induced by such treatment, however, tends to regress if estrogen is withdrawn, and it must be borne in mind that prolonged overdosage with this hormone may result in mammary pathology. Estrogen has also been used for the

treatment of painful breasts and other forms of chronic cystic mastitis (see Chaps. 11 and 28).

Adolescent Male Breast and Androgenic Effects

Jung and Shafton believe that the normal enlargement of the human male breast at puberty is due to a hormone from the testes but offer no experimental data. Estrogen as well as androgenic hormone (testosterone) is present in increased amounts and is found in normal male urine (Oesting and Webster). It is still uncertain whether some form of androgenic hormone or estrogen is responsible for the slight increase in the size of the normal human breast in boys during adolescence. Since androgenic hormones stimulate mammary

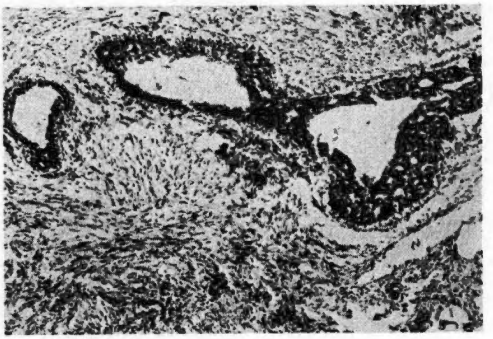


FIG. 60. The effect of estrogen on the human male breast. The patient 40 years old had gynecomastia resulting from the injection of 20 mg. estradiol benzoate given for migraine over a period of three months. (Patient of Dr. C. Dunn of Philadelphia.)

development, it is probable that such secretions from the testicle play a role. Mammary enlargement in men has been observed following the administration of methyl testosterone and also androstenedione. On the other hand, growth of the human male breast is also readily stimulated with estrogen, but the response is not so great as in the female breast.

Dunn observed a growth of mammary ducts and periductal connective tissue in a man of 40 years following the administration of 20 mg. estradiol benzoate for the treatment of migraine. (Fig. 60.) He reported a similar hypertrophy in a man treated with the synthetic estrogen, stilbestrol. The author also has produced mammary hypertrophy in a boy of 16 by administering stilbestrol orally in a case of pituitary giantism. In the author's experience, on the other hand, and in that of Vest and Howard, injections of testosterone propionate in adolescent males or adult men, in doses varying from 50 mg. weekly to 10 mg. daily, do not induce noticeable changes in

the mammary gland. Hoffman obtained decrease, not increase, in the size of the male breast in cases of gynecomastia treated with testosterone. Significant microscopic changes were not observed in three cases of gynecomastia in which biopsies were performed by the author before and after injections of testosterone propionate in amounts up to 150 mg. No marked effects were observed in the normal adult female breast after treatment although some increase was noted in the epithelial lining of the ducts (Figs. 61, 62).

FIG. 61 FIG. 62

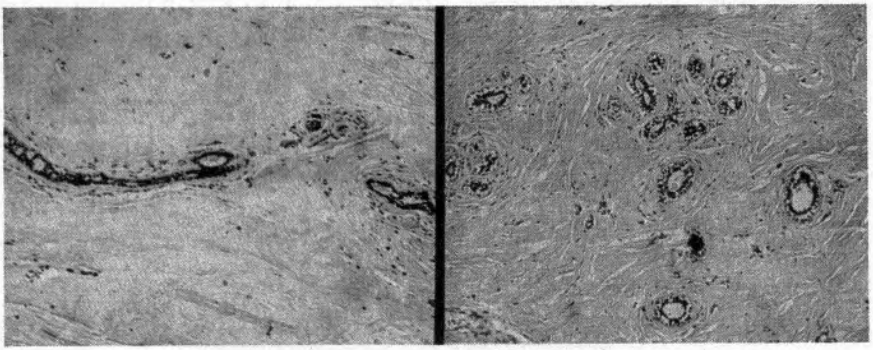


FIG. 61. The effect of testosterone on the human female breast. The patient, 48 years old, had had her menopause two years previously. The atrophy of lobular epithelium and sclerosis of connective tissue before injection are clear.

FIG. 62. Here there is regeneration of the lobular epithelium and a moderate proliferation of periacinar connective tissue. The patient received 215 mg. testosterone propionate over a period of one month.

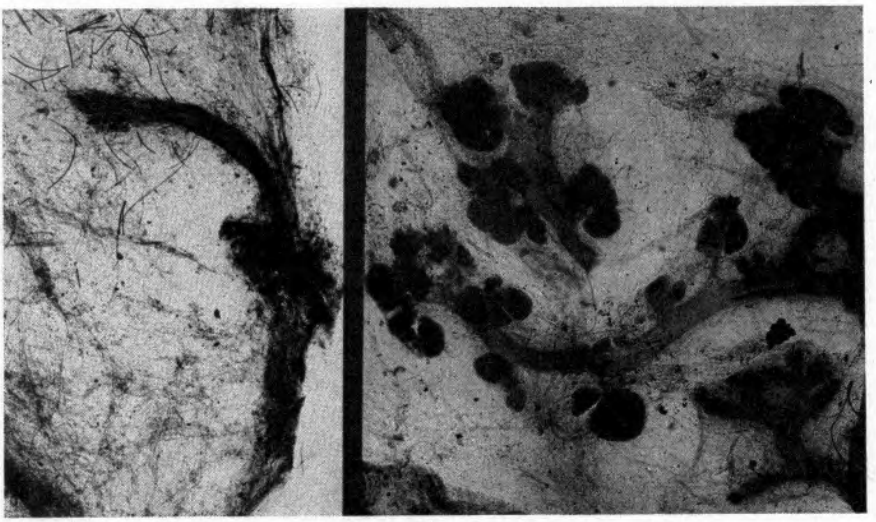
Dunn produced mammary enlargement in a man with injections of androstenedione; in the author's laboratory, lobular growth was stimulated in castrated rats and monkeys with this hormone. McCullagh and Rossmiller observed gynecomastia in 6 of 11 men with hypogonadism treated for four to six weeks with a total of 3 to 8 grams of methyl testosterone.

Animal experimentation suggests that the male mammary gland responds less readily to estrogen than that of the female. Prolonged stimulation with estrogen in castrate rats produces a greater degree of development in the female than in the male (Astwood and Geschickter). Gardner and Van Wagenen found that the male gland of the monkey was more variable in its response to estrogen than the female. The size of the glands in the untreated animal had no correlation with body weight. Injections totaling 36,000 to 88,000 international units over a period of nine to twenty-two weeks caused the gland to double in size. In experiments performed by the author,

the growth of lobular buds in the male monkey is less pronounced than in the female with corresponding doses of estrogen but with high doses lobule formation will occur. (Figs. 63, 64.)

In the mammary gland of the rat or monkey the effect of testosterone propionate is similar to luteal hormones and stimulates lobule formation (Figs. 65, 66) (Geschickter and Astwood, confirmed

FIG. 63 FIG. 64



The Effect of Estrogen on the Mammary Gland of the Male Monkey.
FIG. 63. Prepuberty gland before treatment.
FIG. 64. Gland, showing lobule formation after 50,000 I. U. of estrone daily for six weeks.

by Speert). These androgenic effects are discussed later. At the present writing, specific growth effects produced by androgenic hormones[1] on the male or female human mammary gland have not been established. Inhibitory effects during lactation have been demonstrated (Kurzrok and O'Connell).

MAMMARY GLAND OF MATURITY

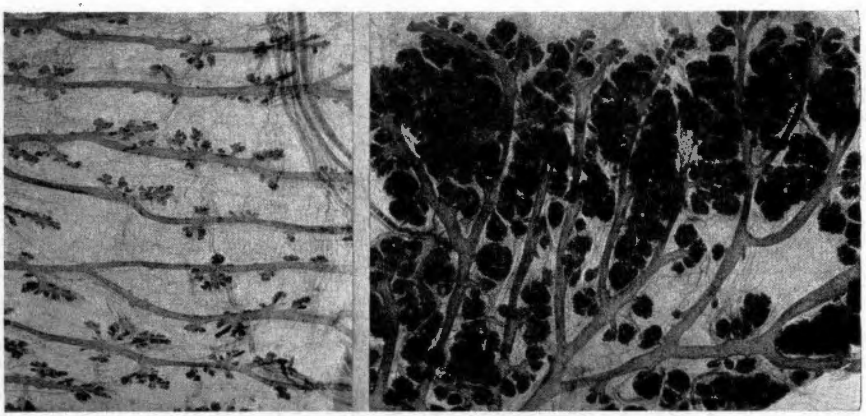
Lobule Formation and Pregnancy Changes in Relation to Luteal Hormones

Prior to Pregnancy. Lobule formation in the human breast is not found in the normal male, and it does not occur in the normal female

[1] The androgenic hormones isolated or synthesized to date including androsterone, androstenediol, androstenedione and the various derivatives of testosterone vary more widely in their mammotropic effects on laboratory animals than the various estrogenic hormones.

prior to the advent of the corpus luteum. These acinar structures appear following sexual maturity in the female and reach their full development during pregnancy. Hormones from the corpus luteum acting in combination with estrogens from the ovarian follicles are apparently responsible for the growth of mammary lobules during the premenstruum in cyclic women.[1] The lobular development found

FIG. 65 FIG. 66



The Effect of Testosterone on the Mammary Gland of the Female Monkey.
FIG. 65. The small lobular buds in a castrate female monkey after 15 days of 100 R. U. daily of estrone. (× 12).
FIG. 66. This shows lobular development 15 days later in the same monkey. The daily injections of estrone have been reduced to 25 R. U. but 50 mg. of testosterone propionate have been injected daily. (× 12). (Courtesy of Dr. Harold Speert).

in pregnancy exceeds, in degree, the development found in the luteal phase of the menstrual cycle. This added development is stimulated by hormones from the placenta.[2]

The size and number of lobules formed in the human breast are proportional to the intensity of the hormonal stimuli. In the majority of women a uniform distribution of well-formed lobules is not seen until after the stimulation of repeated pregnancies (Langer). A definite ratio of estrogen and luteal hormones is necessary to maintain normal lobular structure in cyclic women. Imbalance between these two hormonal functions of the ovary results in irregular epithelial buds at the ends of the mammary tubules (such as is seen in

[1] It has been shown experimentally that lobule formation also results from stimulation by luteal hormones in the absence of estrogens.

[2] Jones and Weil: These authors report a patient in whom the corpus luteum of pregnancy was removed on the 58th day after the last menstrual period. Abortion did not occur. Following this operation the authors measured the urinary content of pregnandiol. Pregnandiol which had been absent since the third day following operation began to increase rapidly. The authors conclude that progesterone is probably produced by the placenta, beginning, in this case at least, at about the end of the second month and probably continuing to the end of pregnancy. Seegar and Delfs have reported a similar case in which abortion did not occur following removal of both ovaries.

cystic mastitis) rather than in normal lobule formation (see Chap. 11). Speert has shown that in the cyclic monkey there is definite lobular growth during the premenstruum and that removal of the

FIG. 67 FIG. 68

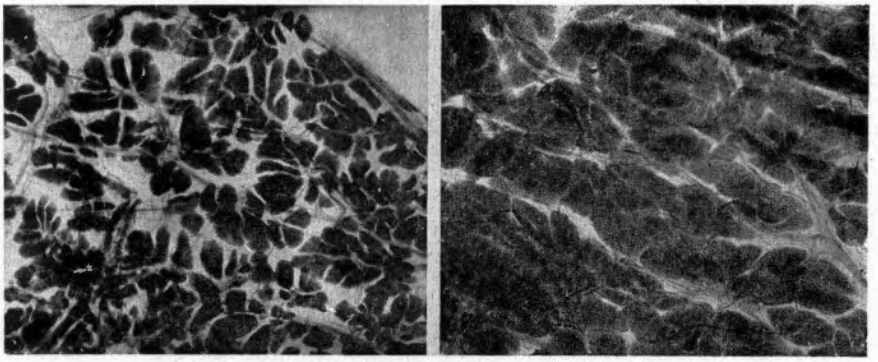


FIG. 67. Lobular growth in the cyclic female monkey. Whole mount showing the size of the lobules on the second day of the menstrual cycle in the normal female monkey. (× 12).

FIG. 68. Whole mount from the same monkey on the 24th day of the cycle. There is premenstrual growth. Small light points in the lobules indicate increased size of the acini. (× 12). (Courtesy of Dr. Harold Speert).

corpus luteum results in rapid involution of the mammary lobules (Figs. 67, 68).

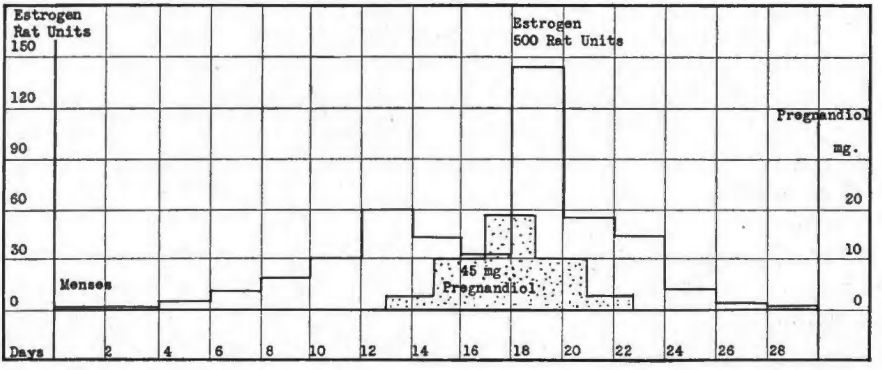


FIG. 69. Chart showing the recovery of estrogen and pregnandiol from the urine in a normal menstrual cycle.

The ratio of estrogen to corpus-luteum hormone necessary to promote normal lobular development in cyclic women has been esti-

mated from assays of the urine. Determinations based upon methods of extraction for total estrogen show between 10 and 60 rat units per 24 hours of output; the average total output for a normal cycle is variously stated as between 400 and 600 rat units (4000 to 6000 international units) by Frank, Mazer, Smith and Smith, and Palmer.

The corpus-luteum–hormone function during the menstrual cycle has been measured by determining the quantity of pregnandiol (an excretion product of progesterone) in the urine. Following ovulation values varying from 2 to 10 mg. per 24 hours are obtained, and for the total menstrual cycle between 15 and 60 mg. depending upon the method of extraction (Browne and Venning; Stover and Pratt; Hamblen, Ashley and Baptist; Bucher and Geschickter). The curves of both estrogenic and luteal hormones excreted in the normal menstrual cycle are shown in Fig. 69. The values shown provide a fairly reliable standard for the comparison of the normal with the abnormal if the same methods of assay are used for both.[1]

During pregnancy when larger and more numerous lobules are developed, correspondingly higher values for estrogen and corpus-luteum hormones are obtained, as high as 10,000 rat units per 24 hour output of urine for estrogen and as high as 100 mg. of pregnandiol (Fig. 70).

Clinical Evidence of Luteal-Hormone Action. The influence of the corpus-luteum hormones on the growth of mammary alveoli and on lobule formation was first suggested by Ancel and Bouin in 1911. These authors based their conclusions on observations made during pseudopregnancy or the first half of pregnancy in the rabbit, where the formation of corpora lutea is accompanied by a rapid proliferation of mammary alveoli. However, the relation of luteal hormones to lobule formation has been difficult to establish experimentally because of species differences and because the various corpus-luteum preparations available are not equally effective. The quantity of the hormone, the absence or presence of simultaneous estrogen stimulation and the length of time over which the hormone is administered are important factors.

No reports describing the effects of corpus-luteum–hormone injections on the human mammary gland, which are supported by histologic studies, have appeared in the literature except those herein reported. MacBryde combined high doses of estrogen with relatively

[1] In the Surgical Pathological Laboratory, the estrogen and pregnandiol determinations are both made on the same 48-hour specimen of urine. The total specimen is acidified to pH 6 and incubated until it is pH 8. This liberates the estrogens and the pregnandiol from their respective complexes, and they are then extracted with butanol. The butanol is distilled off, and the dry residue treated with acetone and aqueous sodium hydroxide. The pregnandiol precipitates, is filtered off, purified and weighed. The acetone–sodium-hydroxide filtrate contains the estrogens; it is neutralized and assayed on castrate female rats.

small doses of progesterone in the treatment of underdeveloped breasts and observed that the mammary tissue was more nodular to palpation than when estrogen alone was given.

Case Reports. The author administered progesterone (Progestin-Roche-Organon) to a girl, 20 years old, who had functional amenorrhea from

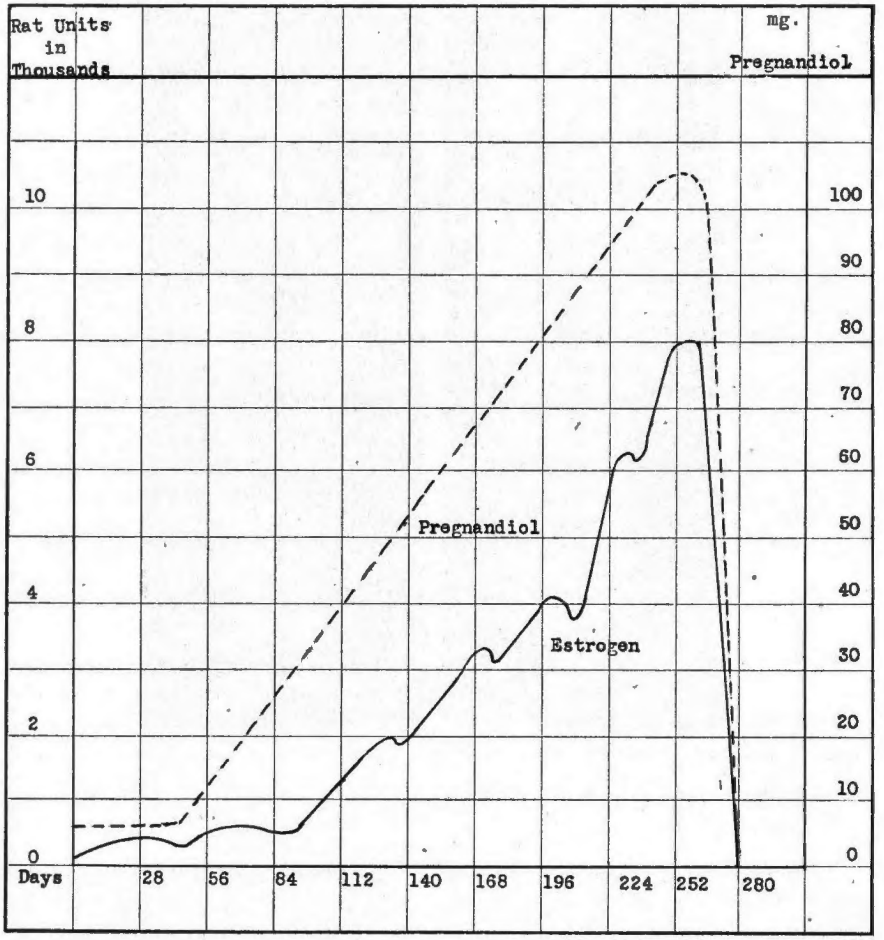


FIG. 70. Chart showing estrogen and pregnandiol values from the urine in normal pregnancy (diagrammatic).

January, 1935, to January, 1938. Urine assays showed an occasional trace of estrogen. The breasts were adipose and pendulous (Fig. 71). A control biopsy was done; it showed a few small rudimentary lobules scattered in sclerotic fibrous tissue. The number of alveoli comprising the lobules varied from two to six (Fig. 73). Following the biopsy, 145 mg. progesterone was administered over a period of six weeks. The patient men-

struated twice during this treatment. A bilateral plastic operation was then performed on the breasts. The tissue excised showed numerous well-developed lobules containing 10 to 20 alveoli and pale-staining intralobular connective tissue. The number of lobular capillaries was increased (Fig. 74).

FIG. 71 FIG. 72

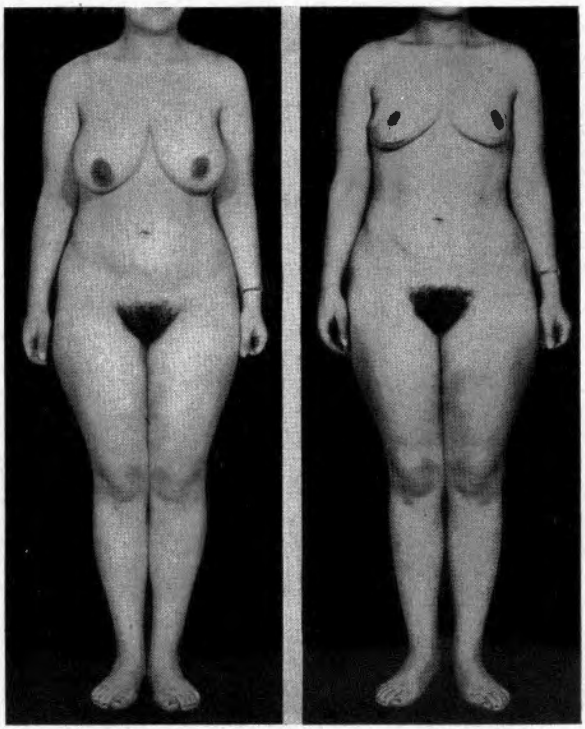


FIG. 71. Functional amenorrhea treated with progesterone. Patient before treatment. (See Fig. 73.)

FIG. 72. Patient after progesterone therapy and plastic surgery of the breasts. (See Fig. 74.)

In a girl of 15 who had normal breast development but had never menstruated, the urine assays were positive for estrogen in excess of 20 rat units per 24 hours of output. A biopsy of the breast showed adolescent development without lobule formation. Menstruation was not established and lobule formation was not induced although the patient received 246 mg. progesterone (including 15 units of progestin, Upjohn) over a period of two months. The endometrium remained atrophic.

Thus, progesterone may stimulate lobule formation in the human breast. The extent of maturity in the duct system prior to the administration of progesterone may be a possible controlling factor and during adolescence estrogen may be present in inhibiting amounts.

Experimental Evidence. In the mammary gland of prepubertal, female, castrate monkeys prolonged estrogen stimulation alone results in the formation of lobules (Figs. 75, 76) but lobular development is enhanced if corpus-luteum hormone is administered in combination with estrogen. In adult female monkeys in which castration has been performed a year or more previously the lobules disappear and the duct system atrophies. Estrogen in moderate amounts

FIG. 73 FIG. 74

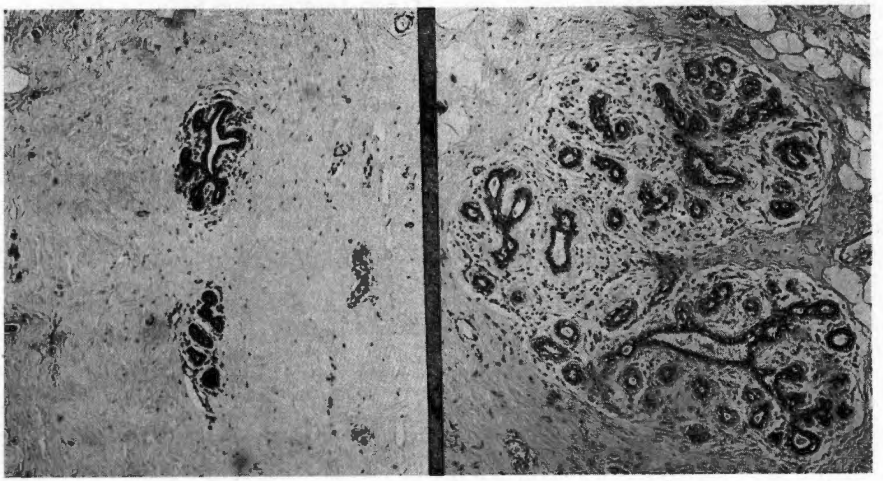


FIG. 73. Biopsy of breast before progesterone injections showing atrophic lobules and sclerotic fibrous tissue.

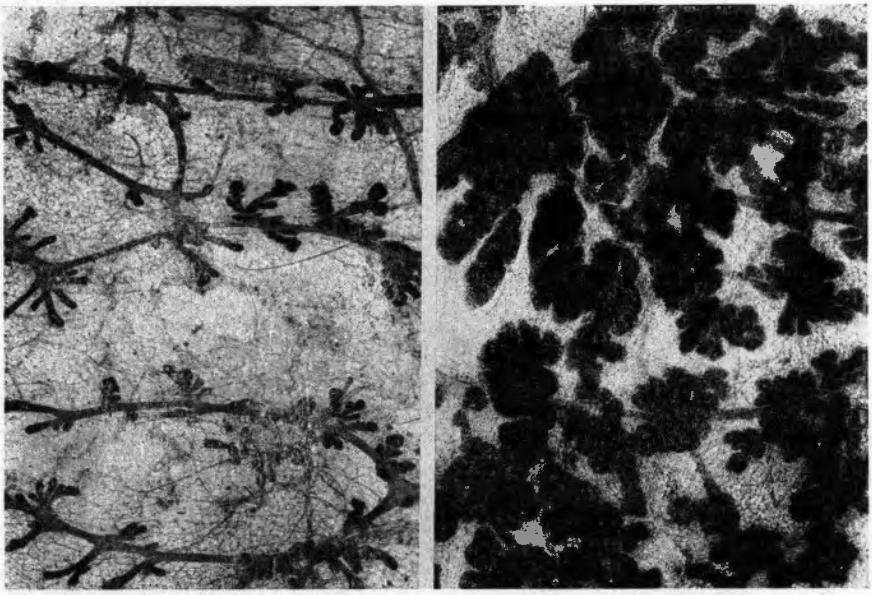
FIG. 74. Biopsy after six weeks of progesterone injections totalling 145 milligrams. Lobule development is marked and there is proliferation of intralobular connective tissue. Figs. 73, 74 are the same magnification.

does not restore lobule formation although it promotes the growth and regeneration of the duct system. On the other hand, progesterone alone restores lobule formation. (Figs. 77, 78.)

Lobule formation was enhanced and secretory globules similar to those seen in the second half of pregnancy were produced in six female, castrate adult monkeys (*Rhesus macacus*) subjected to the combined stimulation of estrogenic and luteal hormones.[1] These monkeys had not been pregnant but had normal menstrual cycles prior to castration. Some received estrone and progesterone, others estrogen, progesterone and testosterone.[1] (Figs. 79, 80.)

[1] The synthetic hormone, testosterone propionate, is closely allied in its formula to hormones present in the corpus luteum of pregnancy and can be substituted for them in the experimental production of mammary lobules in the rat and monkey. The sensitivity of the mammary gland to this otherwise masculinizing hormone is also shown in the normal adult male rat where lobule formation approaches that seen during early pregnancy in the female. Van Wagenen and Folley have reported lobule formation and secretion in the mammary gland of the monkey following injections of 100 to 200 mg. per week of testosterone over a period of 10 to 70 days.

FIG. 75 FIG. 76

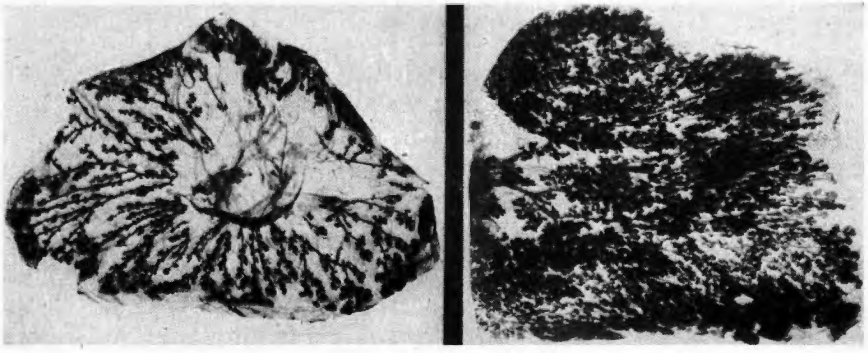


Lobule Formation in the Prepubertal Monkey in Response to Estrone.

FIG. 75. Whole mount of a mammary gland of prepubertal female monkey at the time of castration. There are lobular buds but no lobules. (× 13).

FIG. 76. Whole mount of the opposite breast of the same monkey 34 days later, after the injection of 1,000 I. U. of estrone daily. There is marked lobule formation. (× 13).

FIG. 77 FIG. 78



Comparison of the Effects of Estrone and Progesterone on the Adult Castrate Monkey.

FIG. 77. Whole mount of the mammary gland of an adult female monkey castrated more than a year previously and receiving 60,000 I. U. of estrone over a period of six weeks. There are large lobular buds but very few lobules. (× 2).

FIG. 78. Whole mount of an adult female monkey castrated a year previously and receiving 80 mg. of progesterone over a period of 30 days. There is dense lobule formation. (× 2).

In the mouse, rat and rabbit with intact ovaries, mammary lobules form as a result of follicle ripening and corpus-luteum formation following injections of chorionic gonadotropin. If artificial pregnancy is established in these animals by such injections or if pseudopregnancy by sterile copulation is produced, the lobular formation seen resembles that which is to be found in mid-pregnancy. (Figs. 81-86.)

FIG. 79 FIG. 80

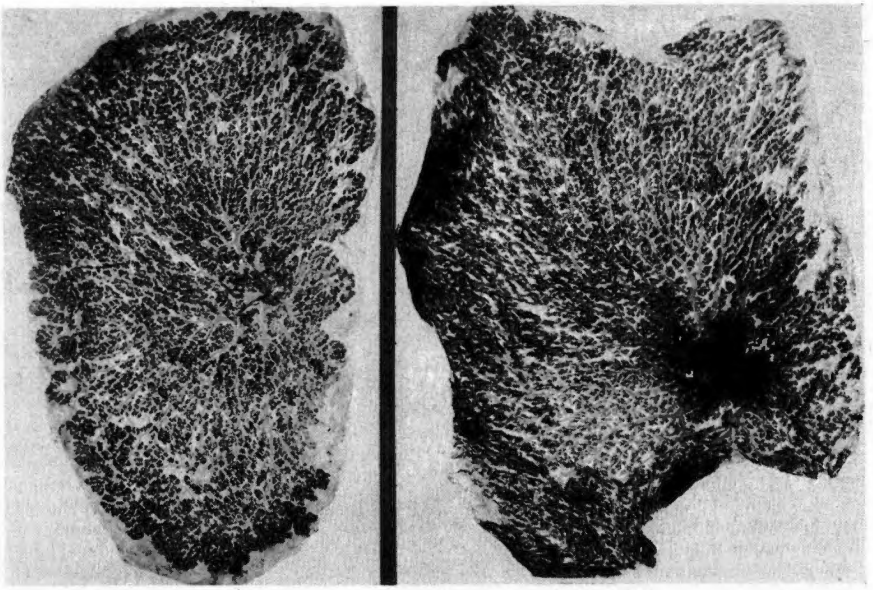


FIG. 79. Whole mounts of an adult castrated female monkey showing lobular development after injections of estrogen combined with injections of progesterone. Mammary gland three weeks after the implantation of one pellet of estrone and six pellets of progesterone. (Each pellet contained 3 mg. of crystalline hormone). (× 2).
FIG. 80. Mammary gland three weeks after the implantation of one pellet of estrone, six pellets of progesterone and four of testosterone propionate. (× 2).

In the mammary gland of the rat, estrogen combined with extracts of the corpus luteum obtained from the ovaries of pregnant cows or pregnant sows produces lobule formation. A ratio of 5 gamma estrone to one unit progestin prepared by extraction by the method of Wintersteiner and Allen produces lobule formation in female castrates, if given daily over a period of three weeks. (Figs. 81-86.) Lobules are formed if the synthetic corpus-luteum hormone, progesterone, is substituted for the natural extracts, but only if the hormone is administered daily for a period of six weeks or more, or

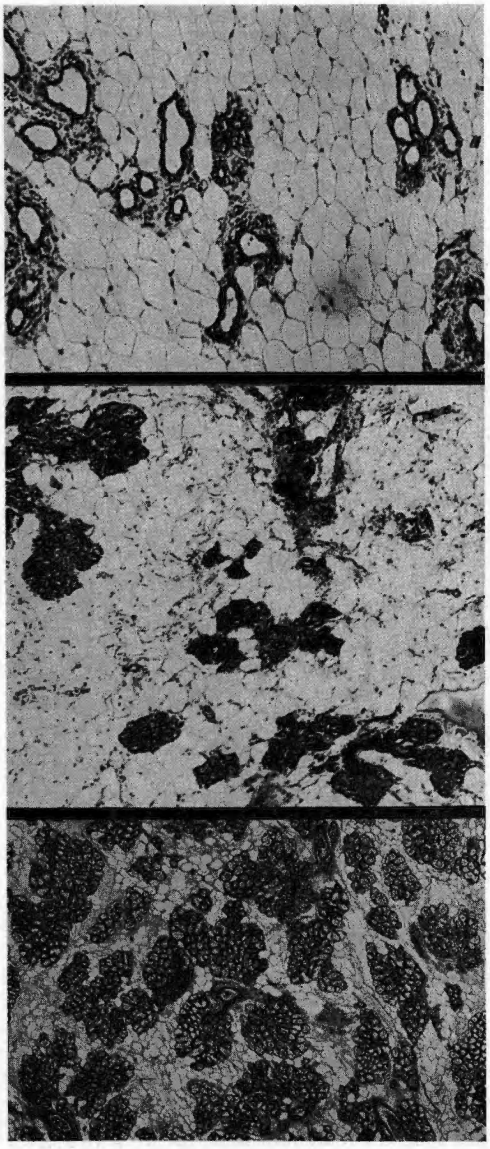


FIG. 81. The effect of five gamma of estrone daily for 21 days in a female rat castrated at 21 days. Lobule formation is absent.

FIG. 82. The effect of five gamma of estrone combined with one unit of progestin (corpus-luteum extract) daily for 21 days (female rat castrated at 21 days). Moderate lobule formation has occurred.

FIG. 83. The effect of 20 rat units of chorionic gonadotropin daily for 30 days on the intact female rat treated from the 31st day of life. Lobule formation resembling that in pregnancy is seen.

Photomicrographs Showing the Effects of Estrone, Progestin and Pregnancy Urine Hormone on the Mammary Gland of the Rat.

when it is implanted in the breast in the form of pellets.[1] This has been recently confirmed by Selye. If the synthetic hormone, testosterone propionate, is given combined with estrogen in a ratio of 5 gamma estrone to 2 mg. testosterone, fairly normal lobule formation results. Astwood has obtained lobule formation in the hypophysectomized rat injected with rat placental extracts.

FIG. 85

FIG. 84

FIG. 86

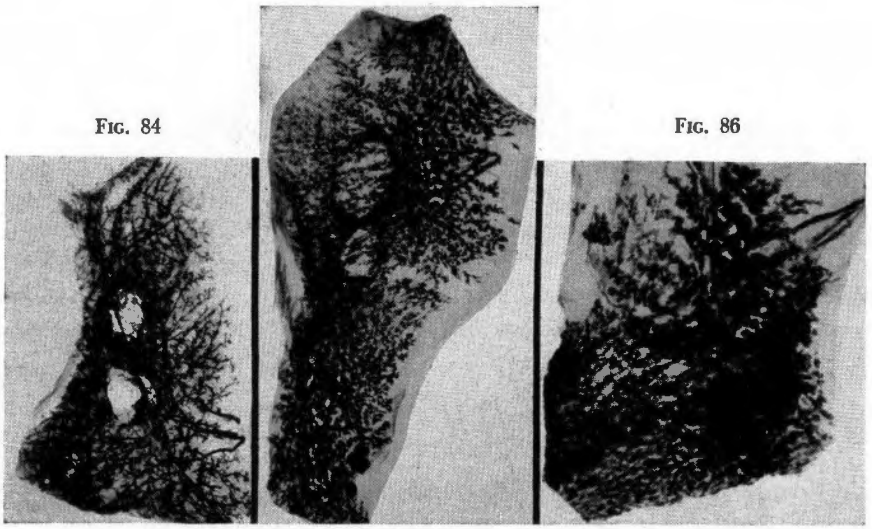


FIG. 84. Whole mount of the mammary gland of the animal in Fig. 81.
FIG. 85. Whole mount from the mammary gland of the animal in Fig. 82.
FIG. 86. Whole mount from the mammary gland of the animal in Fig. 83.

Turner and Frank injected both progestin (natural extract of corpus luteum) and estrogen into castrate male rabbits in order to reproduce normal lobular development experimentally and their observations in the rabbit were later confirmed by Anselmino, MacDonald, and Pallot. Turner and his co-workers repeated these experiments on the rat, mouse, and cat.

In summary, luteal hormones in combination with estrogen stimulate lobule formation in the mammary gland. The synthetic hormone, progesterone, is active on the human and monkey mammary

[1] Because the mammary gland of the rat does not respond as readily with lobule formation to synthetic progesterone, as it does to natural extracts of corpus luteum (progestin); it is probable that the entire hormonal complex of the corpus luteum of pregnancy is not represented by synthetic progesterone. Fully developed lobules, with secretory changes such as are seen at the end of pregnancy, are obtained more readily in castrated nonpregnant monkeys, when progesterone and testosterone are given simultaneously rather than the progesterone alone.

That synthetic progesterone does not replace corpus-luteum extracts is also indicated by the work of Allen and Heckel who found that corpus-luteum extract (progestin) would maintain pregnancy in rabbits, castrated 18 hours after conception, whereas progesterone would maintain pregnancy following castration only after the eleventh day.

gland but relatively inactive on the gland of the rat. The synthetic hormone, testosterone propionate, resembles progesterone in its action on the mammary gland of the monkey and rat, but to a less extent, if at all, in the human being. The rapid lobule development seen during pregnancy surpasses that obtained experimentally by injecting progesterone and estrogen and it is probable that a hormone supplied by the placenta is a more effective stimulus. This is suggested by the production of mammary lobules in the rat by the injection of rat placental extract. The physiology of lobule formation is further complicated by the fact that in the monkey and guinea pig, lobule formation may be stimulated by estrogen alone.

The forms of mammary dysplasia known as chronic cystic mastitis are intimately related to the physiology of lobule formation in the human breast and to the function of the corpus luteum. Lobule formation is defective in all forms of chronic cystic mastitis and good results in the treatment of this condition have been reported following injections of progesterone (Geschickter). Normal lobule formation is a prerequisite for normal lactation and some cases of deficient lactation are apparently the result of deficient lobule formation.

Relation of Anterior-Pituitary Hormones to Ovarian Function and to Mammary Development

The physiologic effects produced on the mammary gland by estrogen and luteal hormones described above are in turn dependent upon the stimulation or maintenance of ovarian function by hypophyseal activity. Precocious sexual maturity with mammary development is produced in animals by implants and extracts of anterior-pituitary glands (Engle, Zondek, Van Dyke). Separate gonadotropic hormones of the anterior hypophysis are responsible for follicle stimulation and corpus-luteum formation (the follicle stimulation and luteinizing factors) and for corpus-luteum function (luteotrophin, Astwood).

Mediation of Effects. There is no evidence to indicate that the pituitary gonadotropic hormones act directly on the mammary gland since these hormones are without mammary effect in castrated animals. Clinically, patients in whom castration has been performed frequently show increased gonadotropic secretions (as determined by assays on the urine) while studies on the mammary gland show marked atrophy.

Although the mammary effects of the pituitary gonadotropic hormone are mediated through the ovaries, there is experimental evidence to show that the effects of the ovarian hormones, estrogen and

progesterone, may be mediated through the pituitary gland or at least require the presence of an intact hypophysis. Nelson and Tobin reported that estrogen had little effect on the mammary gland in hypophysectomized rats. Lyons and Pencharz reported a similar absence of mammary effect on hypophysectomized guinea pigs and

FIG. 87

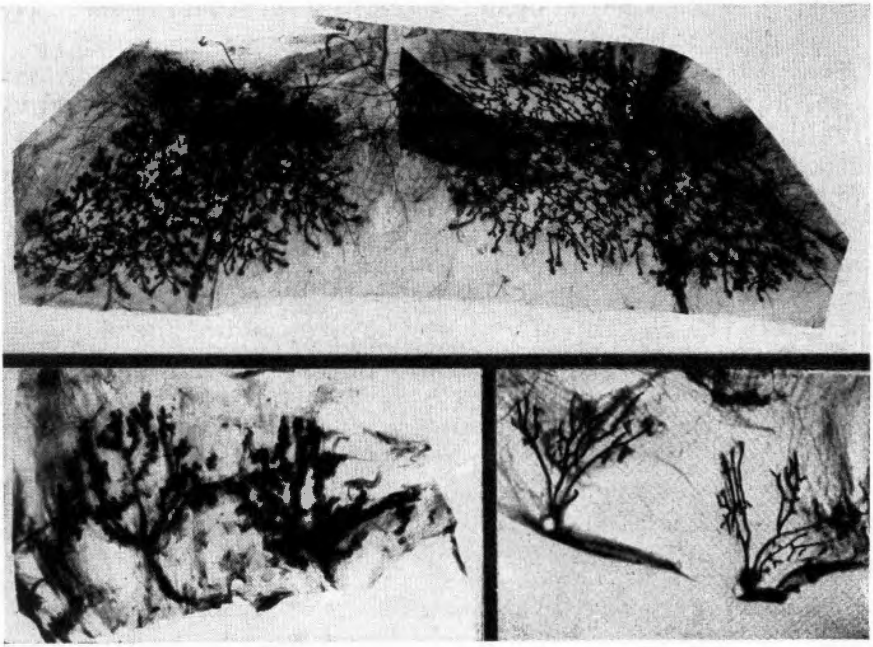


FIG. 88

FIG. 89

FIG. 87. Results of hypophysectomy and starvation on the mammary gland of the rat. Whole mount of two mammary glands of a normal 63-day old male which had received 50 gamma of estrone for eight days. (× 4).

FIG. 88. Whole mount of two mammary glands of a male 63 days old, hypophysectomized nine days previously and treated with 50 gamma of estrone daily for eight days. The extent of regression over the control in Fig. 87 is shown. (× 4).

FIG. 89. Whole mount of two mammary glands of a 35-day old female on a restricted diet treated from 21 days with five gamma of estrone daily. Body weight 28 Gm. Regression has occurred in spite of estrone administration. (× 4).

Gomez and Turner reported that progestin and estrogen were incapable of stimulating mammary-gland growth of male or female rats or guinea pigs after hypophysectomy. In our experiments, estrogen is incapable of maintaining the mammary gland in hypophysectomized rats (Astwood, Geschickter and Rausch).

It has been shown by Zondek, Cramer and Horning and others, that high and prolonged doses of estrogen inhibit the gonadotropic activity of the hypophysis. Makepeace has shown that adequate injec-

tions of progesterone inhibit the gonadotropic function of the anterior pituitary. Recently Geschickter, Hartman, and Speert have demonstrated that, in the monkey, intense treatment with estrogens inhibits the hypophysis.

On the other hand, small physiologic doses of estrogen may stimulate hypophyseal secretion, particularly the luteinizing factor (Wolfe and Wright), and, by causing luteinization of the ovaries, produce lobule formation in the breast. Recently, Turner and Gomez have concluded that the growth of the mammary gland is dependent upon a mammogenic hormone, a protein-like substance secreted by the hypophysis, and that the secretion of this hormone is stimulated by the ovarian hormones. These animal experiments have not been repeated in the monkey and no conclusions in regard to the growth of the human breast may be drawn from them.

It is possible that nutritional deficiencies after hypophysectomy may account for failure of the ovarian hormones to stimulate mammary growth under these conditions (Astwood, Geschickter and Rausch). The majority of authors who have studied the effects on the mammary gland of the ovarian hormones after hypophysectomy are agreed that the hypophysis is essential for their action (Figs. 87-89). Leonard found that estrogen and testosterone would not stimulate the breast of hypophysectomized rats if the hormones were administered more than one week after removal of the pituitary gland, or if the animals were old enough to weigh over 70 grams at the time of hypophysectomy.

Relation of Lactogenic Hormones to Secretory Changes in the Mammary Gland

During lactation, the mammary gland shows actively secreting epithelium, dilatation of ducts and acini, condensation of intralobular and periductal connective tissue and increased vascularity. These changes are influenced by the pituitary lactogenic hormone (lactogen or prolactin) acting upon a gland previously stimulated to full lobular development during pregnancy by estrogenic and luteal hormones. The mechanical stimulus of nursing is necessary to maintain active secretion.

Investigations demonstrating the effects of extracts of the anterior lobe of the hypophysis on mammary secretion have been made by Corner, Nelson and Pfiffner, Gardner and Turner, Riddle, Bates and Dykshorn. These studies have shown that when the mammary glands of rats, guinea-pigs, rabbits and dogs have been stimulated by ovarian hormones, injections of anterior-lobe extracts may initiate secretory changes.

Purified pituitary lactogenic hormones have been prepared by Turner and his associates and by Riddle and his co-workers and by others.

Turner has cited experiments showing that hypophysectomy prevents the appearance of lactation or causes the immediate cessation of milk secretion in lactating animals. In hypophysectomized animals, lactation can be maintained or initiated if lactogenic hormone is combined with pituitary adrenotropic hormone and glucose (Gomez and Turner, 1937).

Lactation is impossible in the absence of development of the duct system, and it is limited if complete lobule development is lacking. Mammary involution caused by castration makes the gland unresponsive to lactogenic hormone. The same is true of senile involution. Turner concluded that immature or involuted female glands and male mammary glands unstimulated by estrogen are incapable of responding to lactogenic hormone. Physiologic doses of estrogen prepare the mammary gland and also stimulate increased lactogen secretion by the pituitary. If large doses of estrogen are given simultaneously with lactogenic hormone, however, lactation is inhibited. Robson obtained inhibition in both normal and castrate guinea pigs by injecting 0.1 mg. of estrone daily.

The lactogenic content of pituitary, blood, and urine may be studied if the specimens to be assayed are injected subcutaneously over the crop gland of pigeons. Increase in the weight of the crop indicates the presence of lactogenic hormone. Reece and Turner studied the lactogenic content of the pituitary and found that animals in estrus had more lactogenic hormone in their pituitary than those in anestrus. The hormone did not increase in pregnancy, but rose markedly following parturition regardless of nursing. Lactogen was higher in the pituitary of dairy cattle than in beef cattle. Injections of 10 cc. blood plasma from a woman five days postpartum gave a positive reaction in the crop gland. Blood of lactating animals gives a positive response. Hoffman, in 1936, found no lactogen in the urine before delivery but obtained positive results on the third and fourth day and thereafter. The urine was negative in seven of eight cases of deficient lactation.

Clinical Evidence of Lactogenic Hormone Effects. Kurzrok and others gave lactogenic hormone to 37 women who had been delivered of normal children. Of these, 29 were thought to have insufficient milk. Twenty-one showed an increase in the amount of milk after the sixth day postpartum, when from 75 to 400 bird units of lactogenic hormone was injected intramuscularly. In eight, the response was unsatisfactory. In eight other women in whom the

secretion was normal, no increase was noted after the use of the lactogenic substance.

Werner gave injections of lactogenic substance (220 bird units daily for from four to 14 days) to 10 castrated women, ranging in age from 21 to 35 years. The breasts were prepared by injections of estrogen to which was added the gonadotropic factor from the urine of pregnant women, or progestin in eight cases. All noted enlarge-

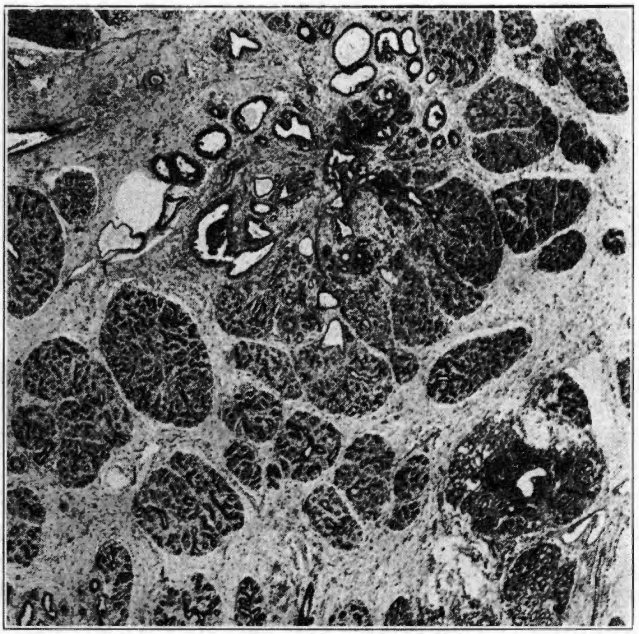


FIG. 90. Lactogenic Effects. Photomicrographs of the mammary gland of a nulliparous woman aged 25, before injection of pituitary lactogenic hormone. (See Fig. 91.)

ment or engorgement of the breasts suggesting the onset of lactation. In no case did lactation occur, however. Ross reported that injections of lactogenic hormone varying from 400 to 1000 units increased the amount of milk and the length of nursing.

In experiments previously reported (Geschickter and Lewis), injections of pituitary extracts were given to 15 menstruating women who had various forms of chronic cystic mastitis but who had not been recently delivered. Small amounts of a watery mammary secretion occurred in eight of the 15 cases after injections of estrogen followed by lactogenic hormone. The mammary changes produced were studied by biopsies taken before and after injections in five cases. Dilatation of acini and secretion were observed but no active lactation (Figs. 90-92).

The results obtained indicate that a lactogenic substance in anterior pituitary extracts may cause mammary secretion in nonpreg-

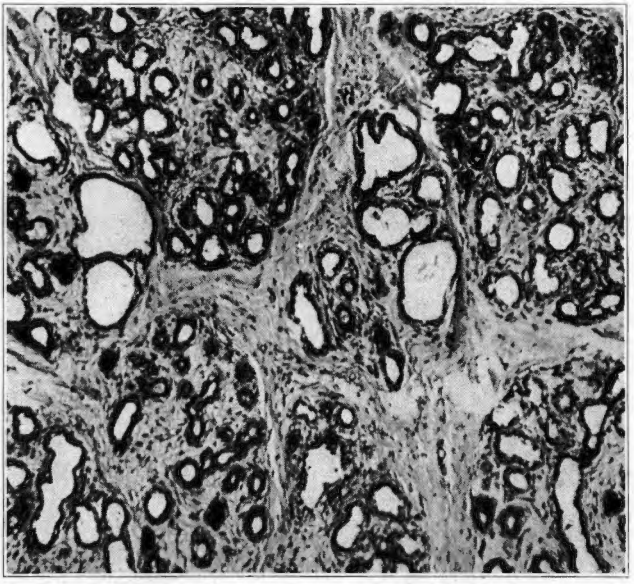


FIG. 91. Lactogenic effects. Photomicrograph of the mammary gland shown in Fig. 90 after injections of 2600 bird units of pituitary lactogenic hormone. The hormone has caused dilatation of and secretion in the acini.

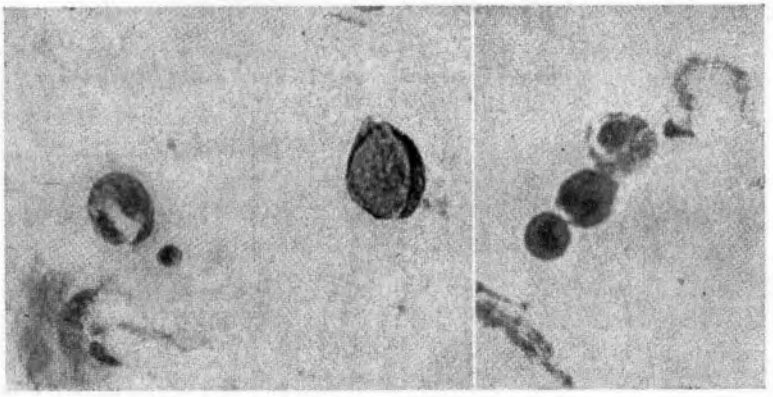
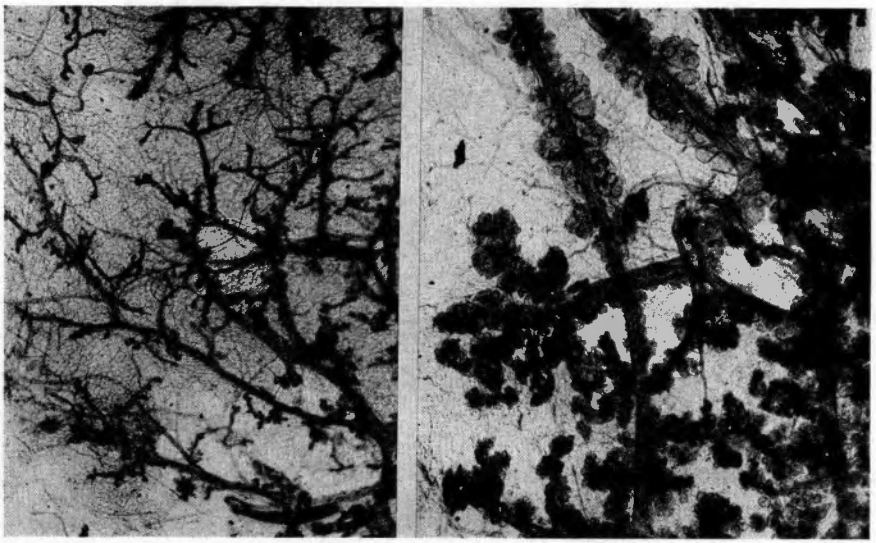


FIG. 92. The microscopic appearance of the secretion of the gland shown in Fig. 91.

nant women when they have been previously stimulated with estrogenic hormone but true lactation does not occur. Secretion was also obtained in two adult men with gynecomastia after injections of lactogenic hormone.

The appearance of secretion was preceded by a feeling of engorgement and heaviness of the breasts and accompanied by an increase in their size. The secretion was creamy white and in no case lasted longer than five days. No more than 10 or 12 drops could be expressed from the nipple at any time. Secretion ceased spontaneously in all cases even when the pituitary extracts were administered after

FIG. 93 FIG. 94



Effect of Pituitary Lactogenic Hormone on the Rat's Breast.
FIG. 93. Control gland from a female rat castrated and receiving 10 gamma of estrone daily for 100 days. (× 14).
FIG. 94. Mammary gland from same rat 6 days later after 20 units of anterior pituitary (complex) hormone injected twice daily for five days. The ducts and lobules are distended by secretion. (× 14).

the secretion appeared and the nipples were stimulated by the patient. Microscopically, the secretion in all the cases resembled colostrum, fatty droplets and desquamated cells being found (Fig. 92).

Experimental Evidence. While recent research tends to emphasize the importance of the pituitary gland in the control of lactation (Figs. 93, 94) and also in the growth of the mammary gland through its interaction with the ovary, metabolic factors and mechanical stimulation in the act of suckling are important.

Van Dyke has summarized the experiments showing that the lactating mammary gland uses glucose extensively (10 to 30 mg. per cent are removed from the blood during each passage through the cow's udder). The metabolism of sugar, believed to be controlled by a "carbohydrate metabolism" hormone from the pituitary, plays an

important role in the level of secretion maintained by the lactating gland.

In a series of papers by Selye and his co-workers, it has been shown that the act of suckling, by stimulating the pituitary through nervous pathways, maintained lactation in rats and mice. Ingelbrecht severed the spinal cord in rats between the dorsal and lumbar vertebrae and inhibited lactation in the glands in the paralyzed region.

Posterior pituitary hormones may be concerned in the discharge of milk in response to suckling. If this mechanism is disturbed by interrupting the nervous pathways, milk stasis followed by mammary involution may result.

Summary. Pituitary lactogenic hormone plays a dominant role in the initiation of lactation. The formation of mammary lobules with differentiation of acini such as those of normal pregnancy is a prerequisite for this secretory activity. The mechanical stimulus of nursing is an added factor. Moreover, the withdrawal of the estrogenic and luteal hormone upon the expulsion of the placenta at childbirth appears to act as a stimulus to hypophyseal secretion of lactogenic hormone.

Women with deficient lactation may be benefited occasionally by injections of lactogenic hormone during the puerperium. The frequency with which a history of inability to nurse is obtained in such conditions as chronic cystic mastitis suggests, however, that the failure of the mammary gland to respond to the sex hormones with normal and adequate lobule formation is a more common cause of deficient lactation.

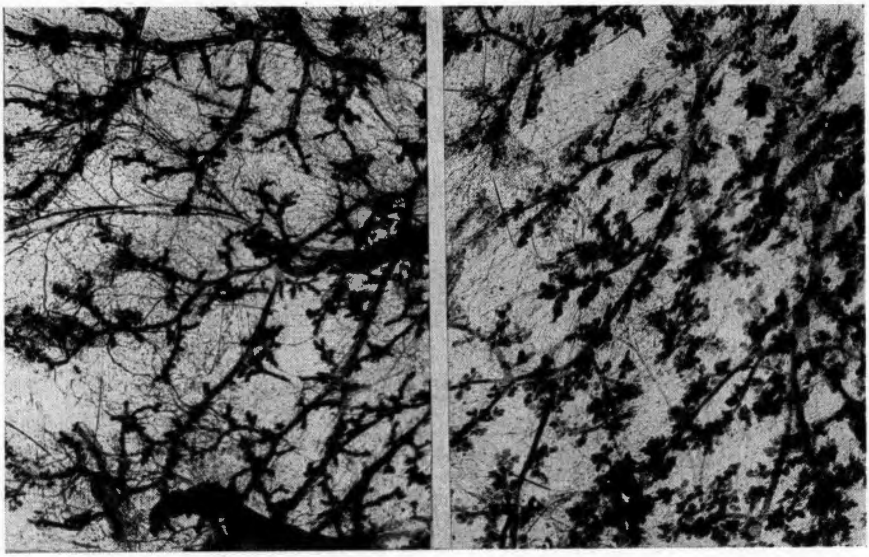
The inhibition of lactation by the injection of high doses of the sex hormones, such as estrogen and testosterone, is important clinically in handling cases of galactorrhea or those in which nursing is impossible because of deformities of the nipple. Abarbanel has reported diminished milk secretion in lactating women after administering large amounts of the synthetic estrogen, stilbestrol, orally. He could not obtain a similar inhibition with injections of large amounts of androgens (testosterone propionate) although painful engorgement on the cessation of nursing was prevented. Beilly and Solomon reported complete inhibition of lactation in 58 per cent of a group of postpartum women receiving three injections of 25 mg. testosterone propionate at 12-hour intervals. It is hard to establish a control for these observations, however, since lactation usually ceases in a few days if nursing is discontinued. (See Chap. 5, p. 138.)

Influence of the Adrenal Cortical and Thyroid Hormones

Adrenal Cortical Hormone Effects. Clinical evidence indicates hyperplasia or tumors of the adrenal cortex may lead to mammary

hypertrophy. Cases of infantile mammary hypertrophy and gynecomastia associated with changes in the adrenal cortex have been reported (see Chap. 4). It is doubtful, however, if hormones peculiar to the adrenal cortex are responsible for the variety of mammary effects observed. It seems more likely that androgenic and estrogenic substances occurring in the adrenal cortex are also active factors and that their action is similar to that discussed above for the sex hormones.

FIG. 95 FIG. 96



Effect of Adrenal Cortical Hormone on the Mammary Gland of the Rat.
FIG. 95. Control gland from a castrated and adrenalectomized female rat 6 months old. (× 14).
FIG. 96. Mammary gland from the same rat 6 days later after 1 cc. of cortin (adrenal cortical extract) given twice daily for five days. There is lobular development. (× 14).

Adrenalectomy in animals interferes with lactation. Normal lactation can be restored in such animals by administering the adrenal cortical hormone. Gaunt and Tobin performed such experiments on the rat and Swingle and Pfiffner made similar observations on the dog. Turner believes that the effect of the adrenal cortex is upon the salt-water balance necessary as a precursor to milk synthesis. On the other hand Brownell et al. give the name "cortilactin" to adrenal extracts which would maintain lactation.

In experiments performed by the author in association with Dr. Grollman in the Department of Physiology of the Johns Hopkins School of Medicine, it was found that the adrenal cortical extracts and the synthetic hormone, desoxycorticosterone, had moderate but

definite effect on the growth of the mammary gland in the rat and mouse. (Figs. 95, 96.) Speert confirmed these findings and showed that desoxycorticosterone produced lobule-alveolar growth in the mammary gland of the castrated female monkey.

Thyroid Effects. In cases of hypothyroidism in children, the mammary glands and sexual organs may show delayed development in keeping with underdevelopment of the rest of the body. In such cases, general body growth and the secondary sexual characteristics may develop normally with the administration of the thyroid substance. Specific effects on the mammary gland cannot be demonstrated by feeding desiccated thyroid or by injections of thyroxin; or by combining these estrogen injections. However, Gardner reports increased duct growth in the breasts of male mice fed desiccated thyroid. The effect was an indirect one, since it was not observed in castrated male mice.

Thyroxin augments lactation but its action is indirect. Recent experiments show that lactation will proceed in the absence of the thyroid gland, but the level of secretion is materially reduced. Graham suggested that the action of thyroxin upon lactation is through its effects upon general metabolism, whereas Jack and Bechdel believe that thyroxin stimulates the secretion of lactogen through the pituitary. Turner suggests increased circulation through the mammary glands as a possible cause.

INVOLUTION

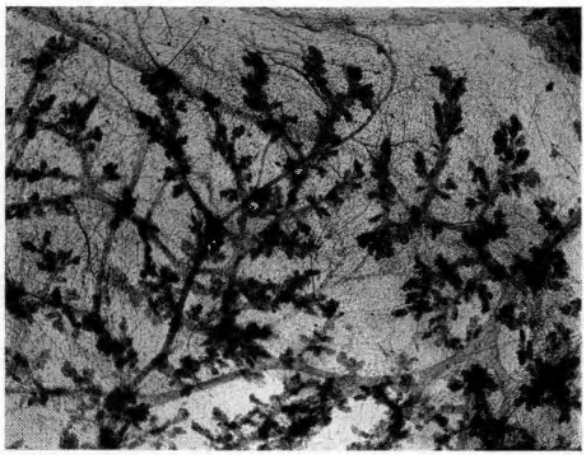
Relatively little attention has been given to the physiology of mammary involution. Regressive changes in the gland occur during menstruation, after lactation, and at or after the menopause. The subject of mammary involution therefore cannot be restricted to the phenomena of castration or senile atrophy.

Menstrual Involution. Microscopic regressive changes in the breast during the menstrual period in cyclic women are due to the fall in the secretory level of the ovarian hormones. These changes indicate that continued hormonal stimulation is necessary to maintain the normal mature developmental state of the gland. Hartman and Speert have confirmed these cyclic changes in the monkey.

Premenopausal involutional changes may appear in the mammary gland about the age of 40 in women who have borne few or no children. Lobular irregularities appear, consisting of cystic dilatation of alveoli or epithelial proliferation of the lobular buds. Similar changes appear in rats maintained over a period of weeks on constant daily doses of estrogen and progressively diminishing doses of luteal

hormones (see Chap. 11). Apparently these changes coincide with the decline in luteal function of the ovary in women approaching the menopause.

Menopausal involutional changes characterized by the formation of minute cysts and cystic dilatation of the mammary tubules must be considered a normal regressive change according to autopsy findings in clinically negative breasts. Certain authors (Borchardt and Jaffe) estimate that approximately 70 per cent of the cases in which the mammary gland of adult women is studied at autopsy show such changes (see Chap. 1). No sharp dividing line can be drawn between the lobular irregularity found in premenopausal involution



Postlactation Involution in the Mammary Gland of the Female Rat.
FIG. 97. Mammary gland following stimulation with estrone (ten gamma daily for twenty days following castration). (× 14.) (See Figs. 98, 99.)

or in the cystic changes of menopausal involution and that in the various forms of chronic cystic mastitis. Apparently the pathologic changes in cystic involution are produced by relatively high and irregular estrogenic secretion at or near the menopause or by diminishing luteal function. These endocrine findings associated with the clinical manifestations of mammary dysplasia have been reported by Bucher and Geschickter and are discussed in Chap. 11. Doses of estrogen beyond physiologic limits (15 to 25 gamma) or high intermittent doses (100 gamma every 10 days) given to castrated rats produce cystic involutional changes similar to those found at the menopause. Cystic changes are accompanied by collapse of the mammary ducts and atrophic changes in other portions of the gland (see Chap. 11). These involutional changes in the breast at or near the menopause or in women with cystic disease result from estrogenic overstimulation when corpus-luteum function is diminished or absent.

Involutional Changes of Castration. Castration is followed by the eventual disappearance of the lobules, collapse of the mammary tubules, involution of the lining epithelium and condensation in the fibrous stroma. It is observed clinically following surgical or roentgen-ray castration in young adults. The same type of atrophy also is found in the senile mammary gland. In monkeys, castration atrophy of the mammary gland begins within a few days after the removal of the ovaries. Concurrent with the atrophic changes, localized nodules of hyperplastic tissue appear and cystic dilatation of

FIG. 98 FIG. 99

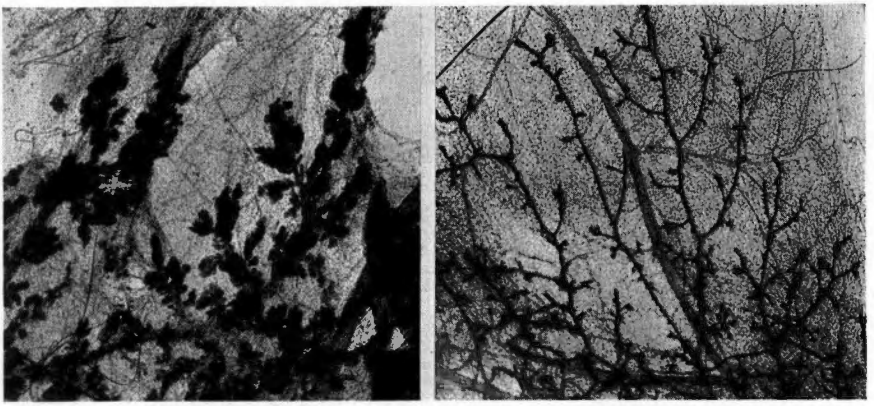


FIG. 98. Mammary gland after lactogenic stimulation (40 bird units of prolactin (Squibb) twice daily for five days.) (× 14).

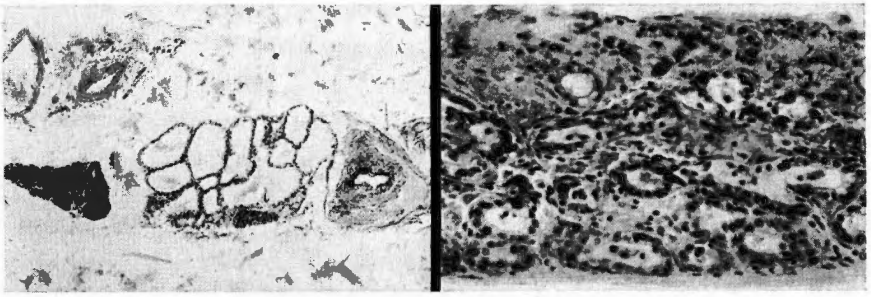
FIG. 99. Mammary gland, 8 days after lactogenic stimulation and 13 days after estrogenic stimulation. Note the rapid shrinkage in the mammary tubules and lobular buds. (× 14).

acini is found (Figs. 100-101). Speert has met these hyperplastic nodules in the mammary gland of the monkey from one to 18 months after castration. They correspond to the presenile involutional changes found at autopsy in the breast of women more than 35 years of age, discussed above; frequently they have been mistaken for forms of cystic mastitis. Speert has shown that these neoformations may be prevented by administering adequate doses of various estrogenic, luteal or androgenic hormones.

Postlactation Involutional Changes. Withdrawal of the estrogenic and luteal hormones of pregnancy is followed by lactation changes in the mammary gland after the third month of pregnancy. Involutional changes appear with the cessation of nursing or in the absence of nursing. Apparently postlactation involution may be accompanied by more rapid regressive changes than are seen following the with-

drawal of ovarian function at castration. During lactation, both of the ovarian hormones and the other mammogenic hormones are probably inhibited. Cessation of lactation therefore leaves the gland in a completely quiescent state. A factor which adds to the effects of postlactation involution is the previous crowding out of the fibrous stroma by the lactating lobules.

FIG. 100 FIG. 101



Lobular Irregularities during Castration Involution in the Mammary Gland of the Adult Female Monkey.
FIG. 100. Cystic dilatation with secretory change 2 months after castration. (× 85).
FIG. 101. Adenomatous nodule 76th day after castration (× 350). (Courtesy of Dr. Harold Speert.)

SUMMARY

Estrogenic hormones stimulate the growth of the duct system and the formation of lobular buds. The extent of such development in response to estrogen has inherent limitations and estrogen stimulation beyond physiologic limits leads to involutional changes. Continued estrogenic stimulation in combination with luteal hormones results in the lobule-alveolar development from the lobular buds and brings about differentiation of the secretory epithelium. During pregnancy luteal hormones of placental origin and possibly a mammogenic pituitary hormone are the most effective stimulants to lobule-alveolar formation. While estrogen stimulates the growth of lobular buds and may initiate the formation of lobules, the combined action of estrogen and luteal hormones is necessary to maintain lobular development. The presence of an intact hypophysis is essential for the mammary effects observed in response to these hormones. The functional activity of the anterior hypophysis also initiates secretion in the mammary alveoli. The mechanical act of suckling is important in maintaining this secretion.

While the differentiation of the duct epithelium is primarily under estrogenic control, the hormonal control of lobular development is more complicated. The lobular buds proliferate during

estrogenic stimulation; differentiate in response to the luteal hormones; and secretion in them is initiated by the lactogenic hormone of the anterior hypophysis. These changes in the mammary epithelium under hormonal stimulation presuppose adequate metabolism and nourishment. This adequacy is apparently lacking in hypophysectomized animals and those subjected to starvation.

The growth of periductal connective tissue is stimulated during the estrogenic phase of development. In the luteal phase, the intralobular stroma becomes increasingly collagenous and vascular. During lactation, vascularity is increased and the stromal elements are compressed or resorbed.

The lobular system is most sensitive to deficiencies of the sex hormones and shows regressive changes following lactation, at or after the menopause and following castration. Lobular atrophy is accompanied by regressive changes in the stroma and in the epithelial lining of the ducts. The earlier phases of involution, at the menopause or following surgical castration, are accompanied by the development of irregular hyperplastic nodules and cystic dilatation of the acini in the mammary lobules, resulting from a withdrawal of ovarian hormones.

In addition to pituitary, ovarian, and placental hormones, the adrenal cortical hormones must be included among the endocrine regulators of mammary physiology. Experiments demonstrate that thyroxin augments lactation, but the effect is probably an indirect one.

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3

Examination and Diagnosis

The frequency of mammary cancer and its high mortality make it imperative that lesions of the breast be diagnosed early and with certainty.

EXAMINATION

History

The physician must endeavor to learn from each patient the factors which may have had an influence on the development of her breast and its physiologic activity, as well as any specific factors bearing on the mammary complaint. The history of the case should, therefore, include data on the following:

1. The presence of mammary cancer in other members of the family.
2. The character of breast development during adolescence.
3. The number of pregnancies and lactations.

4. The character and complications of lactation and the presence or absence of lactation mastitis.
5. The menstrual history, the character of the periods, the onset of menarche and menopause.
6. A record of pelvic operations.
7. The presence or absence of thyroid disturbances.
8. The weight of the patient, including previous maximum and minimum in adult life.
9. Any previous trauma to the breasts.
10. A history of previous mammary operations.
11. The presence and degree of premenstrual pain and swelling in the mammary gland.
12. The presence and character of discharge from the nipple.

In inquiring into the symptoms of the present illness or complaint, such as pain, discharge, rate of growth and time of appearance of a lump, etc., it is well to caution the patient not to disclose whether the right or left breast is involved. Examination of both breasts will be more thorough if the examiner is uninformed as to the site of the trouble. It is also important to estimate the nervous stability or instability of the patient and the degree of fear in regard to cancer. Many patients with minor breast complaints are cured when adequately reassured against the presence of cancer, provided optimism and cheerfulness on the part of the physician do not camouflage an inaccurate diagnosis.

Inspection

Inspection of the breast is carried out with the patient exposed to the waist and in a sitting position. Attention is directed in turn to the skin, the nipples and areolae, the breasts, the axillae, and the neck. The skin in the submammary folds should not be neglected. To bring out early dimpling of the skin, the arms should be raised and lowered slowly. The breast should also be compressed slowly between both hands. (The latter movement is carried out with the patient in the recumbent position.) The presence or absence of supernumerary nipples or accessory mammary tissue should be noted. The skin is examined for discoloration, dimpling, ulceration, edema and fixation, as well as for epidermal and subepidermal nodules.

A note should be made on the size and pigmentation of the nipples and areolae. The presence of inversion or retraction of the nipples should be recorded (and if present) whether congenital, intermittent or recent. The excursion of the nipples when the arms are raised and lowered, and the distance of both nipples from the supra-

sternal notch in the midline should be measured. The nipples should be carefully examined for scales, warts, or fissures.

A note should be made on the symmetry and comparative size of the two breasts, and any visible sinus, masses, etc., noted. The size and character of the breasts may be recorded by the following descriptive terms used by the author. (Table I.)

TABLE I

THE MAJOR TYPES OF MAMMARY GLANDS

TYPE OF BREAST		CHARACTERISTICS	LESIONS COMMONLY PRESENT
I. Small	1. Pseudomasculine	Breasts flat, nipples prominent	Cosmetic complaints
	2. Hypomastic	Breasts small, deficient in fat	Adenosis, mastodynia
II. Parous[1]	3. Functional (note month of pregnancy or lactation)	Development coordinated with stage of pregnancy or lactation	Mastitis, rapidly growing fibro-adenoma, or cancer
	4. Nonfunctional	Breasts pendulous Postlactation atrophy	Cysts or cancer, usually discovered in early stages
III. Adolescent	5. Virginal	Breasts fair size, firm and erect	Fibro-adenoma
	6. Hypervirginal	Breasts large, firm and erect	Mastodynia, virginal hypertrophy
IV. Fatty	7. Adipose	Breasts fair size Menopausal involution of gland replaced by fat	Cancer, cysts, dilated ducts beneath the nipple, papilloma
	8. Obese	Breasts large, fat predominating	Fat necrosis, inflammatory cancer

[1] Rarely, pseudoparous breasts are seen. These are dense, pendulous breasts of fair size, rich in parenchyma, found sometimes in women of small stature.

Transillumination

The breasts should be transilluminated routinely in a completely dark room or closet, with a strong, cool light. The light is directed from beneath the breast, upward. The light should emanate from a single surface or focus so that it can be moved successively to different portions of the breast. In determining whether small lesions of the breast are translucent or opaque a light of decreased intensity should be used. This is best accomplished by means of a rheostat, but a pocket flashlight may be employed or a Cameron lamp with a rubber shield. Cutler has devised a special lamp for the purpose.

The lamp used by the author is inexpensive and was designed by Dr. Harold Nagel of Philadelphia. An ordinary 50- or 100-watt bulb is housed in a tin can insulated with asbestos and wrapped in

FIG. 102

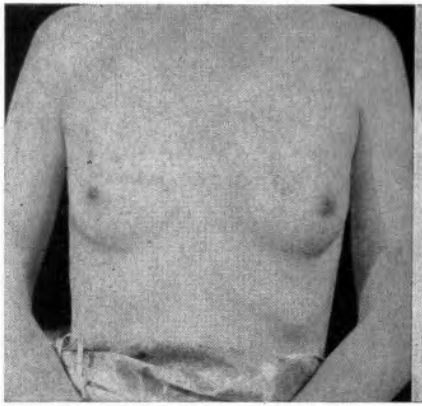
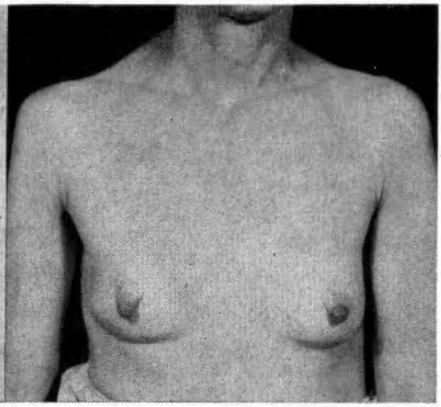


FIG. 103



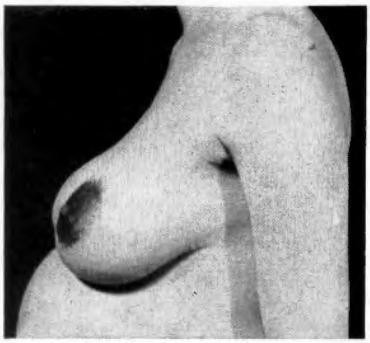


FIG. 104

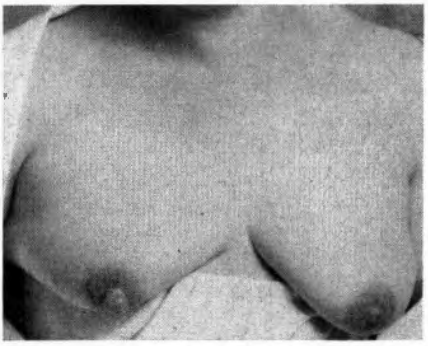


FIG. 105

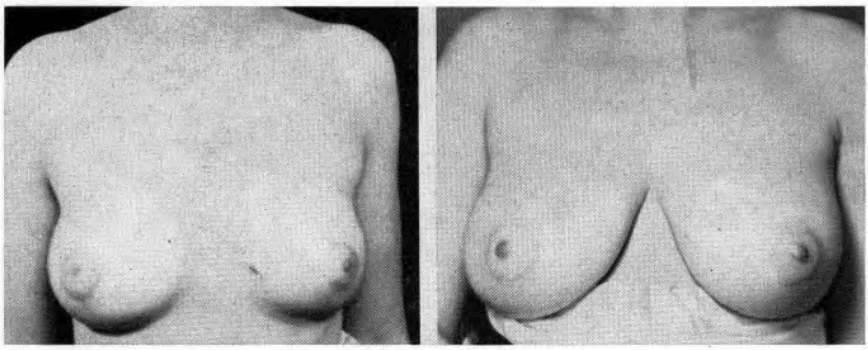
Photographs of the Major Types of Mammary Glands.
FIG. 102. Small, pseudomasculine type.
FIG. 103. Small, hypomastic type.
FIG. 104. Parous, functional type.
FIG. 105. Parous, nonfunctional type.
(See also Figs. 106-109.)

black paper. A single opening near one end admits a rod of plexiglass three-fourths inch in diameter and four inches long. The outer surface of this rod is painted black. The plexiglass transmits a cool light to the under surface of the breast.

Fatty tissue transilluminates well, the glandular tissue less well.

Cysts filled with clear or cloudy fluid also transilluminate, as do most small solid tumors less than 2 cm. in diameter. Vessels, cysts filled with blood, hematomas, and dilated ducts distended with in-

FIG. 106 FIG. 107



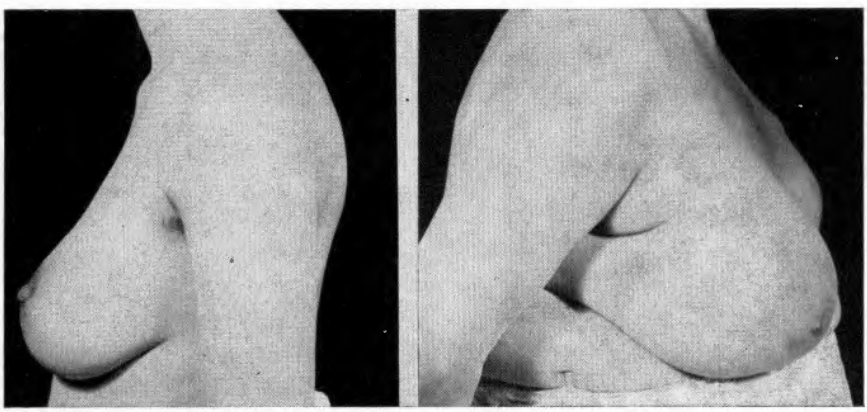


FIG. 108 FIG. 109

Photographs of the Major Types of Mammary Glands.
FIG. 106. Adolescent, virginal type.
FIG. 107. Adolescent, hypervirginal type.
FIG. 108. Fatty, adipose type.
FIG. 109. Fatty, obese type.
(See also Figs. 102-105.)

spissated secretion cast shadows as do most cancers and fibro-adenomas 2 cm. or more in diameter. Lesions in the upper half of the breast, and those which are fixed to the chest wall, as well as small, flat, nonpendulous breasts, are unsuitable for transillumination. It must be remembered that transillumination is an aid to diagnosis but not a substitute for a complete examination.

Palpation

All of the mammary tissue as well as the axillary and supraclavicular regions should be palpated using the fingers (as in playing the piano) or the palm with the fingers extended. The mammary tissue is gently compressed between the palpating hand and the chest wall, with the patient lying flat on her back, her hands resting on the top

FIG. 110 FIG. 111

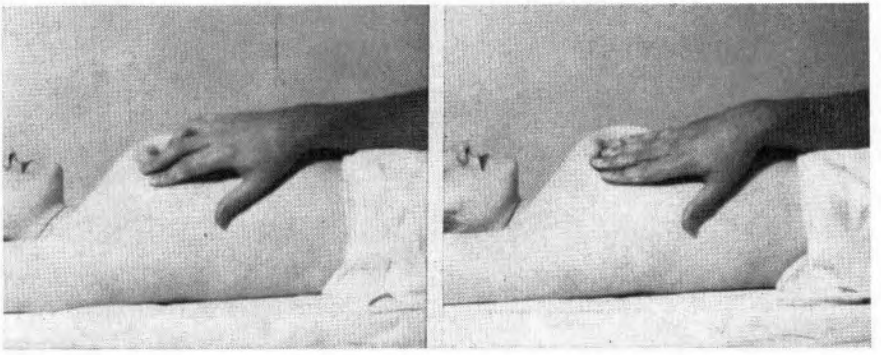


FIG. 110. Palpation of the breast with the tips of the fingers.
FIG. 111. Palpation of the breast with the flat of the palm.

of her head. (Figs. 110-111.) It is convenient to chart the size and location of any nodules in the quadrants of a circle, using a tangent to indicate the axillary fold, so that palpable nodes may also be noted.

Only long experience in palpation teaches the characteristics peculiar to the various mammary lesions. Cysts, abscesses and lipomas are most frequently fluctuant, while benign fibro-adenomas and papillomas have a characteristic feeling and mobility. Cancer is usually hard, irregular and adherent to the neighboring tissues. In the last analysis, however, the clinical impression on palpation must be repeatedly correlated with the gross and microscopic findings before expertness is achieved.

The information obtained by palpation is more complete and reliable if the attention of the examiner is directed in methodical fashion to the following aspects of the lesion:

1 SIZE

The dimensions should be given in centimeters.

2. CONTOUR
   The surface may be smooth or rough, rounded, lobulated or irregular.
3. DISCRETENESS
   The tumor may be encapsulated, circumscribed, or its margins ill-defined.
4. CONSISTENCY
   This may be fluctuant, soft, resilient, firm or hard.
5. MOBILITY
   The mass on palpation may be freely movable, attached or fixed.
6. RATE OF GROWTH
   After determining the size of a mass by palpation, further questioning of the patient in regard to its duration and the size when first noted, may yield valuable information in regard to the rate of growth.

Roentgenograms

Because of the accessibility of the mammary gland to inspection, palpation, and transillumination, roentgen-ray examination is not as valuable here as it is for most internal organs. With special soft-tissue technic, it is possible to bring out the contour and density of various lesions of the breast. Lockwood has described the roentgen-ray appearance of a variety of mammary conditions. Cancer appears as a solid tumor with fine projections extending from the periphery. Involvement of the axillary nodes may be frequently demonstrated. The penetrating power of the rays must be increased in studying chronic cystic mastitis if the presence of cancer is suspected. In adenosis, the breast casts a diffuse hazy shadow. Most frequently when cancer is present the mammary tissue has undergone involution and the substituted fatty tissue offers an excellent contrast medium. When a cyst contains fluid a round, clearly demonstrated shadow is seen. The shadows of the ducts are coarser and denser. Roentgen-ray examination is useful for lesions in the upper half of the breast where transillumination is difficult. It is not a substitute, however, for an exploratory operation.

Hicken and others have advocated filling the larger ducts of the breast, by way of the nipple, with injections of a contrast medium in order to study the duct tree in roentgenograms. If the tumor is in the periductal regions, injections of air are recommended. Since biopsy must be performed in all doubtful cases, the use of complicated roentgen-ray procedures is rarely justifiable from a clinical standpoint.

In cases of suspected mammary cancer in which the radical operation is contemplated, the study of the chest and skeleton for the possibility of metastasis is more important than roentgenograms of the breast itself. Since the presence of metastasis in these organs is a contraindication to radical surgery, this information should be learned before, rather than after, operation. The two most valuable films are those of the chest, including the upper humeri, and of the pelvis, including the lumbar spine and upper femurs.

Biopsy

Aspiration biopsy has a definite place in the diagnosis of mammary lesions. When a benign cyst of appreciable size is suspected, the cavity can usually be reached readily with a sterile 22-gauge needle on a lock-barrel syringe. The skin should be cleaned and sterilized but need not be anesthetized if the puncture is quickly and skillfully made. Aspiration of the clear to cloudy fluid of a benign cyst is usually diagnostic and may suffice for treatment in some cases. The same method of biopsy may be used to recover pus to confirm the presence of an abscess. The aspirated fluid should be examined microscopically as well as grossly: Simple cysts contain desquamated epithelium; a smear crowded with leukocytes is obtained from an abscessed cavity: and red blood cells predominate when an intracystic papilloma has been aspirated.

If tissue is to be withdrawn for microscopic diagnosis, the skin should be anesthetized and an 18-gauge needle used. The skin is incised with a bistoury to prevent carrying epidermis into the biopsy needle.

The needle is inserted at right angles to the surface of the tumor while exerting suction on the syringe. When the tumor has been penetrated, for a short distance, the needle is partially withdrawn and pushed forward again at a different angle. The negative pressure is gradually released. The needle is then slowly withdrawn and the aspirated tissue expelled from the needle and placed between two slides. These are pressed together and then pulled apart horizontally so that the tissue is spread out in a thin film. After fixation, staining, and mounting of the cover slip, the preparation is ready for examination. Hoffman has devised a more elaborate method which employs a trochar and punch.

Aspiration biopsy is suited to fairly large, clinically malignant tumors where irradiation rather than surgery is the treatment of choice. There is, however, a group of mammary lesions where accurate diagnosis is extremely difficult even under the most favorable conditions and for such lesions surgical biopsy is indicated.

Surgical Biopsy. It is generally conceded today that the advantages of biopsy of a mammary lesion suspected of malignancy outweigh the disadvantages. The old rule that a clinically malignant tumor should be treated by radical mastectomy without exploration used to be applied not infrequently to cancers which by modern standards are inoperable and best treated by irradiation. Tumors less than 3.5 cm. should be excised with a margin of normal tissue without squeezing. They should be bisected by the surgeon and a piece removed for immediate frozen section. If the pathologist's report is cancer, the wound should be packed with a sponge, soaked in 50 per cent zinc chloride or 10 per cent formalin, gloves and instruments should be changed, and the complete operation carried out. If the tumor is larger and aspiration biopsy is equivocal, the tumor should be incised and a piece removed for frozen section. Electrosurgical biopsy is preferable to the knife since there is less danger of bleeding and dissemination of cells. (Ward and Geschickter.)

The FROZEN SECTION TECHNIC preferred by the author is as follows:

The unfixed tissue is hardened on the freezing microtome. Intermittent blasts of compressed carbon dioxide are used to avoid overfreezing which renders the tissue brittle.

The tissue slices, cut at 15 to 25 microns, are wiped off the knife with the finger and floated in distilled water whence they are picked up by a glass rod and immersed in the staining solution. The solution used is a mixture of equal parts of 1 per cent aqueous solution of Azure A with a similar solution of Erie Garnet. The solutions are mixed rapidly, and rapidly filtered, to avoid precipitation (Geschickter).

The sections are floated in this solution for 15 to 30 seconds, again immersed in distilled water and floated on a slide and covered with a cover glass containing a drop of 20 per cent glucose solution.

They are examined over a strong yellow light which gives the sections the appearance of hematoxylin and eosin staining. The entire frozen-section technic, including diagnosis, rarely requires more than 4 to 5 minutes.

A properly organized history sheet simplifies the recording of the data and minimizes the chance to overlook important points in the history and examination. The history sheet used by the author covers two sides of a standard page and is reproduced here.

DIAGNOSIS OF MAMMARY LESIONS

Microscopic study is the only reliable basis on which to establish the final diagnosis in mammary lesions. Clinical diagnosis, however, may achieve a fair degree of accuracy in most instances. If one takes

BREAST CHART

Patient | Case No. | Diagnosis | Benign | Malignant
Note by | Date
Race | Age | Complaint | Duration | Right | Left | Impression
Zone

Referred by
Previous observation

HISTORY

Family	Puberty	Marital	M S W D	Menstrual
	Menarche	Pregnancies		Regular Irregular
	Breast	Lactations		L.M.P. Menopause

Other history: Breast pain, breast operations, trauma, infection, pelvic, thyroid, obesity

Present illness: Duration, pain, nipple discharge, skin change, nipple change, tumor, rate of growth, nodes

Mental status (cancerphobia, menopausal syndrome, etc.)

EXAMINATION

Type of breast | Small | Parous | Adolescent | Fatty

Inspection: Skin
Nipples
Breast

Transillumination:

Palpation: Breasts

Tumor (size, contour, discreteness, consistency, mobility)

Nipples
Axillae
Neck

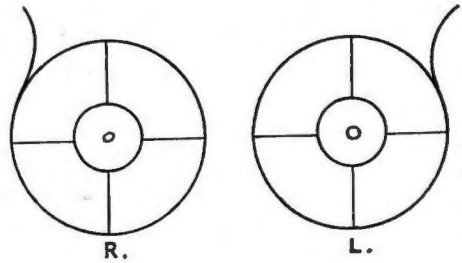
Height	Thyroid	Pelvic
Weight	Chest	
B.P.	Abdomen	
Oral	Extremities	

Laboratory findings: Wassermann | Urine | Blood count

Other Findings:

(Over)

Additional examination notes:



Treatment and progress notes:

Pathologic report:

Follow-up notes (Give name and address of two relatives or friends)

into consideration the age of the patient, whether the lesion is single, multiple, or diffuse, the location of the lesion, its characteristics on palpation, the presence or absence of inflammatory signs, and evi-

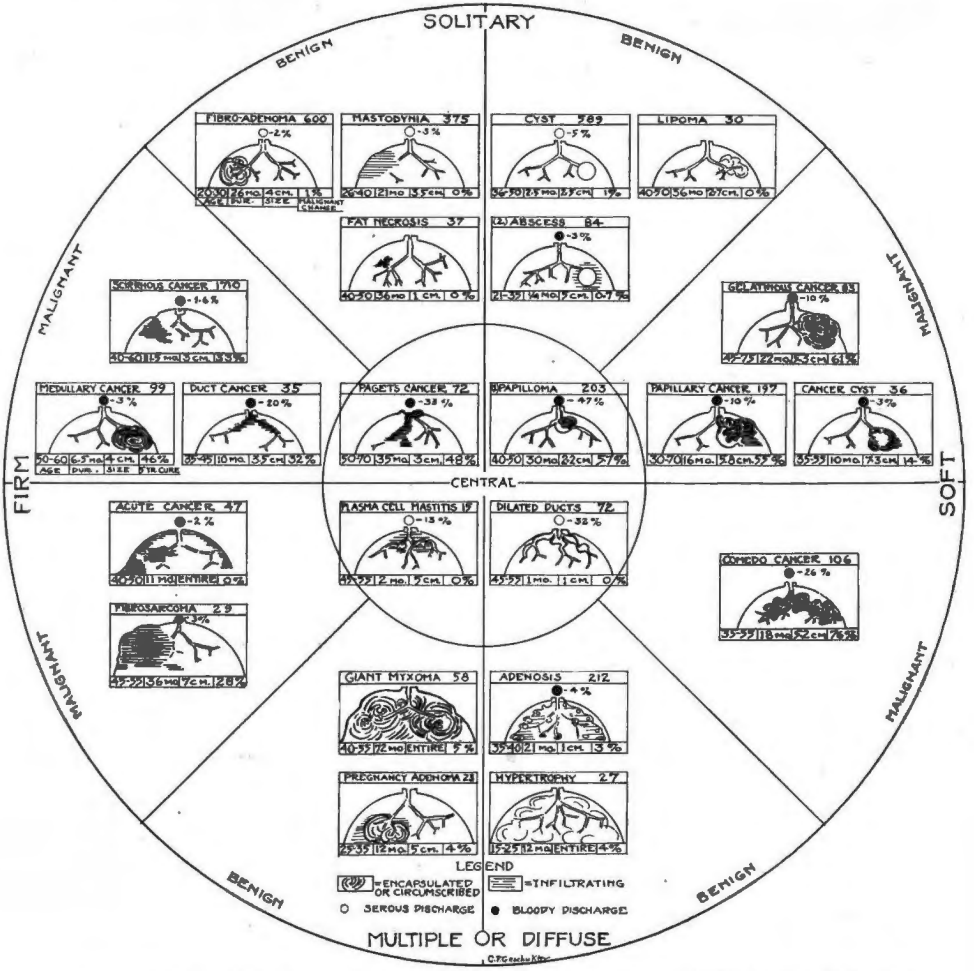


FIG. 112. The chief diagnostic features of common mammary lesions. The lesions in the upper half of the circle are solitary, those in the lower half are multiple or diffuse; the lesions in the left half of the circle are firm or hard, those in the right half are soft or fluctuant. Benign and malignant conditions are found in separate sectors of the circle. In the center are those commonly found near the nipple. The relative frequency of the lesion is shown by the number above which represents the cases in the author's series. The data given in the block directly below the lesion relates to the age incidence, the duration of symptoms, the size, the percentage of malignant change for benign lesions and the per cent of five-year survivals for malignant lesions, in the order given.

dence of injury, the number of possibilities to be considered in the differential diagnosis are definitely limited.

Role of Injury: Inflammatory Signs

Injury may be of significance in two mammary lesions: hematoma and traumatic fatty necrosis. Injury of the nipple during nursing may be a factor in lactation mastitis. Inflammatory signs are present in acute and chronic lactation mastitis and in some cases of tuberculosis and syphilis of the breast. Such signs are found in cases of dilated ducts beneath the nipple with an associated plasma-cell mastitis. An erysipeloid appearance of the skin is seen in cases of acute cancer, and reddening and edema with or without ulceration and infection are seen in the late stages of all forms of mammary cancer.

Age of Patient

The age of the patient is important in determining the physiologic states of the mammary gland. The decade between 15 and 25 years is the period of adolescence and early sexual maturity. This is the time of appearance for most cases of diffuse virginal hypertrophy and benign fibro-adenoma. The decade between 30 and 40 years in nonparous women is the period of menstrual cycles and it is at this time that the various forms of mammary dysplasia or cystic mastitis are found. In relation to childbearing, naturally, are found the acute and chronic forms of lactation mastitis, galactorrhea and galactocele, and the rapidly growing fibro-adenomas and cancers of pregnancy. At the time of the menopause large fibro-adenomas or giant myxomas may appear, also dilated ducts beneath the nipple with inspissated secretion, papillomas beneath the nipple associated with a sanguineous discharge, solitary cysts and the various forms of mammary cancer. With advancing age, mammary carcinomas and fibrosarcomas of the breast are the predominant lesions.

Number and Position of Lesions

The majority of mammary lesions are solitary rather than multiple and few are bilateral or diffuse. Mammary hypertrophy in the male and female is diffuse and often bilateral. Among the types of mammary dysplasia or cystic mastitis, adenosis is most often a multiple and bilateral condition. Cystic disease is multiple and bilateral in some instances and small intracystic papillomas may occur in multiple form and may be bilateral. Dilated ducts with inspissated secretion are often multiple and may be bilateral. Recurrent mammary cancer may give rise to multiple nodules (so-called carcinoma en cuirasse). Large fibro-adenomas during adolescence, giant myxomas, and large mammary cancers and sarcomas may occupy the entire breast and give the impression of a diffuse lesion.

TABLE II
DIFFERENTIAL DIAGNOSIS IN MAMMARY LESIONS

LESION	NO. OF CASES	AGE DISTRIBUTION	AGE GROUP				DISTRIBUTION		LOCATION		PALPATION	
			ADOLESCENT	CYCLIC	PUERPERAL	MENOPAUSAL	SINGLE	MULTIPLE OR DIFFUSE	CENTRAL	PERIPHERAL	SOFT	FIRM
BENIGN												
Hypertrophy	27	(12–18)	+					+		+		+
Fibro-adenoma	600	(21–30)	+				+			+		+
Pregnancy adenoma	23	(25–35)			+		+			+		+
Mastodynia	375	(26–40)		+			+			+		+
Adenosis	212	(36–40)		+				+		+	+	+
Cystic disease	589	(36–50)		+		+	+			+	+	
Papilloma	203	(36–50)				+	+		+		+	
Giant myxoma	58	(40–55)				+		+		+	+	+
Mastitis (puerperal)	124	(20–45)			+		+			+	+	
Mastitis (plasma-cell)	15	(45–55)				+	+		+			+
Fat necrosis	37	(40–50)				+	+			+		+
Dilated ducts	72	(40–55)				+		+	+		+	+
Lipoma	30	(40–50)				+	+			+	+	
MALIGNANT												
Infiltrating mammary cancer	1859	(40–45)		+		+	+			+		+
Acute cancer	47	(25–45)			+			+		+		+
Gelatinous cancer	83	(50–80)				+	+		+	+	+	
Paget's disease	62	(50–65)				+	+		+			+
Papillary cancer	197	(35–65)				+	+		+		+	
Sarcoma	62	(45–55)				+		+		+		+
Duct and comedo cancer	141	(35–45)				+		+	+			+

Tissues Involved

The majority of mammary lesions are found in the glandular tissue in any of the various portions of the breast. A few have a characteristic location beneath the nipple. Such lesions are papillomas in the larger ducts, dilated ducts beneath the nipple, Paget's cancer of the nipple, and some forms of papillary cancer and duct cancer.

Palpation

The most important data from the standpoint of clinical diagnosis are those obtained by palpation. Whether the lesion is soft or circumscribed, firm or infiltrating, is important. Cysts, benign papillomas, dilated ducts, and the papillary and mucoid forms of mammary cancer may be soft or circumscribed on palpation. The same is true of mammary abscesses, galactoceles, lipomas, and the rare angiomas. The tender tissue in mastodynia, benign fibro-adenomas, and nonsuppurating mastitis is firm but not infiltrating. The major forms of mammary cancer are hard, infiltrating lesions. This is also true of fat necrosis, and most forms of sarcoma.

DIFFERENTIAL DIAGNOSIS

These various characteristics of mammary lesions from the standpoint of differential diagnosis are shown in the accompanying table and diagram (Fig. 112).

Diagnostic Difficulties

Lesions of the breast are encountered in which the distinction between the benign and malignant states is difficult to establish even though adequate clinical and pathologic study has been made. The term "border line" which Bloodgood used for such lesions is misleading since it is the pathologist who is in doubt rather than the nature of the tumor. In the following tabulation the benign lesion and the malignant tumor with which it may be confused are listed. For a discussion of the differential diagnosis of these conditions the reader is referred to Chap. 26.

RULES OF PROCEDURE

Although clinical judgment must rest upon the individual experience of the physician there are certain rules of procedure in the diagnosis and treatment of breast conditions which it is well to enumerate.

TABLE III

THE BENIGN LESION

And the Malignant Condition with Which It May Be Confused in the Microscopic Diagnosis of Mammary Lesions

BENIGN	MALIGNANT
1. Chronic puerperal mastitis	Cancer in residual lactation mastitis
2. Fat necrosis	Early infiltrating cancer
3. Duct adenoma in adenosis	Comedo or duct cancer
4. Irregular acini "fibrosing adenoma" in adenosis	Early infiltrating cancer
5. Fibro-adenoma in pregnancy and lactation	Mammary cancer or sarcoma
6. Benign intracystic papilloma	Papillary cancer
7. Benign papilloma within ampulla of nipple	Paget's cancer
8. Giant myxoma with cellular areas	Mammary sarcoma

1. Do not overlook early pregnancy in taking the menstrual and marital history; this may be responsible for the sudden growth of a benign or malignant tumor.
2. Do not neglect a history of puerperal mastitis. Cancer occurring in the scar of a lactation mastitis has a grave prognosis.
3. Do not neglect microscopic examination of any discharge from the nipple if present. This is necessary to distinguish between blood and inspissated secretion.
4. Do not neglect transillumination. It may reveal a nonpalpable tumor.
5. Do not palpate the breast with the patient in the upright position, but have her lie flat and palpate the gland against the chest wall with the flat of the palm or the tip of the fingers, using gentle pressure. Include the region of the axillary and supraclavicular nodes in the palpation.
6. Do not fail to determine the mobility of the tumor, if present, the mobility of the overlying skin and that of the nipple. Evidence of traction or adherence of any of these structures may be the earliest sign of malignancy.
7. Do not omit a pelvic examination. It is important in the diagnosis and treatment of chronic cystic mastitis.
8. Do not omit a Wassermann reaction. A lesion of the nipple cannot be diagnosed without a serologic test.
9. Do not rule out the possibility of cancer without a biopsy if a definite nodule can be palpated or transilluminated.
10. Do not do a biopsy without being prepared to interpret the section and to proceed with a radical operation if indicated.

11. Do not omit roentgenograms of the chest and pelvis (including the lumbar spine) if a radical mastectomy is contemplated.
12. Do not give endocrine or radiation therapy unless the diagnosis is established.

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4

Mammary Hypertrophy

Excessive enlargement of one or both breasts may occur in males or females and at varying ages. The major forms of mammary hypertrophy are (1) precocious or infantile hypertrophy occurring in girls before puberty, (2) virginal and gravid hypertrophy, occurring in the female during adolescence or following childbirth and (3) gynecomastia occurring in males during or after adolescence.

Infantile hypertrophy is rare. The earliest case reported to our knowledge is that of Bevern in 1801. Galen described hypertrophy of the adult female breast and thought the size depended upon the accumulation of fat. Aristotle reported that he examined several cases of gynecomastia. Deaver and McFarland, who reviewed the literature on the various forms of mammary hypertrophy in 1917, were able to collect 19 cases of infantile hypertrophy, 240 cases of virginal and gravid hypertrophy, and 162 cases of gynecomastia. The

cases studied by the present author include six cases of infantile hypertrophy, 27 of virginal hypertrophy, and 108 of gynecomastia. Endocrine disturbances play a predominant role in infantile hypertrophy and account for a minority of cases of gynecomastia. In virginal hypertrophy the underlying factor is apparently an inherent sensitivity of the mammary tissue to growth stimuli.

PRECOCIOUS MAMMARY DEVELOPMENT

(Infantile Hypertrophy)

Enlargement of the breast may be observed in girls in the first few years of life. The enlargement is bilateral and progressive over a period of months or years and is associated with other signs of sexual precocity. The condition must be distinguished from the transient physiologic changes observed in the breast of the newborn. (Chap. 1.) Infantile mammary hypertrophy has not been reported in boys.

Etiology

In the 19 cases of infantile hypertrophy collected by Deaver and McFarland in 1917, the age of onset (with three exceptions) varied between one and five years. In addition to the precocious mammary development, menstruation and growth of pubic hair were noted. In one of the patients, pregnancy occurred at the age of nine years. From the more recent literature and from our own records 52 additional cases have been collected. These cases were associated with four varieties of endocrine disturbance:

1. Ovarian granulosa-cell tumors or cysts lined with granulosa or theca-lutein cells.
2. Ovarian chorio-epitheliomas or teratomas containing chorionic tissue.
3. Hyperplasia or neoplasia of the adrenal cortex.
4. Destructive lesions near the floor of the third ventricle or hypothalamus.

Infantile Mammary Hypertrophy with Granulosa-Cell Tumor. The data on 20 cases of proved and probable granulosa-cell tumors associated with mammary hypertrophy are summarized in Table V. These patients varied in age from 19 months to 12 years, eleven being between four and seven years. Mammary hypertrophy was associated with precocious menstruation, increase in stature, growth of the external genitalia and growth of axillary and pubic hair (Figs. 113, 114). At operation the uterus was usually about one-third larger than the normal for the corresponding age. Early union of the

TABLE IV

DATA ON 52 CASES OF INFANTILE MAMMARY HYPERTROPHY ASSOCIATED WITH SEXUAL PRECOCITY

ETIOLOGIC FACTOR	NO. OF CASES	AGE
Ovarian Tumors		
Granulosa cell	20	1½–12 years
Thecal cysts	13	½–11 years
Ovarian teratoma	8	5 –13 years
Adrenal Cortex		
Tumor or hyperplasia	4	3½– 9 years
Hypophyseal		
Eosinophilic cell hyperplasia	1	13 years
Mid-brain		
Hypothalamic lesions	6	6 – 9 years

epiphysis of the long bones was demonstrated by roentgen rays in some cases. In the case of Habbe and that of Bland and Goldstein,

FIG. 113

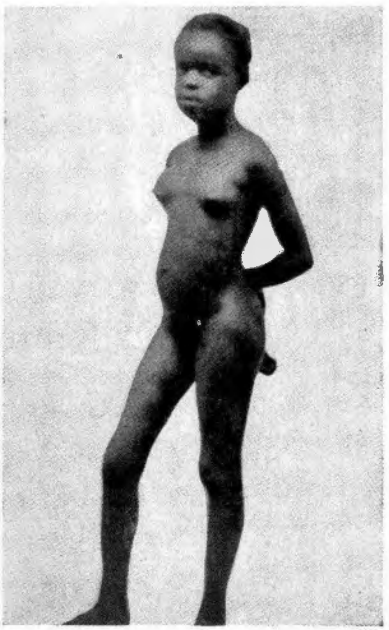


FIG. 114

FIG. 113. Infantile hypertrophy. Case of precocious puberty in a girl of six resulting from granulosa cell tumor of the ovary. (Courtesy of Dr. E. A. Park.)
FIG. 114. Mammary hypertrophy in a girl of two years associated with thecal-cell cyst of the ovary.

the mammary hypertrophy and menstruation regressed with the removal of a granulosa-cell tumor from one ovary, but reappeared with

TABLE V

SEXUAL PRECOCITY WITH MAMMARY HYPERTROPHY IN CASES OF GRANULOSA-CELL TUMOR[1]

AUTHOR	AGE	PATHOLOGY OF TUMOR	RESULT	REGRESSION OF ABNORMAL DEVELOPMENT
1. Blau—1926	5	Granulosa cell	Well 1 yr.	
2. Pahl—1931	9	Granulosa cell	Recovery	
3. von Habbe—1931	5	Granulosa cell	Well 10 yrs.[2]	Yes
4. Meyer—1931	11½	Granulosa cell	Well 10 yrs.	
5. Novak—1933	4	Granulosa cell	Well 2 yrs.	Yes
6. Novak—1933	5	Granulosa cell	?	
7. Novak—1933	6	Granulosa cell	Well 1 yr.	Yes
8. Bland and Goldstein—1935	7	Granulosa cell	Well 6 mos.[2]	Yes
9. Best—1935	6	Granulosa cell	Recovery	Yes
10. Geschickter—1940	12	Granulosa cell	Well 16 yrs.	
11. White—1939	11	Granulosa cell	Well 2 yrs.	Yes
12. Wyatt—1939	4	Granulosa cell	Recovery	Yes
13. Mengert—1939	5	Cystic granulosa cell	Well 3 yrs.	Yes
14. Croon[3]	7	"Round cell myxosarcoma"	Improvement	Yes
15. Geinitz[3]	19 mos.	"Sarcoma"	Dead	
16. Hoffman[3]	2	"Cystic sarcoma"	Dead	
17. Lucas[3]	7	"Round cell sarcoma"	Improvement	Yes
18. Wenger[3]	2½	"Adenosarcoma"	Recovery	Yes
19. Riedel[3]	6	"Round cell sarcoma"	?	
20. Verebely[3]	4	"Sarcoma"	?	

[1] This table is based, in part, upon the articles of Elterich and Bland and Goldstein.
[2] Bilateral (recurrence).
[3] Probable granulosa-cell tumors from the early literature.

a recurrent tumor in the opposite ovary, and again disappeared with the removal of the tumor from the second ovary. In nine additional cases, a similar regression of precocious development followed the removal of the tumor, demonstrating the endocrine activity of the tumor to be the cause of the precocity.

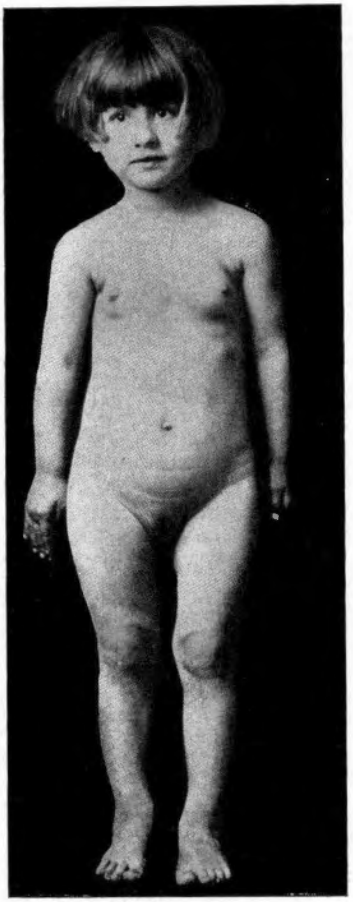


FIG. 115. Mammary hypertrophy in a girl aged three associated with an ovarian tumor. Laparotomy was not done and the histopathologic diagnosis was not established. (After Elterich.)

Assays of the blood, urine and tumor tissue indicate that ovarian-granulosa-cell tumors produce precocious puberty with mammary hypertrophy because of the estrogen secreted by the neoplasm. In the case of Bland and Goldstein, high values for estrogen were obtained from the blood and the urine. In the case of Ingrahm and Eastlake (reported by Novak) assay of the tumor tissue was reported positive for estrogen by Frank. The urine and the fluid from the cystic tumor showed 1000 and 20,000 R.U. per liter of estrogen respectively in Mengert's case. Palmer, in a case of granulosa-cell tumor, found urinary excretion of 86.6 gamma estrogen (calculated as estrone) per 24 hours, and 11.7 milligrams of estrogen per kilogram of desiccated tumor tissue. The excretion of estrone fell after removal of the tumor. Comparable values from 11 other cases in the literature were tabulated by Palmer.

Tissue has not been excised to determine the histology of the mammary hypertrophy associated with the granulosa-cell tumors. Since estrogen is elaborated by the ovarian tumor, however, it is reasonable to conclude that the enlargement is identical with that of normal puberty, consisting of a growth of ducts and periductal connective tissue. In none of the cases in young girls was there a localized tumor in the breast. In all, the enlargement was described as diffuse and symmetrically rounded, simulating normal maturity. The time of occurrence, but not the character of the mammary development, is abnormal.

Infantile Mammary Hypertrophy and Thecal Tumors. Mammary hypertrophy and precocious puberty may result from ovarian cysts lined by granulosa- or theca-lutein cells which secrete estrogen. The cysts in the ovary may be large enough to palpate or the swelling may be inconstant and the ovaries apparently normal on examination per rectum. Such patients may be observed over a period of years without any marked growth of the ovarian tumor. Novak has dis-

FIG. 116 FIG. 117

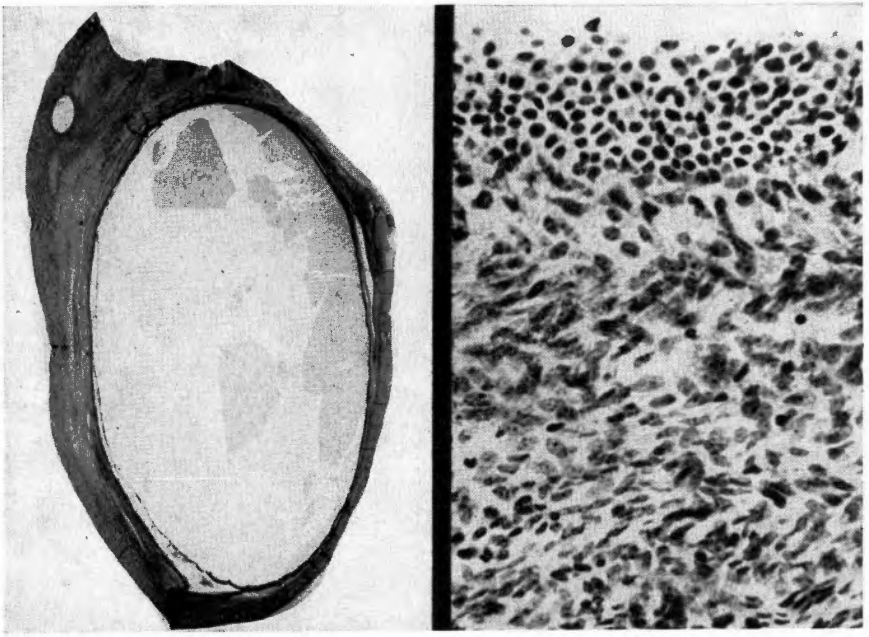


FIG. 116. Cystic thecal-cell tumor of the ovary associated with precocious mammary development. Cross section of cyst.
FIG. 117. Photomicrograph showing granulosa-cell lining of cyst.

cussed such a case reported by Lenz. The case reported by Elterich (Fig. 115) is apparently similar. The ovary contained a tumor about 5 cm. in diameter; it was not explored. The records of four such cases are available to us. In three, the ovaries were explored and typical cysts disclosed. (Figs. 116, 117.) In one, the urine was examined for gonadotropic substances with positive results. The history of one of these is given below.

A white girl, 2 years old, had started to menstruate a year previously. Shortly afterward, pubic and axillary hair were noted. (Fig. 114.) Her breasts were of adolescent size. The abdomen was explored for an

TABLE VI

MAMMARY HYPERTROPHY AND PRECOCIOUS PUBERTY WITH FOLLICULAR OVARIAN CYSTS

AUTHOR	AGE, YEARS	SEX CHANGES	PATHOLOGY
Elterich	4	Breasts enlarged	Ovarian tumor not explored, measured 5 cm.
Brohl	7	Precocious secondary sexual characteristics	Ovarian cysts
Campbell	Birth	Sexual characteristics like grown woman, enlargement of pelvic organs	Ovaries enlarged
Gedicke	7	Precociously matured	Cyst of ovary
Harle	14 mos.	Prominent secondary sexual characteristics	Follicular cysts
Meuer	6	Precocious secondary sexual characteristics	Follicular cysts
Pawlik and Lenz	11	Secondary sexual characteristics developed	"Multilocular sarcoma"
Schwartz	4	Precocious secondary sexual development	"Cystosarcoma"
Lenz	3 mos.	Breasts enlarged, precocious secondary sexual characteristics.	Left ovary size of pigeon egg. "Swelling of left ovary not constant"
Author's Case #1	2	Breasts enlarged, precocious secondary sexual characteristics. Positive Friedman test	Follicular cysts
Author's Case #2	6	Breasts enlarged, precocious secondary sexual characteristics	Follicular cysts
Author's Case #3	15 mos.	Breasts enlarged, precocious secondary sexual characteristics	Follicular cysts
Author's Case #4	4	Breasts enlarged, precocious secondary sexual characteristics	Follicular cysts

ovarian neoplasm in 1934. The left ovary was normal and measured 2 cm. across its greatest diameter. The right ovary showed a cyst measuring 5 cm. in diameter. This was excised and the opposite ovary biopsied. The lining of the cyst showed granulosa and theca-lutein cells. (Fig. 117.) The section from the right ovary showed normal ovarian stroma with several atretic follicles and one ripened graafian follicle. Palpation at the time of operation failed to reveal any abnormalities in the adrenals. The diagnosis of theca-lutein cyst of the ovary with sexual precocity was made. A Friedman test done on the patient's urine before operation gave a positive Prolan-A reaction.

In Table VI are reported the cases of cystic tumors of the ovary with sexual precocity from the literature in which the ovarian pathology apparently resembled that just described.

These cases of follicular cysts suggest that the primary endocrine disturbance is in the anterior pituitary gland, rather than in the ovary. In favor of this is the positive Friedman test on the urine in the patient recorded above, and the fact that the symptoms of sexual precocity and mammary enlargement persist in spite of removal of the cystic portion of the ovary. In these cases the adenohypophysis is apparently precociously active. Its secretion causes premature ripening of the ovaries, menstruation and development of the breasts and other sex organs.

This interpretation is also suggested by the 30 cases of precocious pregnancy collected from the literature by Elterich. Although no adenoma or hyperplasia of the pituitary gland (according to Engelbach) has been reported in the literature, the following case from our records showed hyperactivity of the anterior pituitary gland.

A white girl, 13 years old, had repeated attacks of epilepsy since infancy. These were of increasing frequency and severity. The diagnosis on admission was status epilepticus. The development of the breasts and the growth of pubic and axillary hair were precocious, and "similar to that of a woman of 25 to 30 years." Her height was 5 feet 4 inches. The patient died within 24 hours. Permission for autopsy was limited to the cranial contents.

Examination of the brain, which weighed 1440 grams, showed an engorged dura and increased vascularity of the pia. On the right side of the brain the convolutions were wide and flat. The pituitary gland was larger than normal. The sections (Fig. 118) showed enlargement of the anterior lobe with increased numbers of eosinophils. Chromophobe and basophile cells were present in decreased numbers.

The immediate cause of mammary hypertrophy in these cases of thecal-cell tumors is the elaboration of estrogens by the lining cells of the cysts, and in this respect they resemble the cases of granulosa-cell tumors. The histogenesis of these tumors of the ovary and their

endocrine activity have been described by Traut and Butterworth and by Adair and Watts.

Mammary Hypertrophy Associated with Chorio-epitheliomas and Teratomatous Tumors of the Ovary. In view of the established endocrine activity of chorionic tissue, chorio-epithelioma of the ovary occurring in children should lead to changes in the sexual organs and result in precocious development. Such sexual precocity, including menstruation and mammary hypertrophy, was first re-

FIG. 118 FIG. 119

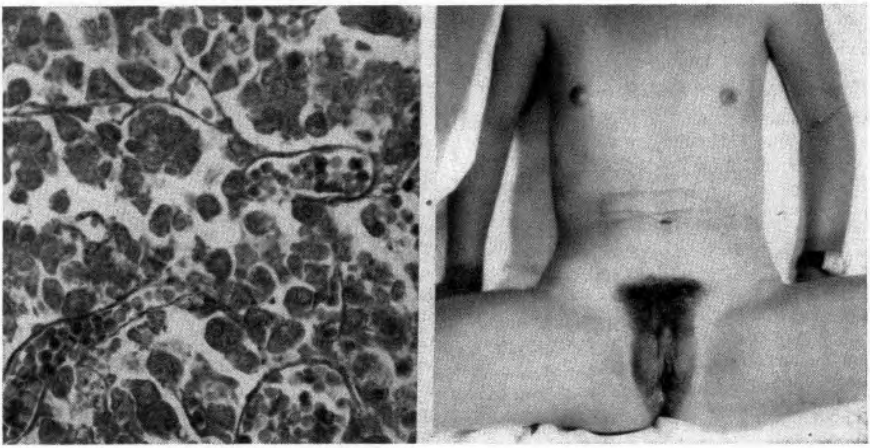


FIG. 118. Hyperplasia of the adenohypophysis in a case of precocious mammary development. There is marked eosinophilic cell hyperplasia.
FIG. 119. Precocious mammary development and hypertrophy of the clitoris in a girl aged four with hyperplasia of the adrenal cortex. (Courtesy Dr. H. H. Young.)

ported in 1904 by Pick who performed an autopsy on a girl, 9 years old, with precocious puberty and mammary development, who had a chorio-epithelioma of the ovary. We have been able to find four additional cases, those by Bock, Read, Freund, and Klaften. The case of Freund gave a positive Aschheim-Zondek test.

Since chorionic tissue in the testis or ovary is usually associated with a teratomatous tumor, growths described as teratomas of the ovary or testis frequently contain chorionic tissue and yield positive endocrine assays. Hence, sexual precocity with mammary hypertrophy should also occur among cases of teratoma of the ovary in girls.

Frank, in 1932, described a malignant teratoma, of the ovary in a girl of 9½ years who had enlarged breasts (equivalent to a girl

aged 15), pubic and axillary hair and regular menstruation. Estrogen tests on the urine were positive. The tumor at the site of the right ovary was reported pathologically as a teratoma. Harris, in 1917 and 1925, reported a similar case. A teratoma was removed at the age of five and one-half years and the patient was apparently normal when examined at the age of 16. Harris was able to collect 12 cases of teratoma of the ovary in children 9 years old or younger. Only two had sexual precocity. That the endocrine effects observed in ovarian teratoma are produced by the chorionic tissue of the tumor is indicated by the case of Fasoldh. The child was 8 years old, and had marked mammary hypertrophy, a fully developed uterus, regular menses, precocious skeletal development, and abundant pubic and axillary hair. There was a positive Aschheim-Zondek test on the urine. At autopsy a typical teratoma of the ovary was found but the metastases had the structure of chorio-epithelioma.

TABLE VII

MAMMARY HYPERTROPHY AND PRECOCIOUS PUBERTY WITH OVARIAN CHORIO-EPITHELIOMA AND TERATOMA

AUTHOR	AGE YEARS	OBSERVATION	PATHOLOGY	RESULT
Pick	9	Breasts enlarged Precocious puberty	Chorio-epithelioma of ovary	Dead
Bock	13	Breasts enlarged Precocious puberty	Chorio-epithelioma of ovary	Not followed
Read	11	No note on mammary development Menstruation	Chorio-epithelioma of ovary	Dead
Freund	7	Breasts enlarged Precocious puberty Aschheim-Zondek positive	Chorio-epithelioma of ovary	Not followed
Klaften	11	Breasts enlarged Precocious puberty	Chorio-epithelioma of ovary	Not followed
Fasoldh	8	Breasts enlarged Precocious puberty Aschheim-Zondek positive	Ovarian teratoma with chorionic tissue in metastases	Dead
Frank	9½	Breasts enlarged Precocious puberty Estrogen test positive	Malignant teratoma	Recovery
Harris	5½	Breasts enlarged Precocious puberty	Teratoma	Well 11 yrs.

Infantile Mammary Hypertrophy Associated with Abnormality of the Adrenal. Young, in his recent treatise on "Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases," states

> that 31 cases of the hypergenital syndrome associated with adrenal cortical tumors in children have been reported to date (1938). Twenty-six were in females and five in males. The majority of the girls showed heterosexual precocity, hair on the face, deep voice, overdeveloped clitoris simulating a phallus, and lack of breast development.

The height of these patients is increased, dentition is premature, and there is a tendency to premature union of the epiphysis in the long bones of the extremities. The tendency to sexual inversion and hirsutism distinguishes these cases having hyperfunctioning adrenal cortical tissue from the ovarian type of sexual precocity just described. Nevertheless, girls showing the adrenal form of pubertas praecox may show mammary hypertrophy and premature menstruation.

Bulloch and Sequeira report the case of a girl whose menses began at 9 years and 9 months. The breasts were fully developed. There was hypertrichosis of the genitalia and marked adiposity. She died at the age of 11 years. Autopsy revealed a large tumor of the left suprarenal cortex, with metastasis. There was hyperplasia of the thyroid and parathyroids. The uterus was fully developed; the ovaries were large, with corpora lutea of recent date.

The following case of a girl with premature development of the breasts, pseudohermaphroditism, and hyperplasia of the adrenal cortex has been previously reported by Dr. H. H. Young (Case No. 9) and is included here through his kind permission.

A child, four years old, was brought up as a girl, but the family sought advice because the child had a phallus and no vagina. The child when first seen weighed 56 pounds and was 45¾ inches in height. The build was that of a boy of six. The nipples, however, were somewhat prominent and there was slight increase in the underlying mammary tissue. (Fig. 119.) There was no hair on the face and body. There was a hypospadic phallus, 1 inch in length, between folds of a bifid scrotum but no testes could be palpated. The urinary meatus was in the perineum with ridges on each side which suggested labia minora.

Examination with a cystoscope revealed a vagina and cervix. A small body resembling a uterus was palpated, but no ovaries were felt.

Laparotomy in 1933 showed a small uterus and two tubes with fimbriated ends and attached to these, ovaries which measured 4 × 1 cm. A portion of the left ovary was removed. Microscopically it showed ovarian tissue with incomplete development.

The patient was readmitted in 1934 when five years old. Roentgenograms showed a normal sella turcica. The glucose tolerance test showed

a diabetic curve. Deep roentgen-ray therapy was administered to the right adrenal without apparent effect. Estrogen determinations on the urine showed 1200 rat units per liter; prolan determinations were negative. On October 16th, 1934, the adrenals were explored and one-third of each adrenal was removed. Microscopic studies showed hypertrophy of the fascicular layer of the cortex which was about 60 cells in length (normal for this age 18-20 cells in length). A week after operation the estrogenic substance in the urine was less than 5 rat units per liter.

TABLE VIII

PRECOCIOUS MAMMARY ENLARGEMENT IN GIRLS ASSOCIATED WITH HYPERPLASIA OR NEOPLASIA OF THE ADRENAL CORTEX

AUTHOR	AGE YEARS	DIAGNOSIS AND RESULT
Bevern and Romhild[1] 1802	3½	Autopsy—tumor left abdomen
Tileus 1803	4	Autopsy—tumor left adrenal cortex—metastases to liver
Bulloch and Sequeira 1905	9	Autopsy—tumor left adrenal with metastases
H. H. Young 1937	4	Well 2 years. Bilateral partial resection of adrenal cortex for hyperplasia

[1] L. A. Hoag: Malignant Hypernephroma in Children, Amer. Jour. Dis. Child., 25, 441, 1923.

In April, 1936, at the age of eight years, a vaginoplastic procedure was done and the enlarged clitoris amputated. The vaginal orifice was dilated at regular intervals. In October, 1936, the child was 4 feet, 8 inches tall, weighed 76 pounds and had the social reactions of a girl. There was marked evidence of breast development and the nipples were fairly prominent. The patient's voice had a definitely high pitch. There was axillary and pubic hair but not more than noted on the first admission. Estrogen determinations showed 3.75 rat units per liter of urine.

In 1937 the child was more feminine in type, was 4 feet, 9 inches tall, weighed 83 pounds and the breasts were further increased in size.

A variety of androgens as well as estrogens have been isolated from the urine of patients with tumors of the adrenal cortex. Callow isolated dehydroisoandrosterone; Butler and Marrian a metabolic end-product, pregnanetriol; and Burrows, Cook and Warren a number of similar compounds. Frank recovered large amounts of estrogen. The predominance of the androgenic hormones in such cases in females accounts for the adrenogenital syndrome in which there is growth of hair, deepening of the voice, growth of the clitoris and atrophy of the breast. In the rare instances in which mammary development occurs there are apparently increased amounts of estrogen

as in the case just cited. It is possible that some of the intermediate forms of androgens affect mammary development directly.

Mammary Hypertrophy and Lesions of the Mid-Brain. The pineal and thymus glands, which frequently have been assigned a role in the production of sexual precocity in the older literature, are no longer regarded as controlling factors. In discussing a teratoma of the pineal region associated with hypergenitalism in a male, Dandy expressed the opinion that it is the character of the tumor and not its position that is responsible for the hypergenitalism. Broster states that Dott observed the first case of pubertas praecox associated with a hypothalamic lesion. The patient died of scarlet fever at 8½ years. She had been menstruating since the age of 6 months and the mammary glands began to enlarge at 9 months. At 12 months she developed pubic hair and increased rapidly in stature. Autopsy revealed a benign astrocytoma of the mammillary bodies. The tumor bulged into the third ventricle.

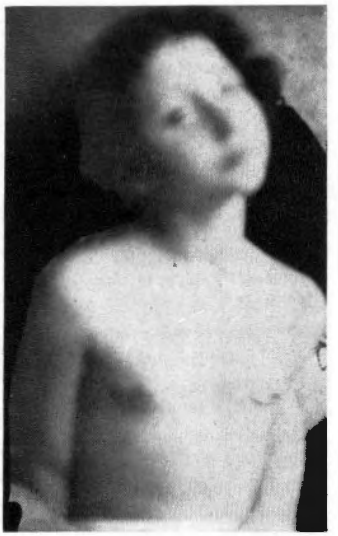


FIG. 120. Postencephalitic mammary hypertrophy in a girl aged six. A lesion in the hypothalamus apparently caused precocious puberty. The photograph is blurred because of the athetoid movements of the patient.

Ford and Guild reported two cases of hypergenitalism in girls. Each had encephalitis following measles at the age of 6½ and 9 years respectively. Within a few months the breasts began to develop and menstruation began. There was no increase in the size of the clitoris or the vagina, and the sella turcica was negative. Boenheim and Schlesinger each reported similar cases in girls. The author has had under observation a girl who had had encephalitis at 4 years. She had lost her speech and had marked athetoid movements. At the age of 6 years her breasts enlarged and menstruation began (Fig. 120).

Ford and Guild believe that the site of the lesion is in the hypothalamus. They state that the relation of the hypergenital syndrome to tumors of the pineal body is debatable. On the other hand, there is no experimental evidence to account for precocious puberty following lesions of the hypothalamus. It has been suggested that interruption of nervous pathways to the anterior lobe of the pituitary gland may release inhibitory influences and result in increased secretory activity.

TABLE IX

MAMMARY DEVELOPMENT AND PRECOCIOUS PUBERTY ASSOCIATED WITH LESIONS OF THE HYPOTHALAMUS[1]

AUTHOR	AGE YEARS	SEX CHANGES	PATHOLOGY
Ford and Guild	6½	Breasts enlarged Precocious puberty	Measles, encephalitis
Ford and Guild	9	Breasts enlarged Precocious puberty	Measles, encephalitis
Schlesinger	7	Breasts enlarged Precocious puberty	Meningitis
Boenheim	7	Breasts enlarged Precocious puberty	Measles, encephalitis
Dott and Cappell	6	Breasts enlarged Precocious puberty	Astrocytoma of the mammillary bodies
Author's Case	6	Breasts enlarged Precocious puberty	Encephalitis following measles

[1] Practically all cases of sexual precocity associated with lesions about the hypothalamus and third ventricle have been in boys. The above cases were all in girls.

Treatment and Summary

Although infantile mammary hypertrophy may result from disturbances in various endocrine organs, including the pituitary gland, the ovary, and the adrenal cortex, the immediate factor producing the enlargement is usually an increased secretion of estrogenic hormone. Assays of the urine and blood for estrogen should not be omitted, therefore, and palpation of the ovaries per rectum should be performed and repeated if negative at the first examination. That increased estrogen will produce infantile hypertrophy has been demonstrated experimentally by the cases of mammary enlargement occurring in young girls treated with large doses of estrogen for gonorrheal vaginitis.

In nearly all cases of infantile mammary hypertrophy, enlargement of one or both ovaries will be found. A laparotomy, which is justifiable with such findings, may reveal a granulosa-cell tumor, ovarian teratoma, chorio-epithelioma or follicular cysts.

Oophorectomy is indicated for granulosa-cell tumor, teratoma and chorio-epithelioma. The follicular cysts should be biopsied but removal of any great amount of tissue is unjustifiable since it does not influence the syndrome of precocious puberty. In such cases, hyperactivity of the anterior lobe of the pituitary may be demonstrated by urine assays for gonadotropic hormone. Irradiation of the hypophysis is of doubtful value.

Exploration of Adrenal. Cases of infantile hypertrophy associated with lesions of the adrenal cortex are rare. They can usually be distinguished clinically by hirsutism and enlargement of the clitoris. Exploration of the adrenal as practiced by Young is indicated.

In the cases of precocious puberty following encephalitis or accompanying lesions of the hypothalamus, the indications for treatment depend upon the nature of the lesion in the brain.

MAMMARY ASYMMETRY AT PUBERTY

(Early Ripening and Adolescent Mastitis)

The time of onset and the extent of the development of the mammary glands in girls at puberty vary in different races so that it is

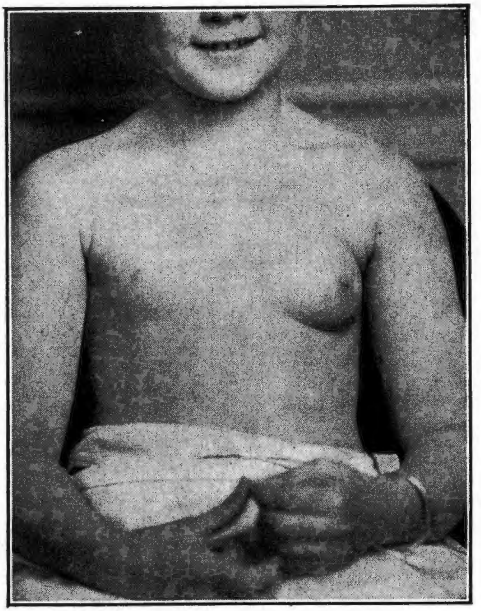


FIG. 121. Asymmetrical mammary development at the age of nine years. This condition is known as early ripening.

difficult to distinguish premature or excessive enlargement at puberty from normal development. During this period, however, one breast may exceed the opposite one in rate or in degree of development. This condition is known as "early ripening." (Hofstätter.) It must be distinguished from pathologic, unilateral or bilateral virginal hypertrophy. In the condition known as early ripening the inequality in the size of the breast is temporary and development, which is not

excessive, becomes bilaterally symmetrical by the time puberty is fully established. In true virginal hypertrophy—the size of one or both breasts greatly exceeds that of the mature gland and the enlargement, once established, remains.

Early ripening is observed in girls between the ages of 8 and 11 years. By the time the menarche is established the inequality in the size of the two breasts has been reduced to normal. In the rarer form of "early ripening" both breasts are well developed but there is marked asymmetry. The larger breast, however, regresses without any form of therapy and the inequality in size between the two breasts is lost. (Fig. 122.)

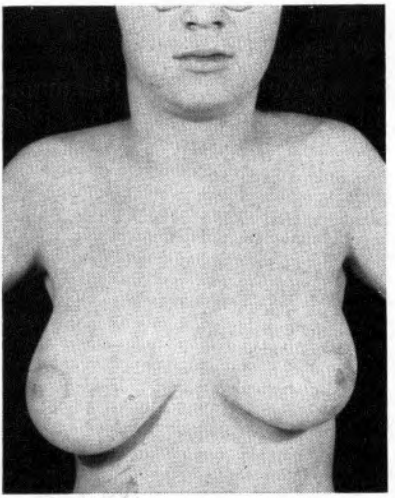


FIG. 122. Asymmetrical mammary development at puberty. In this girl of 14, the enlarged right breast returned to approximately the size of the left six months later.

Onset

In the 10 cases reported in this series, the onset of the asymmetric development was in the ninth year in six cases. In the remaining cases it was 8, 10, 11 and 12 years. The enlarged breast was slightly tender, the areola was larger than on the unaffected side and the developed breast was indefinitely lumpy. The enlarged breast varied in size between that of a lemon and of an adult fist, while the opposite breast was either infantile or showed incipient development. This form of mammary asymmetry occurring during puberty DOES NOT REQUIRE THERAPY, for it is a temporary manifestation.

Early ripening may have its onset with pain and swelling in one breast. On examination, a tender button-shaped mass is found under a slightly enlarged areola. This was the initial finding in two of the cases in this series. The lump in the next few weeks lost its definite character and was replaced by diffuse enlargement of the breast. The appearance of such a tender subareolar node bilaterally or unilaterally, with or without the complication of early ripening, is frequently termed "adolescent mastitis." In spite of the pain and tenderness, it must be looked upon as a physiologic phenomenon and does not require surgery. It may be necessary to protect the nipples if they become sensitive, usually after exposure to cold. No other treatment is necessary.

Etiology

The inequality in the size of the breasts in early ripening results from the excessive response in the larger rather than from diminished response in the smaller breast. This is indicated by the early age at which the abnormality becomes manifest (usually at nine years); by the occasional case in which the larger breast is temporarily larger

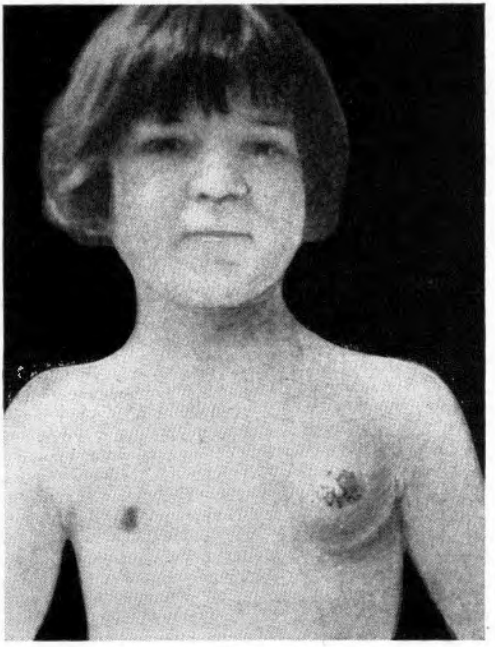


FIG. 123. Unilateral mammary hypertrophy resulting from estrogen therapy.

than normal at the end of adolescence; by the cases in which there is a history of excessive response on the part of the breasts to maternal hormones during infancy; and finally by those cases of pathologic virginal hypertrophy in which the size of one or both breasts greatly exceeds normal and in which a previous history of early ripening can be obtained.

The increased sensitivity of the larger breast is apparently too slight to be manifest except under intense hormonal stimulation. Such intense stimulation is supplied at puberty by the secretion of estrogen. This condition may be produced in girls by administering large doses of estrogen for gonorrheal vaginitis. Such a case is shown in Fig. 123 and Preissecker has reported a similar case. When the intense stimulation of puberty is withdrawn, the hypersensitivity is no longer apparent.

VIRGINAL AND GRAVID HYPERTROPHY

Excessive and persistent enlargement in one or both breasts in the female may occur during adolescence or with pregnancy. Such enlargement is more common at puberty but both types are relatively

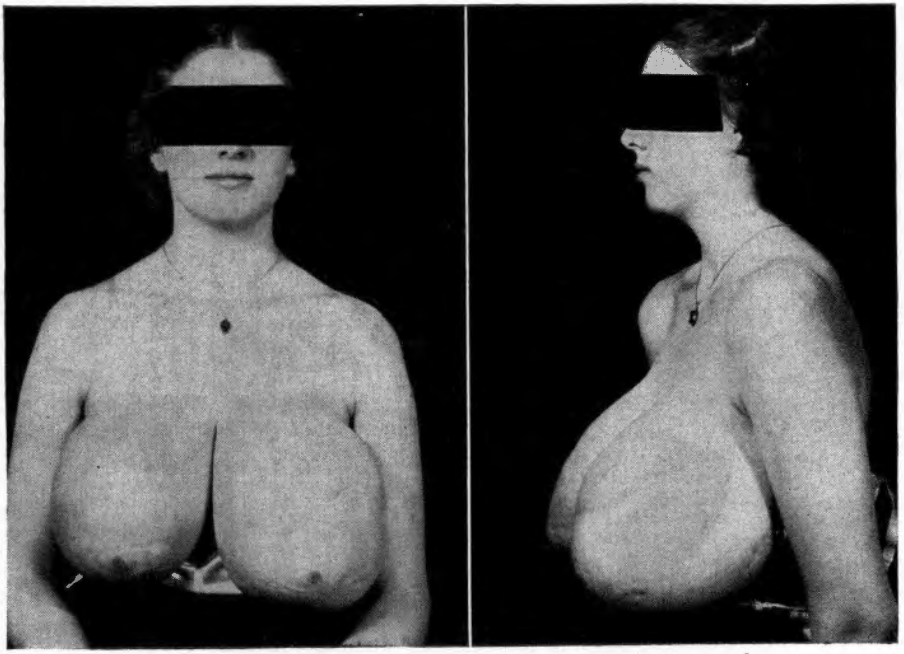


FIG. 124. Bilateral virginal hypertrophy in a girl, 15 years old.

rare. Among 30 cases in the present series, 24 showed abnormal enlargement during adolescence and four during pregnancy. In the remaining two cases the mammary hypertrophy was associated with menstrual disturbance. In 15 cases, the condition was unilateral and in 15 bilateral. (Table X.)

Onset

In the diffuse virginal hypertrophy which occurs during adolescence, most of the patients state that the mammary enlargement began about the time of the first menstruation, the majority of the cases occurring between the eleventh and fourteenth years. The enlargement proceeds rapidly for a period of from 3 to 6 months, as a rule. In a typical case recently reported by Fisher et al, in a

girl of 11, the breast development passed from the dormant juvenile stage to a size where each gland weighed 17½ pounds, within a period of 7 months. In some of the cases the mammary enlargement preceded menstruation by one or two years. In the cases observed by the author, careful questioning revealed that abnormal growth was first noted prior to the onset of menstruation or the menstrual periods were fewer or more scanty than normal during the period of maximum growth. In the following case, however, no variation in menstrual periods was observed during the period of maximum growth.

The patient, 15 years old, had apparently developed normally until six months prior to the time seen. Her menses started at the age of 13 years and had been regular. The periods were 28-30 days apart; the flow, which was scanty, usually lasted six days. There had never been any soreness or swelling of the breasts prior to the present disturbance. In June, 1938, the patient was the winner of a local beauty contest. Shortly thereafter

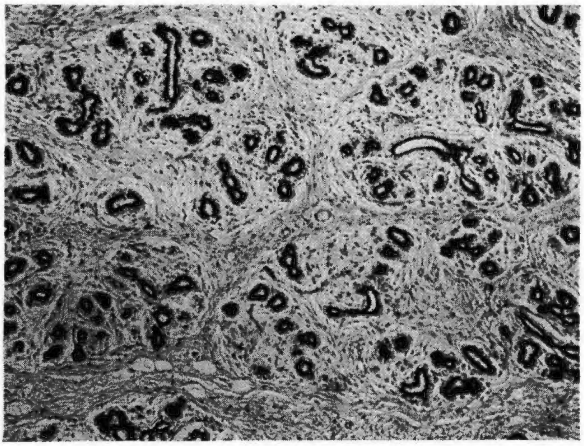


FIG. 125. Histology of virginal hypertrophy in the case shown in Fig. 124. There is hypertrophy of the fibrous tissue and increase in lobule formation.

rapid mammary enlargement began. During this period the menstrual periods continued as before. When examined, both breasts were more than twice their normal size, the left larger than the right. The superficial veins were dilated and the skin edematous. The nipples had practically disappeared. On palpation the glands were firm and coarsely nodular giving the impression of a confluence of dense fibrous masses. The breasts were supported on a scale and the weight thus determined was 7½ pounds for the right and 11 pounds for the left breast. (Fig. 124.) The patient was given injections of lactogenic substance over a period of three weeks. Following this a plastic operation was done. The excised mammary

TABLE X

DATA ON THIRTY CASES OF VIRGINAL AND GRAVID HYPERTROPHY

BREAST AFFECTED		
Bilateral		15 cases
Unilateral		15 cases
ONSET		
During adolescence		24 cases
11-13 years	17 cases	
14-16 years	7 cases	
Following pregnancy (28 to 30 years)		4 cases
Associated with menstrual disturbance (30 and 32 years)		2 cases
ASSOCIATED PATHOLOGY		
Fibro-adenoma		3 cases
Abscess and dilated ducts		1 case
Mammary cancer		2 cases

tissue showed marked hyperplasia of the lobular tissue which is unusual for virginal hypertrophy (Fig. 125).

Gravid Hypertrophy. In this condition the abnormal increase in the size of the breast is usually not noticed by the patient until lactation or weaning of the child. The mammary response to the hormonal influences of gestation is excessive and growth is continued beyond the period of postlactational involution. The character of the enlargement resembles that seen in puberty hypertrophy, except for the formation of lobules in late pregnancy. In two recently observed cases of gravid hypertrophy the enlargement was unilateral rather than bilateral (Fig. 152). The extent of the enlargement in such cases rarely approaches that seen in virginal hypertrophy.

Menstrual Hypertrophy. Moderate degrees of mammary enlargement may occur in menstruating women. The condition is associated with painful breasts and is an early phase of chronic cystic mastitis. The enlargement is rarely marked (about 10 to 25 per cent increase in size) and is not progressive. In the present series, however, there were two cases of unilateral virginal hypertrophy in women aged 30 and 32 years who had not been pregnant. In one case menstruation, previously regular, became scanty and irregular. In the other case, there was no note in regard to the menses. In 1910 her right breast tripled in size, and was amputated. Two and a half years later similar hypertrophy occurred in the left breast following pregnancy.

Diagnosis

The breasts during the active stage of enlargement are firm, tense, and indefinitely lumpy. The superficial veins are dilated. The areolae are enlarged. In severe hypertrophy, the nipples may practically disappear because of pressure from below. The breasts, which protrude during the early stages of growth, become pendulous as their weight increases. Their dependent portions may be cyanotic. Pain and tenderness are transient phenomena; the weight and dragging sensation together with the cosmetic deformity are the chief complaints.

The size of the breasts classed as diffuse virginal hypertrophy in the present series was twice, or more than twice, as large as normal in relation to the size and development of the patient. In one case the two breasts removed by amputation weighed just under 30 pounds and filled a washtub. In another previously reported by Johnston and Bloodgood, the amputated specimens weighed 18 pounds.

Virginal hypertrophy must be distinguished from adipose breasts. Enlargement of the breasts due to deposition of fat may occur in cases of pituitary disturbance. In these patients there is an increase of fat about the hips and in the mammary glands, but the excessive growth seen in virginal hypertrophy does not occur. The obese breasts transilluminate easily in contrast to the opacity of pathologic hypertrophy. Multiple fibro-adenomas or a solitary fibro-adenoma may be associated with moderate degrees of hypertrophy in the surrounding breast. In such instances, however, a definite, encapsulated tumor can be palpated. The degree of mammary enlargement following the removal of the tumor determines whether or not true virginal hypertrophy exists.

Pathology

Pathologic examination of the hypertrophied breast tissue shows an exaggeration of normal adolescent development. (Figs. 126, 127.) The growth consists of an extension of ducts with marked increase in the periductal and interlobular connective tissue. Lobule formation may occur in some cases (Fig. 125). During active growth the mammary ducts show increase in the size and number of their lining cells and are surrounded by moderate lymphocytic infiltration. The ducts are moderately dilated and may contain small amounts of secretion. In the latter stages the preponderance of sclerotic and hyalinized connective tissue compresses the ducts and leads to the atrophy of many of their branches. The proliferating fibrous tissue may be found directly in contact with the pectoral muscles on its inner surface and directly beneath the epidermis on its outer margin.

Diffuse virginal hypertrophy may be accompanied by localized fibro-adenoma. Three such cases are reported in this series. (Fig. 249, p. 300.) In two cases of bilateral hypertrophy, cancer subsequently developed in one breast. Dilated ducts were associated with abscess formation in a fourth case.

FIG. 126

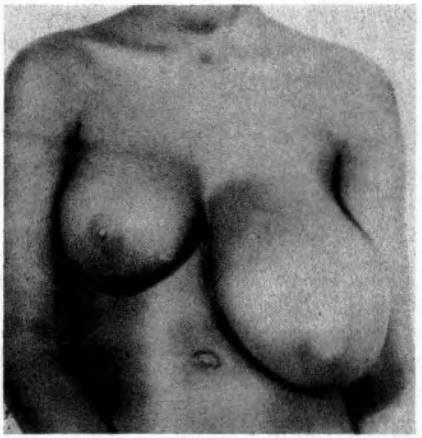
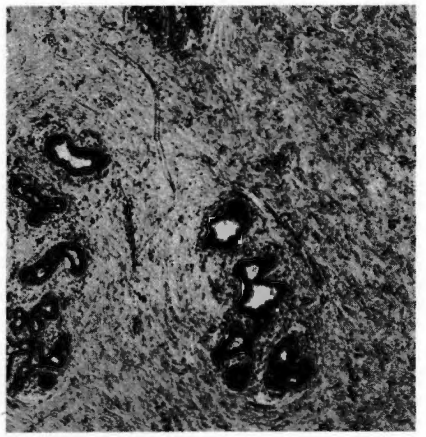


FIG. 127



Unilateral Virginal Hypertrophy.
FIG. 126. Photograph of the patient.
FIG. 127. Photomicrograph showing marked increase in the fibrous stroma and the small size of the mammary lobules.

Etiology

The tremendous overgrowth of the mammary gland observed in virginal and gravid hypertrophy is apparently dependent upon the increased sensitivity of the mammary tissue to hormonal stimuli. The occurrence of the enlargement during adolescence or pregnancy emphasizes the importance of intense estrogenic stimuli in the etiology of this condition. The sensitivity to estrogen may be demonstrated clinically. Injections of estrogen in doses of 10,000 I. U. or more daily given over a period of a few days in cases of virginal hypertrophy will cause further enlargement even though the size of the breasts has remained stationary for months prior to the injections. Abnormal sensitivity on the part of the end organ to hormonal stimuli is indicated also in those cases in which the enlargement is unilateral. In infantile hypertrophy associated with granulosa-cell tumor, the breasts are subjected to a prolonged and abnormally high amount of estrogenic stimulation, but in spite of this rarely exceed their adult size. This again emphasizes the inherent hypersensitivity present in virginal hypertrophy. Another indication of over-

response on the part of the mammary tissue is the history of hypertrophy with secretion in infancy or of "early ripening" at puberty which can be obtained by painstaking inquiry in these cases. If the mammary gland in normal animals such as the rat or monkey is subjected to continuous doses of estrogen, two to five times the normal (20 to 50 I.U. daily), the degree of mammary enlargement remains at the upper limits of normal. Thus, there is a limit beyond which no increase in size is noted with increased hormonal stimulation and instead stunting and involutional changes occur. In virginal and gravid hypertrophy of the human breast, this limitation of growth is lacking and under physiologic stimuli such as occur in adolescence or pregnancy, the size attained by the breast may be 10 to 30 times normal.

Treatment

Because the end-organ rather than the hormonal functions are at fault in virginal and gravid hypertrophy, endocrine therapy is unsuccessful. However, an insignificant decrease in the size of the breasts (insufficient to affect the deformity) has been obtained in two patients following treatment with 1000 bird units of lactogenic hormone. This is an attempt to produce postlactation atrophy. Testosterone propionate in amounts of 100 to 200 mg. over a period of one to two months was unsuccessful.

The usual treatment is amputation of the enlarged breasts. In young girls, plastic surgery with an attempt to save some portion of the mammary tissue may be attempted. It is important to realize that the circulation is impaired in such mammary glands because of their great weight and dependent position. Hence, before undertaking operation, rest in bed with proper support to the breasts is desirable to avoid infection and delayed healing. Tremendous enlargement with marked edema and atrophy of the nipples should influence the surgeon in favor of amputation rather than plastic surgery. (See Chap. 28.)

GYNECOMASTIA

Onset

Microscopically, the mammary glands in boys between the ages of 13 and 16 years show hyperplasia of duct epithelium and periductal stroma similar to that occurring in girls. In 77 per cent of boys at this age (Jung and Shafton) this normal puberty reaction is manifested as a button-shaped subareolar node of palpable size. These authors believe that nearly all boys at some time during puberty have

such a node, to which the terms adolescent mastitis, mastalgia and gynecomastia are incorrectly applied. The node tends to disappear at about the age of 17 years. At the age of 20 years, less than 15 per cent of men have any palpable vestiges of it.

Rarely the subareolar enlargement may be two or three times its normal size and persistent. This pathologic hypertrophy is known as gynecomastia. It may be unilateral or bilateral and occur not only in males at puberty but in adults. In the present series of 108 cases 86 per cent of the patients had a unilateral swelling. Thirty-eight cases occurred between the ages of 13 and 25 years, 40 between the ages of 30 and 45 years, and 15 between the ages of 60 and 70 years. The average duration of the swelling observed by the patient before seeking consultation was 15 months. The extremes varied between 11 days and 12 years. One-third of the patients complained of pain or sensitivity and in approximately 50 per cent there was some tenderness on palpation. In only two cases was there a discharge from the nipple (Table XI).

TABLE XI

DATA ON 108 CASES OF GYNECOMASTIA

Race (white)	88%
Age	31–50 years
Youngest case	12 years
Oldest case	74 years
Duration (average)	14.7 months
Duration (extremes)	11 days; 12 years
Location: left 47.2%—right 40%	
Location (bilateral)	12.8%
Trauma	14 %
Pain	30 %
Tenderness	50 %
Tumor (discrete)	69 %
Tumor (diffuse)	31 %
Result (benign)	100 %

On examination, the swelling usually has a discrete or circumscribed character. It is moderately firm and indefinitely lumpy. In less than one-third of the cases was the swelling diffuse and its fibro-adenomatous character masked by the increased amount of subcutaneous fat. The size of the swelling varies in diameter from 3 to 10 cm. In only three cases in the present series did the swelling attain the dimension of the normal adult female breast. (Fig. 128.) The enlargement may vary in size and recur after subsidence.

Because of the discrete, firm and nodular character of the enlargement in many cases of gynecomastia, some observers look upon the tissue as neoplastic and classify it as benign fibro-adenoma. (Fig.

129B and C.) There is some justification in this, particularly when the fibro-adenomatous tissue is definitely encapsulated (see Chap. 27).

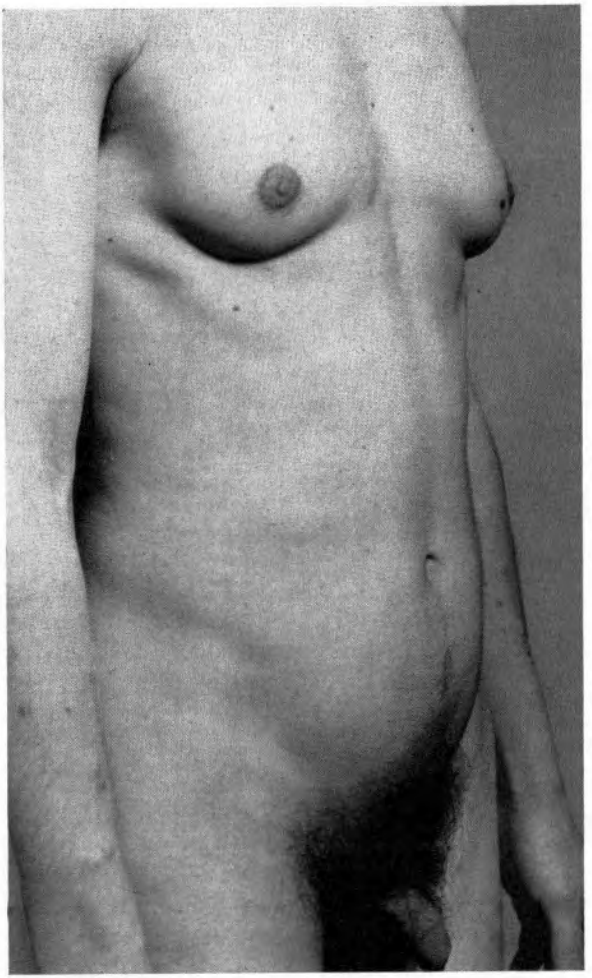


FIG. 128. Gynecomastia. The mammary development approaches that seen in the female breast.

Diagnosis

Gynecomastia presents a variety of clinical pictures, the recognition of which is important from the standpoint of prognosis and treatment. The DIFFUSE HYPERTROPHIC form is often seen early in puberty. In such cases the enlargement is usually moderate and consists of hypertrophied mammary tissue without marked increase in the surrounding fatty tissue. This form often subsides spontane-

ously or it may yield to injections of testosterone propionate. In the more chronic cases seen in adults, which may be classed as the FIBRO-ADENOMATOUS type, more definite nodularity sometimes consisting of almost pure fibrous tissue may be found. This fibro-adenomatous type must be carefully distinguished from carcinoma of the male breast and may require excision for diagnosis and treatment. The rarest form of gynecomastia is that in which true FEMI-

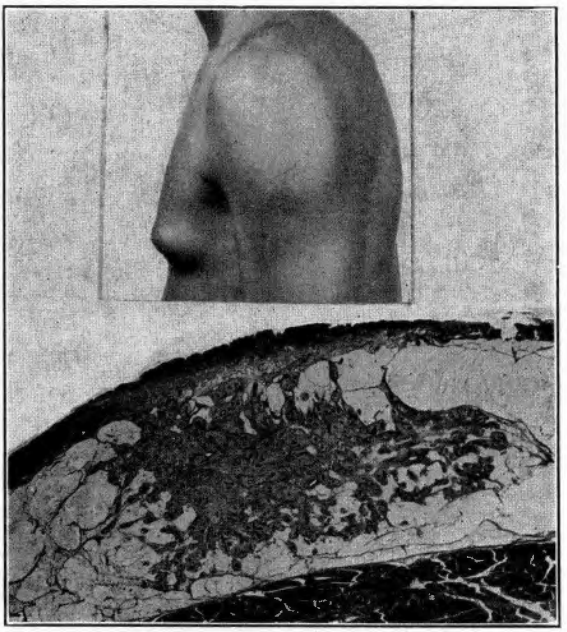


FIG. 129A. Gynecomastia occurring in a colored boy aged eighteen. Photograph of patient and cross section of the enlargement.

NIZATION of the breasts occurs. The size of one or both glands approaches that seen in the adult female and a proportionate amount of adipose tissue is present. In this group careful study may reveal tumors of the endocrine organs or pseudohermaphrodism. Lewin has classed as PSEUDOGYNECOMASTIA obesity with feminine distribution of fat in the mammary region. This is characteristic of obesity in the eunuch and is the result of localized fat deposits, and does not involve hypertrophy of the mammary tissue. It is practically always bilateral and presents soft pendulous swellings which transilluminate readily. Diet and endocrine therapy directed at the underlying condition may be effective.

Pathology

Benign enlargement of the male breast is more common than cancer of that organ (a ratio of more than three to one according to

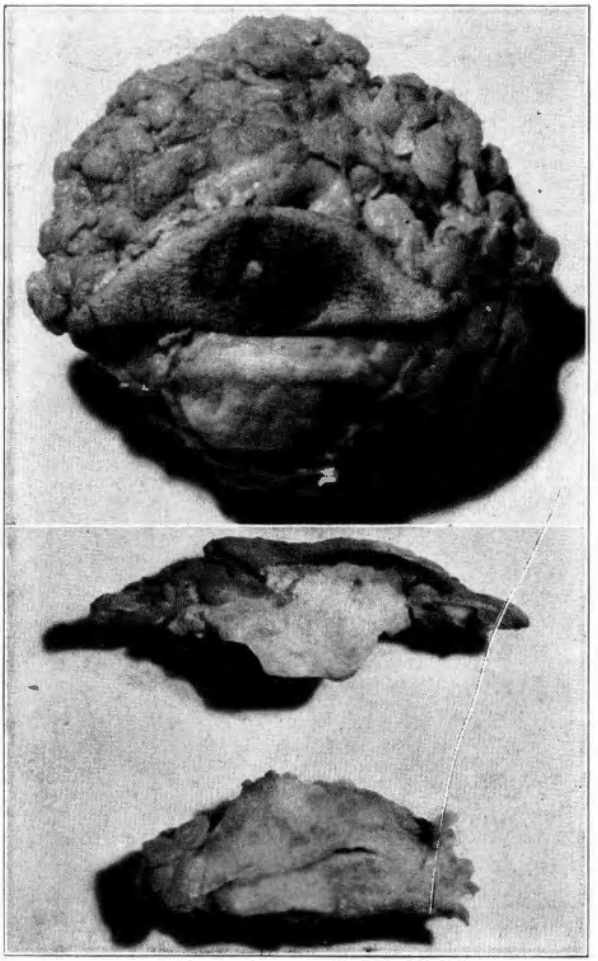


FIG. 129B. Excised tissue in a case of gynecomastia. The specimens show the circumscribed fibro-adenomatous character of the enlargement.

our records). Benign swellings of the male breast other than gynecomastia include dermoid cysts, lipoma, lymphangioma and infections.

Although malignancy was not found on pathologic examination nor in the follow-up reports in this series, it may occur in rare in-

stances. (See Chap. 27.) Menville states that Berns reported a cancer developing in one of two enlarged mammary glands of a man, the case terminating fatally; and that Erdheim included a malignant intraductal papilloma in his reports on gynecomastia. If the mass palpated is discrete, firm, or growing in size, a biopsy should be made to rule out the possibility of mammary carcinoma.

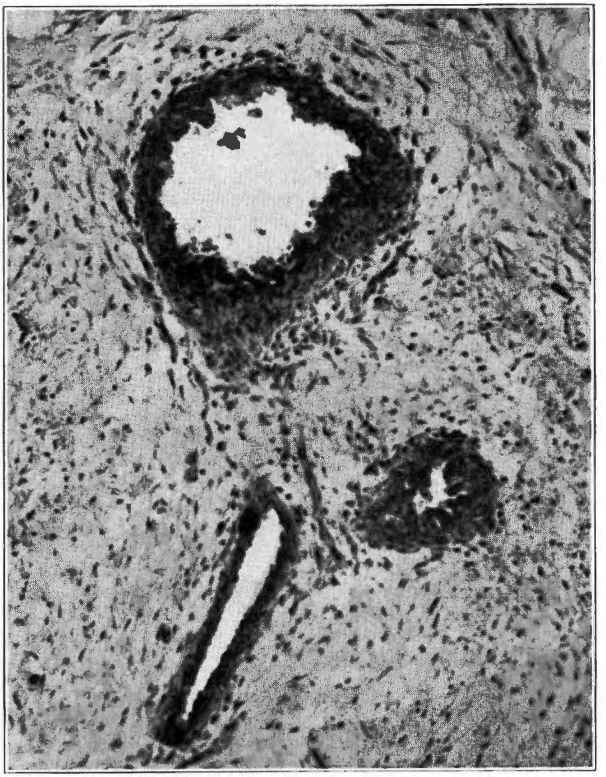


FIG. 129C. Photomicrograph showing the growth of ducts in fibrous tissue composing the tumor tissue shown in Fig. 129B.

In the majority of cases of gynecomastia the enlargement has been treated by surgical removal, with preservation of the nipple. The excised tissue resembles the normal female breast in gross appearance. The subcutaneous fat may be increased in amount. Microscopic examination shows a growth of mammary ducts and periductal stroma. (Fig. 129C.) Lobule formation is absent. There is hyperplasia of the duct epithelium with moderate desquamation of cells into the lumen. Small papillary-like projections may form in the lining of the ducts and occasionally the ducts are dilated and contain secretion.

A moderate periductal infiltration of wandering cells occurs. There may be an accompanying hypertrophy of the subcutaneous sweat glands. The entire picture may be indistinguishable from the early development of the normal female breast at puberty.

Endocrine Considerations

The endocrine disturbances in gynecomastia, like those in infantile hypertrophy of the female breast, may relate to the gonad, adrenal cortex or hypophysis.

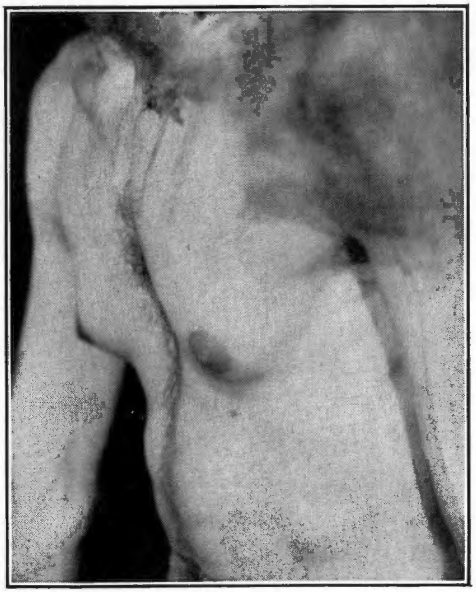


FIG. 130. Gynecomastia associated with teratoma of the testis. The urine was positive for prolan (Courtesy of Dr. R. S. Ferguson).

Gonad. The most common neoplasms of the endocrine organs which may be associated with gynecomastia are teratomatous tumors of the testicle. (Fig. 130.) Two such cases were included in the present series. Gilbert has been able to collect 102 cases of gynecomastia associated with testicular neoplasms, teratoma or chorio-epithelioma predominating. Gilbert estimated that 3 per cent of all cases of testicular neoplasms were associated with gynecomastia. Both gonadotropic and estrogenic hormones have been recovered from the urine in such cases.

Injury to the seminiferous tubules, as pointed out by Lower and Johnston, may result in interstitial-cell hyperplasia. Atrophy of one or both testicles following trauma, orchitis, or varicocele may be

associated with gynecomastia, or mammary enlargement may occur after the removal of one testicle in the repair of a hernia. The injury to the spermatic tubules is followed by increased activity in the interstitial cells or a similar stimulus may be provided by injury to or removal of the opposite testis. The mammary enlargement is probably related to the endocrine activity of these cells. In nine of the cases in the present series, testicular atrophy or the removal of one testis was reported.

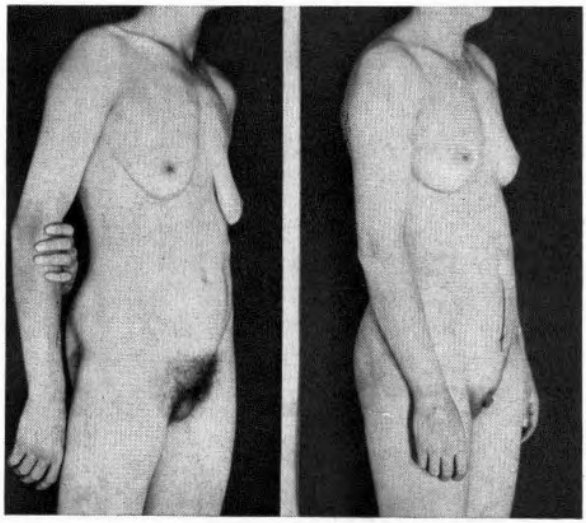


FIG. 131. Gynecomastia in two brothers with pseudohermaphroditism. (Courtesy of Dr. H. H. Young.)

Pituitary. Gynecomastia has been observed in cases of hypophyseal adenoma such as those reported by Roth, Moehling and others. The mammary enlargement may be accompanied by secretion. Gynecomastia has also been seen in patients with tumors of the adrenal cortex, Mathias, Weber, Brutschy and Holl each having reported a case.

The cases of gynecomastia associated with endocrine disturbance referred to above would seem to indicate that hormonal stimuli, present in abnormal concentration, are the etiologic factors bringing about the mammary enlargement. The inherent sensitivity of the breast to such stimuli is probably within normal limits, in the majority of cases. In favor of such a view is the relatively moderate size of the swelling and its variation in size from time to time.

On the other hand an inherent sensitivity in the mammary tissue, which approaches that seen in the female, may be a factor in certain

cases. This is probably true where feminization of the breasts occurs in pseudohermaphrodites. We have had the privilege of studying the specimens of two such cases from the Urological Service of Dr. Hugh H. Young. (Fig. 131,) Similar cases have been reported by Polaillon, by Dennis and by Gilbert.

The role of estrogens and androgens in the production of gynecomastia have both been demonstrated. That estrogen will produce enlargement in the male breast is suggested by the case of chorioepithelioma of the testis reported by Heidrich et al. in which assays for estrogen on the urine showed 500 I. U. per liter. Similar cases of gynecomastia associated with teratoma of the testicle in which abnormally high amounts of estrogen have been found in the blood or urine have been reported by Hinman and Powell and by Bergeret et al. In a case of Dunn, 200,000 I. U. of estrogen were injected for migraine in a male adult, resulting in typical gynecomastia (see Chap. 2). Geschickter, Lewis and Hartman produced gynecomastia in male monkeys with injections of estrogen.

Both androgens and estrogens can be isolated in significant quantities from the urine of normal adult males. Oesting and Webster found that boys during adolescence had an average of 25 international units of estrogen for a 24-hour output of urine. Dorfman and Gruelich obtained similar values. In male adults the output may be proportionally larger. It is possible that gynecomastia may arise in those cases where the output of estrogen is either abnormally high or the androgenic function of the testicle is lowered. Kenyon and his coworkers in four cases of gynecomastia found normal excretion of estrogen in the urine. The androgen in the same cases varied from none to normal amounts. Bronstein reported a case of gynecomastia in a colored boy, 17 years old, in which estrogen assays of the urine were negative; male sex-hormone determinations were not made. From the clinical experience obtained in cases injected with high doses of testosterone propionate, it does not seem likely that this hormone is responsible for gynecomastia (Vest and Howard). However, McCollagh and Rossmiller observed gynecomastia in 6 of 11 men with hypogonadism treated for four to six weeks with a total of 3 to 8 grams of methyl testosterone (Chap. 2).

Treatment

In cases of gynecomastia the possibilities of endocrine therapy must be considered. In those cases where a tumor of the testis or adrenal is found responsible for the condition, removal of the growth results in atrophy or regression of the mammary enlargement. Hoffman has reported favorable results with testosterone therapy, giving 25 mg.

intramuscularly twice weekly for 10 or 12 weeks. However, the majority of cases treated by Hoffman were in young individuals passing through adolescence. In such cases repeated observation will usually disclose regression in the absence of any form of therapy. In persistent cases or in adults the treatment is worthy of a trial although it has not proved successful in the author's cases where a definite

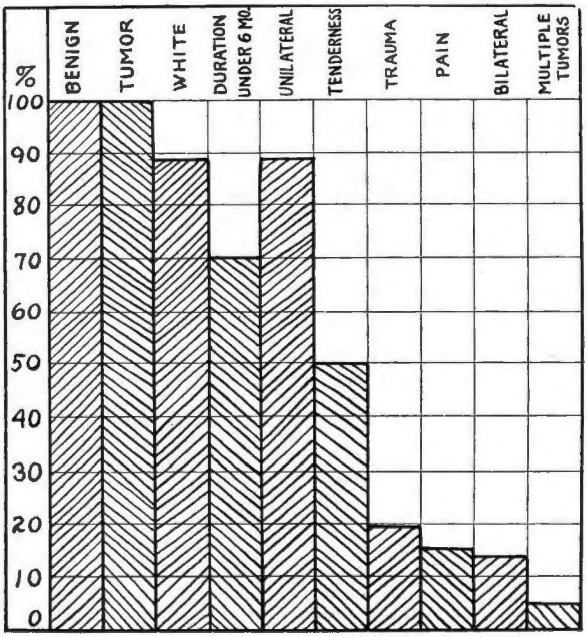


FIG. 132. Chart showing the relative frequency of the leading symptoms and findings in gynecomastia.

fibro-adenomatous nodule has been present or where the accumulation of adipose tissue has been a complicating factor. Excision, where desired for cosmetic reasons, is the treatment of choice.

Surgery should be postponed until it is evident that the enlargement will not regress spontaneously.

MAMMARY UNDERDEVELOPMENT : HYPOMASTIA

The size of the breasts shows great variations and insufficient size or underdevelopment is a more common complaint than excessive enlargement. Complete absence of one or both breasts (amastia) may occur. It is important to distinguish the subvarieties of mammary

underdevelopment. The first variety includes those patients with the tendency toward intersexuality. These patients have a masculine build with breasts resembling those seen in the normal male and a masculine distribution of pubic hair. During pregnancy such individuals may show normal breast development which recedes following lactation and weaning to the masculine state, with only the enlarged nipples as evidence of the former gestational development. Mammary development is difficult to induce or to maintain in such cases by any form of endocrine therapy. (Fig. 102.)

More commonly, breasts of small size are associated with a slight or undernourished build and are an expression of an inadequate distribution of subcutaneous fat. In such patients increase in the size of the breast usually follows gain in weight obtained by augmenting the diet. The breast development may be accentuated at the same time by endocrine therapy. (Fig. 103.)

The third variety includes those patients with hypogonadism or the Fröhlich's syndrome. These patients have a masculine thorax, adipose thighs and buttocks and often suffer from acne. In these cases of pituitary disturbance correction of the underlying endocrinopathy is difficult but successful redistribution of adipose tissue may be obtained by prolonged treatment, combining pituitary, thyroid and ovarian hormones.

The fourth group of cases with mammary underdevelopment is found in patients with mammary dysplasia. These patients either have a form of mastodynia which we have termed mammary deficiency (Chapter 8, p. 189) or have a fully developed adenosis (Chapter 9, Fig. 174). Breast development improves with endocrine therapy for the underlying condition (Fig. 223) but estrogen therapy must be used with caution because there is danger of accentuating the underlying mammary dysplasia with over-treatment.

In the treatment of mammary underdevelopment estrogen preparations are best given by mouth or by local applications of estrogen ointment. In the author's experience the administration of stilbestrol compounds by mouth over a period of 6 to 8 months is an effective means to produce mammary enlargement (stilbestrol monomethyl ether—monomestrol—in doses of 1 mg. daily). Monthly injections of progesterone aid in maintaining the enlargement. The author has obtained more rapid enlargement by applications of estrogen ointment containing the equivalent of 0.5 mg. of estrone (Menformon dosules—Roche-Organon). The ointment is rubbed into each breast nightly and in the premenstruum a single intramuscular injection of 5 mg. progesterone is given.

Pendulous Breasts

Next to underdevelopment, the occurrence of pendulous breasts is the most common cosmetic mammary complaint. The cause of the condition is regression from former increased size, following a period of excessive adolescent development, lactation, or obesity. (Fig. 71.) A moderate degree of pendulosity may be corrected by the same form of endocrine therapy used for underdevelopment. For more marked degrees plastic operation is required (Chapter 28, p. 642). It is important for the physician to evaluate carefully the motivation or psychic component underlying the patient's complaint. The mammary complaint may be "projected" from an unresolved emotional conflict, which will be unrelieved by the treatment of the mammary condition, and the physician's efforts may lead only to a troublesome law suit.

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PART II

THE BREAST IN PREGNANCY AND LACTATION

ORIENTATION

Lactation is preceded by developmental changes in the mammary gland during pregnancy; it is initiated following childbirth by the activity of the pituitary gland, and is maintained by suckling. While the chief interest centers on puerperal mammary secretion, the nonpuerperal gland also may show secretory changes which are of concern to the pathologist and surgeon. The secretory activity of the breast increases its susceptibility to infection, and the developmental changes of pregnancy and lactation influence markedly benign and malignant tumor formation in the organ.

In the chapters of Part II, the clinical aspects of puerperal and nonpuerperal mammary secretion are considered, the various forms of mastitis are described, and the effects of pregnancy and lactation upon lesions of the breast are discussed.

The most common abnormalities of puerperal secretion are deficient lactation, painful engorgement of the breast, and lactation mastitis. Statistical studies by Wainwright and also by MacDonald indicate that abnormal lactation is approximately twice as common among women who develop mammary carcinoma as in the normal population. The milky secretion of normal lactation may rarely continue for years after weaning, as galactorrhea. This abnormality predisposes to mastitis but not to cancer. A serous, watery discharge from the nipple is found in 2 to 4 per cent of all adult women and is more common just after menstruation than in between periods. Such a discharge may occur after sterilization and is more frequent in women with cystic mastitis or in women with large families at the menopause, in whom it is associated with dilated ducts beneath the nipple. In such patients it is an expression of diminished or ceased ovarian function with probable over-activity of the lactogenic function of the pituitary gland. Again, such secretory abnormalities of the non-puerperal state do not increase the susceptibility to mammary carcinoma, although the possibilities of periductal mastitis are always present.

Normal pregnancy and lactation are the safest forms of endocrine therapy for the breast which is the seat of cystic mastitis, and such normal functioning diminishes but does not obviate the possibilities of mammary carcinoma. However, pre-existent benign fibroadenomas, mammary carcinoma, or tuberculous mastitis are adversely influenced by the childbearing and nursing functions.

5

Puerperal and Nonpuerperal Secretion

The increasing prevalence of prenatal care and the co-operation of the obstetrician, the endocrinologist, and the pediatrician have offered a greater opportunity for the systematic observation and care of the breasts during pregnancy, lactation and weaning.

THE BREAST

The normal breast requires little attention during pregnancy. (Fig. 133.) Many authorities recommend that from mid-pregnancy until delivery the nipple be massaged nightly with cocoa butter or mineral oil to increase its pliability. Bland and Montgomery recommend daily bathing with liquid soap and water followed by application of a greaseless cream. On the other hand, not a few experienced obstetricians believe that just as good results are achieved if nothing

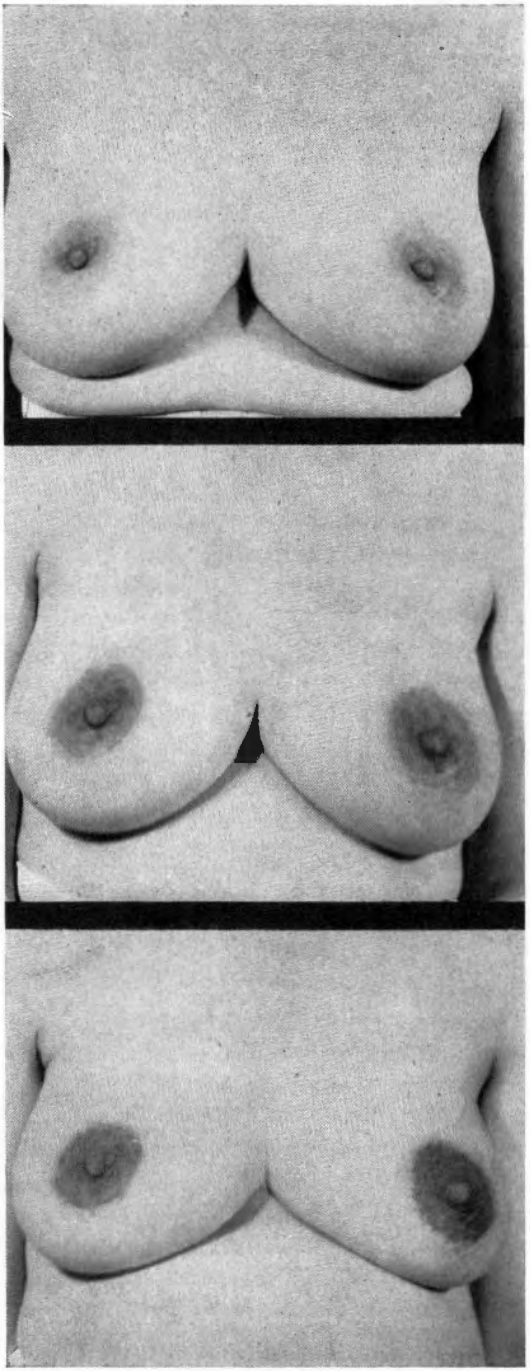

FIG. 133. Normal mammary development during pregnancy. From top down: First third (second month); mid-third (sixth month); last third (ninth month).

whatsoever other than ordinary cleansing is done to the nipples during pregnancy. The breast during this period may be supported by a properly fitted uplift brassiere, compression of the breast, of course, being avoided. If the child is nursed for the usual period and weaned about the ninth month, no special routine is necessary except an adequate diet and vitamin intake for the mother and cleansing of the nipple before and after nursing with boric-acid solution.[1] If the mother complains of tender nipples when nursing, tincture of benzoin may be applied and allowed to dry and the nipple covered with sterile petrolatum. Sterile paraffin paper is then applied to protect the nipples between nursings.

The Nipples

Inverted Nipples. During the latter half of pregnancy non-erectile nipples should be treated daily by gentle traction with the fingers while oil or cream is being applied. A breast pump may be applied to nipples which cannot be everted by traction. The majority of inverted nipples will respond sufficiently to such treatment to enable the infant to grasp them. When inverted nipples fail to respond to treatment, it is advisable to abandon breast feeding and put the baby on a formula. Suppression of lactation is usually effected within a few days to a week if fluid intake is reduced to a minimum and a tight binder applied to the breasts. The breast pump may be necessary from time to time to relieve distention but should obviously be avoided as much as possible because of its stimulating effect. The inhibition of lactation may be expedited by endocrine therapy as described later in connection with painful engorgement.

Fissured Nipples. During the first two weeks of the puerperium the mother should be asked frequently if the nipples are tender and instructed in the proper position of herself and the child during nursing. If tender nipples are treated with tincture of benzoin and protected by petrolatum and sterile paper as outlined above, blisters and cracks can often be avoided. If fissures develop, they should be painted with a 3 per cent solution of silver nitrate and exposed to the air, or an ointment of equal parts of castor oil and bismuth may be used. During this period nursing should be practiced through a nipple shield. It may be necessary to postpone nursing for a few days using a breast pump in the interim. If the fissure does not heal, particularly in the case of deformed nipples, the baby should be weaned rather than risk the danger of mastitis.

[1] In the routine at the Baltimore City Hospitals the nipple is cleansed before and after nursing by wiping with a sponge removed from a 70 per cent alcohol solution.

Painful Engorgement

The clinical syndrome of painful engorgement of the breast is caused by vascular and lymphatic stasis. Pumping the breast to remove milk, therefore, brings little relief. Engorgement may occur on the third or fourth day postpartum before the onset of lactation or when lactation, once established, is interrupted for any reason. The breasts are heavy, painful, and warm, but fever is not present beyond an elevation of one to two degrees. The breasts are hard and tender to palpation, the axillary prolongation is prominent, the overlying skin may become edematous and mottled, milk fails to come, and the nipple may be so flattened that the baby cannot grasp it. The condition is usually not this severe, but when it is the breasts should be bound and ice bags applied. More recently endocrine treatment has been used. Estrogen therapy may be used to prevent painful engorgement. If lactation is to be inhibited because of the condition of the nipples or because the health of the mother contraindicates nursing, estrogen therapy should be started immediately after parturition. Abarbanel recommends 15 mg. of stilbestrol daily by mouth for a period of five to seven days to inhibit lactation. Although other observers have obtained inhibition of lactation with 40 to 150 mg. of testosterone compounds, Abarbanel was unable to duplicate these results even with far larger doses (250 to 500 mg.). If engorgement has already occurred, however, testosterone is useful in relieving the symptoms. For this purpose 5 to 10 mg. testosterone propionate may be injected intramuscularly in a single dose. Relief is generally observed in 6 to 12 hours.

Where painful engorgement has occurred in the first few days postpartum and there are no contraindications to nursing the child, testosterone is preferable to estrogen therapy. The latter decreases the amount of milk for a period of nearly a week if given in sufficient doses to alleviate the symptoms, and in some cases the engorgement returns when treatment is stopped.

TABLE XII

FORMS OF MAMMARY SECRETION

PUERPERAL	NONPUERPERAL
Normal lactation	Anachronistic mammary secretion
Painful engorgement	Inspissated mammary secretion
Insufficient lactation	
Galactocele	
Galactorrhea	

PUERPERAL SECRETION

The Stimulation of Lactation

Normal lactation is dependent upon hormonal influences and the neurogenic stimuli afforded by the act of nursing. The initiation of lactation depends upon a hormone from the anterior lobe of the pituitary (the lactogenic hormone) acting upon a gland which has been properly developed through the influence of estrogenic and luteal hormones. Water balance and nutritional and metabolic factors are also concerned so that in cases of deficient lactation there are a number of possible explanations. Various attempts have been made to increase the milk secretion in nursing mothers by increasing the intake of fluids, particularly of milk, the administration of vitamins A and D, cool baths, and ultraviolet radiation. The use of a breast pump in the absence of vigorous nursing by the infant is the most reliable aid. Injections of the lactogenic hormone to increase the mother's milk have been reported by Kurzrok and his associates, but the use of this hormone has been disappointing as it is of aid only in initiating secretion. The use of progesterone or estrogen in the latter part of pregnancy may be tried in cases where there has been a previous history of poor nursing. No clinical trial of such therapy, however, has been reported.

Accessory Breast Tissue During Lactation

Accessory breast tissue (with or without an opening for milk secretion) may become painfully engorged during lactation. The application of an ice pack to the painful area is usually sufficient to relieve the symptoms. (Daily inunctions of estrogenic hormone into the accessory tissue following parturition may aid in preventing engorgement.)

Milky Discharge or Galactorrhea

A milky discharge may continue for a period of one or more years following the weaning of the last child. When such a discharge is not associated with abnormalities in the affected breast (such as mastitis or a milk cyst) the condition may be referred to as simple or true galactorrhea.

Diagnosis. Galactorrhea is a rare condition and is characterized by the milky nature of the discharge, by the persistence of the discharge since a previous lactation and by the absence of demonstrable pathology in the affected breast. One or both breasts may be affected and the discharge may vary from time to time in character, being at first milky and later serous or thick and creamy. Pain and in-

creased prominence of the ducts beneath the nipple may accompany the discharge.

A history of galactorrhea was noted in only 19 cases over a period of fifty years in the hospital records studied. In the majority of cases, the persistent milky discharge appeared after the second or subsequent weanings (Table XIII). In five patients, galactorrhea occurred after weaning the first child and in two cases the discharge was continuous between the successive weanings of three or four children. Galactorrhea is apparently more common in older women, 11 of 19 patients being 35 years or older. The condition was bilateral in eight cases and unilateral in seven. (The condition existed without attracting the attention of the patient in four cases.) In only three instances did the patient give the history of abscess or caked breast during lactation. One or more dilated ducts were palpated in six cases.

All of the patients were ultimately reported well 2 to 12 years after the last observation. None was treated surgically. The condition usually disappears within 1 to 3 years after weaning but persisted from 7 to 17 years in three cases. The character of the discharge gradually alters from milky to serous, and in bilateral cases of several years' duration the discharge may be milky in one breast and serous in the other.

Differential Diagnosis. Galactorrhea must be distinguished from chronic lactation mastitis and from discharge associated with dilated ducts beneath the nipple occurring toward the menopause.

In PUERPERAL MASTITIS there is a history of "caked breast" or abscess during the period of nursing; an area of persistent induration can be palpated in the affected breast and the discharge, if it occurs, is thicker and has the characteristics of pus when examined microscopically. Lactation, inflammation and a purulent discharge occur in sequence within a period of several months only; in galactorrhea the discharge persists in a normal breast for years after weaning. In rare instances of chronic lactation mastitis, signs of inflammation and a creamy discharge may appear several years after the last lactation but in such instances the patient has been symptom-free in the interim.

DILATED DUCTS beneath the nipple are distinguished from galactorrhea by the characteristic worm-like mass on palpation. The discharge is usually thick and grumous and makes its appearance years after the cessation of lactation, when the patient is at or near the menopause.

Management. Simple hygiene to prevent periductal mastitis is the treatment of choice in cases of galactorrhea. The nipples should be cleansed nightly with soap and water followed by 50 per cent alcohol.

The patient should be assured that the condition has no relation to cancer. Endocrine therapy is worthy of a trial. Injections of estrogen or testosterone may be given in high doses. The results of endocrine therapy are not striking, however. Abarbanel has administered as much as 20 mg. daily of stilbestrol by mouth, with change in the character but without cessation of the secretion.

Galactocele

In the puerperium, mammary cysts with milk-, butter-, cheese-, or soap-like contents may be found. Such milk cysts are extremely rare, and Billroth stated he had never seen a case in his own practice. Schultz was able to find 57 cases, 50 of which had been collected by Nordam prior to 1897.

Onset. The galactocele usually makes its appearance during the course of lactation and is a retention cyst caused by obstruction of

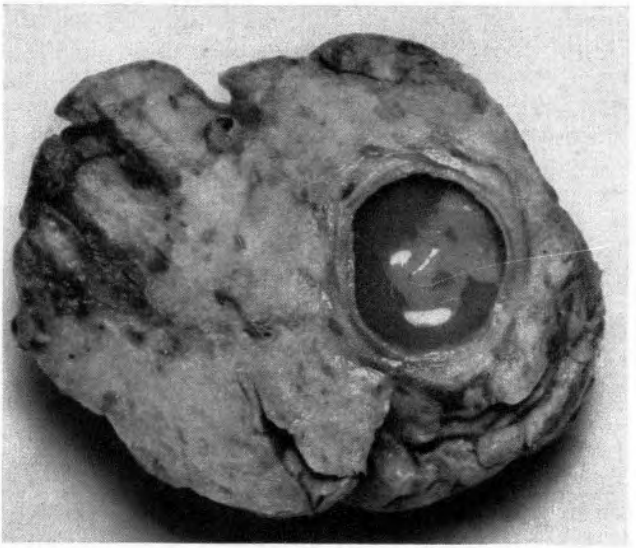

FIG. 134. Cross section of a galactocele. The tumor was removed during lactation and the cavity contained milk.

one or more mammary ducts. Three of the cases collected by Schultz occurred during the latter part of pregnancy and Bouchacourt reported such a cyst which occurred 10 years after the birth of the last child. The cysts vary from 1 to 6 cm. in size and may be unilocular or multilocular. (Fig. 134.) Galactocele is distinguished from abscess formation in lactation by the absence of pain, redness, and other signs of frank infection although the condition may be the result of

TABLE XIII
GALACTORRHEA

J. C. B. NO.	AGE YEARS	NO. OF CHILDREN	AGE YOUNGEST CHILD	MONTHS NURSED	DURATION SINCE WEANING	CHARACTER DISCHARGE	R/L BIL.	OTHER FINDINGS	RESULT YEARS WELL
Ruefly	35	1	16 mos.	4½	1 yr.	Milky	B	Pain	4 discharge continues
24885	36	2	5 yrs.	10	5 yrs.	Gray	B	Breasts lumpy	1
21705	36	4	7 yrs.	9	5 yrs.	Creamy	L	Dark area, few dilated ducts	6
20372	31	3	2 yrs.	12	1 yr.	Milky	L	One small lump	7
20126	34	3	3 yrs.	8	2½ yrs.	Creamy	B	Discharge from one child to next	1
19982	31	1	2 yrs.	5½	1½ yrs.	Milky	R	Cystic area	4
19831	38	2 (9 misc.)[1]	20 yrs.	1	19 yrs.	Milky -r Serous-l	B	Dilated ducts	3
19273	34	3	2½ yrs.	11	7 yrs.	Milky	L	Dilated ducts	1
19241	27	1	16 mos.	4	12 mos.	Milky	B	Dilated ducts Cystic area	7
18887	44	5	2 yrs.	12	15 mos.	Milky	L	Old abscess lump-caking	9
17717	38	6	9 mos.	3	6 mos.	Milky	B	Dilated ducts	6
17606	40	4	3½ yrs.	12	2½ yrs.	Milky	B	Galactorrhea with previous children	3
17443	31	2	2 yrs.	4	20 mos.	Milky	B	Dilated ducts	7
17167	32	2	6 yrs.	10	occasional discharge	Creamy	L	Abscess 2½ yrs. ago—pain	11
17006	38	3	5 yrs.	10	2 yrs.	Milky	R	Pain—lumpy	3
16933	43	1	stillborn 17 yrs.	—	16 yrs. discharge	Milky, then serous	B	Fibro-adenoma removed 4 mos. ago. Dilated ducts	6
16893	31	1	20 mos.	16	3 mos.	Milky Serous	L	Pain—lumpy	3
14512	42	3	9 yrs.	10	2 yrs.	Serous-r Milky -l	B	Lump, since disappeared	12
11728	42	5	2 yrs.	18	3½ yrs.	Serous-l Milky -r	B	Pain	1

[1] Misc. = miscarriage; R = right; L = left; B = bilateral.

infection during a preceding lactation. Its association with lactation differentiates it from cystic disease.

Pathology. At exploration the cysts have a gray or white dome, the contents are milky or resemble butter or cheese. On microscopic examination the wall of the cyst shows an inner necrotic zone, a layer of round-cell infiltration, and several outer layers of compressed connective tissue. The remains of one or more obliterated ducts may be found in the fibrous wall.

Etiology. Usually the obliteration of ducts, which produces the galactocele, is caused by infection during a previous or associated lactation. In rare instances pressure produced by the growth of a fibro-adenoma during pregnancy accounts for the galactocele, and milk cysts may form during lactation in a cystic fibro-adenoma.

Rupture of the galactocele with the formation of a fistula which discharges milk has been reported, and in some cases spontaneous resorption has occurred.

Nine cases of uncomplicated galactocele have been studied.[1] All of these occurred in parous women below the age of 40 years. The age of the last child varied from one to five years with the exception of one patient in whom the galactocele was noted 13 years after the last pregnancy (Table XIV). All the patients remained well following simple excision.

TABLE XIV

GALACTOCELE[1]

PATH. NO.	AGE YEARS	NO. OF CHILDREN	AGE OF YOUNGEST	CAUSE	DESCRIPTION
8166	34	7	2 yrs.	Infection	Milk cyst in areas of infection mastitis
17132	38	several	1 yr.	Infection	Cyst with milk and infection mastitis
27667	29	1	2 mos.	Infection	Cyst containing milk with purulent material
29643	28	1	6 mos.	?	Cheese in cyst
30335	33	3	5 yrs.	Infection	Small cyst with milk
36664	28	3	1 yr.	Infection	Creamy infected material in cyst
39061	25	1	13 mos.	?	Gray-green milky fluid in cyst—2 cm.
39485	20	1	11 mos.	Fibro-adenoma, 3 yrs.	Milk cyst, fibro-adenoma in wall
52000	35	1	13 yrs.	Galactorrhea, 13 yrs. Probably mild infection	Milk cyst

[1] This does not include the asymptomatic cases where the galactocele was found in breasts amputated for cancer.

NONPUERPERAL MAMMARY SECRETION

Incidence

Secretion from the nipple in the form of colostrum, milk, or a serous watery fluid, other than in lactation or pregnancy, has been described under a variety of conditions. Garland examined 400 nonpuerperal women and found that small amounts of serous or milk-like secretion could be expressed from the nipple in 46 per cent of parous women a year or more after weaning. Secretion was found also in 20 per cent of women at the menopause and in 15 per cent of

FIG. 135 FIG. 136

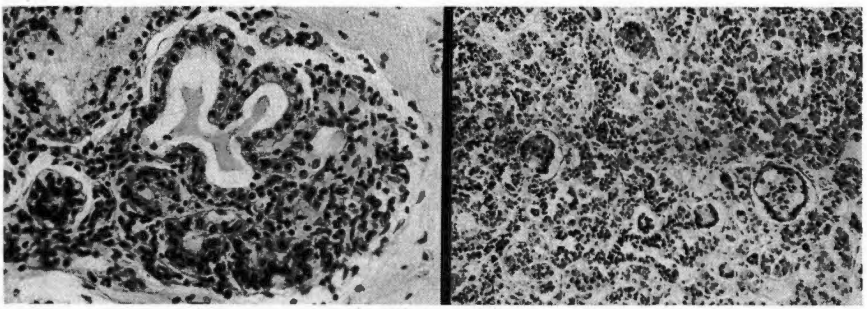

FIG. 135. Anachronistic mammary secretion. Photomicrograph of a partially lactating lobule. Lactation occurred in this breast (removed at autopsy) and was associated with metastases to the pituitary (See text).
FIG. 136. Photomicrograph of metastasis to the pituitary associated with lactation shown above. (Courtesy of Dr. A. Keasbey, Lancaster, Pa.)

women who had not borne children. Weisshaupt termed this ANACHRONISTIC SECRETION. The mammary secretion in women at the menopause is sometimes so marked that it has been referred to as late lactation. Grünbaum described milky secretion in 14 of 21 women recently castrated. Microscopically, the secretion showed fat droplets, colostrum bodies, desquamated epithelium and leukocytes.

In the author's experience, the incidence of nonpuerperal mammary secretion is between 2 and 4 per cent in adult women. A serous or cloudy, milk-like secretion from the nipple (excluding a serosanguineous discharge (see Chap. 14) seen with papilloma or cancer, and the milky discharge of galactorrhea) was found in 27 out of 859 patients with miscellaneous mammary complaints for which no operation was indicated (3.1 per cent).

Etiology

The findings in these cases were as follows: Three subjects had been recently castrated; six were at the menopause; 13, between the ages of 27 and 38, were classified as being in incipient stages of mammary dysplasia (cystic mastitis); and five patients, between the ages of 29 and 37 years, had breasts that were negative for pathology except for a slight increase in the prominence of the ducts beneath the nipple. These findings indicate that nonpuerperal mammary secretion is associated most frequently with deficient or rapidly declining ovarian function. This is borne out by the increased incidence (4.1 per cent) of such secretion in cases of cystic mastitis, where ovarian dysfunction is an etiologic factor in the disease. (Table XV.) In 23 of 72 cases of dilated ducts beneath nipple, which had occurred in parous women near or at the menopause, there was a grumous or serous discharge from the nipple. In 2300 cases of mammary cancer approximately 2 per cent of the patients showed such a discharge. Apparently this is associated with the menopause rather than with the cancer.

TABLE XV

NONPUERPERAL MAMMARY SECRETIONS

(Serous or Cloudy Discharge from the Nipple)

DIAGNOSIS	NO. OF CASES	NO. WITH DISCHARGE	PER CENT
Benign			
Mammary Dysplasia	1176	49	4.1
Mastodynia	375	12	
Adenosis	212	5	
Cystic disease	589	32	
Miscellaneous Mammary Complaints (No operation)	859	27	3.1
Recently castrated		3	
Incipient mammary dysplasia		13	
At menopause		6	
No apparent etiologic factor		5	
Dilated Ducts Beneath the Nipple (Discharge usually thick and dark)	72	23	32.0
Malignant			
Various Forms of Mammary Cancer	2300	45	1.96

Withdrawal of the endocrine stimulation of the ovaries, probably by releasing their inhibitory influence on the anterior pituitary, may lead to mammary secretion. This is probably the explanation of secretion occasionally observed in the breasts of women at the time

of menstruation, the secretion following castration observed by Grünbaum, and the pseudolactation of the menopause reported by various authors. Absent or deficient ovarian function is most common toward the menopause and it is in this group of patients that the most pronounced secretion occurs. The breast at this time has few lobules. The secretion therefore is most pronounced in the small and large ducts; and stagnation of the secretion in the large ducts beneath the nipple gives the clinical picture of dilated ducts beneath the nipple. When the secretion is copious and has the appearance of milk, the condition is more properly termed "late lactation."

The following case illustrates the influence that disturbance of pituitary function may exert on nonpuerperal mammary secretion.

In October, 1935, a married woman, 44 years old, had a radical amputation for extensive mammary carcinoma which involved the lymph nodes. Six months after the operation the patient was readmitted to the hospital with jaundice and an enlarged nodular liver. There was a secretion of milk from the remaining left breast. The patient died two days after the second admission. At autopsy a milk-like secretion could be expressed from the left nipple. The examination of the cranial contents showed no lesion except in the pituitary gland which, on section, contained a distinct, firm, whitish nodule. The pathologic diagnosis was metastatic carcinoma of the liver, primary in the right breast, metastasis to the pituitary gland, and lactating left breast. (Figs. 135, 136.)

Management

In cases with nonpuerperal secretion (excluding serosanguineous discharge) the nipple should be thoroughly cleansed daily in order to guard against periductal mastitis. The breasts require no treatment unless there are independent findings indicating the presence of cystic mastitis, dilated ducts beneath the nipple or a mammary tumor. Secretion following castration or the menopause usually disappears in one to three years. In persistent cases with a copious secretion, high doses of estrogen may be tried for a period of several weeks. If this fails an attempt should be made (by digital pressure in the region around the nipple) to determine the location of the discharging ducts. These may then be excised through a radial incision overlying the ducts at fault.

INSPISSATED MAMMARY SECRETION

(Dilated Ducts Beneath the Nipple)

In senile involution of the mammary gland, cystic dilatation occurs in the terminal tubules and the larger ducts. In parous women at or near the menopause, this dilatation may be most pronounced

in the ducts of the nipple zone and accompanied by inspissated secretion. To this group of cases, Bloodgood gave the caption "dilated ducts beneath the nipple" and referred to it in an article in 1923 as "the varicocele tumor of the breast."

Diagnosis

The condition is characterized by one or more masses beneath the nipple formed by large distended ducts. The women affected are at or past the menopause, have usually nursed two or more children and are inclined to be overweight. The primary symptoms are those of swelling, pain, itching, or redness in the region of the nipple accompanied by a sticky or grumous discharge. The tortuous dilated ducts palpate like a "sac of worms."

The duration of symptoms is brief, usually 1 to 2 months. The condition was bilateral in 30 cases. In our series, dilated ducts beneath the nipple were rarely found in women who had not borne children; there were five single women and one childless married woman. The married patient had had three miscarriages. The five single women were between the ages of 27 and 47 years. Three of these patients had noted a discharge from the nipple and in two of them the condition was bilateral.

A grumous or serous discharge occurs frequently when there are dilated ducts beneath the nipple. The discharge may be creamy, the color of pus, greenish, or brown. The distinct green tinge seen in the inspissated secretion is probably due to its contamination with **Bacillus pyocyaneus.** With further decomposition the color becomes a reddish-brown and must be distinguished from blood by microscopic examination. Occasionally it is thin and resembles milk. A discharge from the nipple was noted by the patient in 23 of our cases. In seven of the patients who had borne children in recent years the discharge was milky or creamy.

On palpation a doughy, worm-like mass is felt beneath the nipple. The dilated ducts form tortuous swellings. Occasionally the impression of a single elongated cyst-like mass is obtained. (Figs. 137, 138.) In some instances induration and retraction of the nipple result from the marked distention of the ducts, giving the impression of cancer.

Infection. Proximity to the surface and the retained secretion render dilated ducts prone to infection. In 12 instances signs of infection, including redness, induration, and increased local heat were leading symptoms. In these cases of periductal mastitis the degree of induration and the tendency for the nipple to be fixed or retracted may lead to an erroneous diagnosis of carcinoma.

Pathology

When the breast has been amputated and subjected to pathologic study the changes in the large ducts are variously interpreted. Some

FIG. 137 FIG. 138

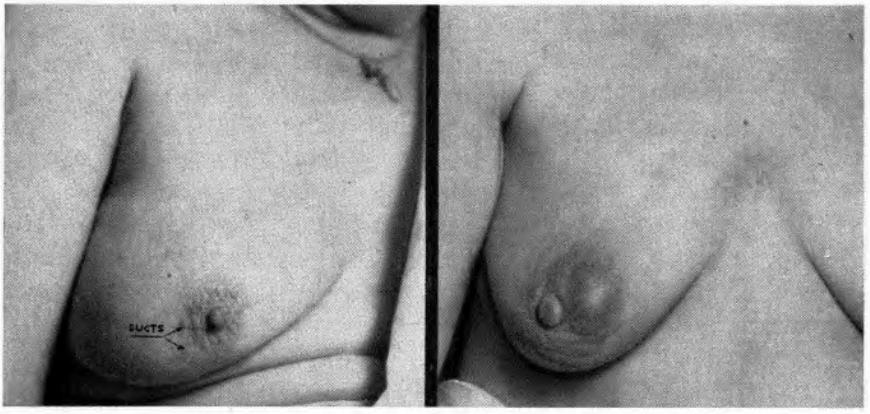

FIG. 137. Dilated ducts beneath the nipple. Photograph showing dilated ducts which palpated like a sac of worms.
FIG. 138. Photograph of cystic dilatation of the ducts.

observers have related the changes to a residual lactation mastitis although the patient may be beyond the menopause and neither

FIG. 139 FIG. 140

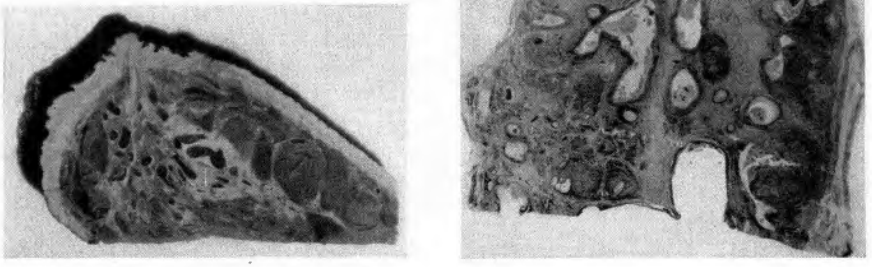

FIG. 139. Gross specimen of dilated ducts.
FIG. 140. Section, from a case of dilated ducts.

lactation nor mastitis has occurred for a period of 15 to 25 years. More recently these changes have been classified as plasma-cell

mastitis, on the basis of the histologic findings. A discussion of these cases is found in the next chapter.

Pathologic study of the breast reveals one or more large ducts distended to a diameter varying from several millimeters to 1.5 cm. (Figs. 139, 140.) The retained material within the duct may consist almost entirely of desquamated intact cells or amorphous inspissated secretion. The desquamated cells are large with pale foamy cytoplasm and have small dense nuclei. The walls of the ducts are lined with several layers of cells; the innermost layer has a secretory border or is undergoing active desquamation. Occasionally the wall of the duct undergoes pressure atrophy with disruption and the retained material may penetrate into the periductal fibrous tissue. The neighboring mammary tissue may contain small lobules or clusters of tubules in which the lining cells show active secretion. In some cases the inspissated material distends even the small tubules. In the neighborhood of the dilated ducts and tubules are aggregates of wandering cells in which lymphocytes and plasma cells predominate. The amount of inflammation is exceedingly variable and is dependent apparently on whether or not infection has taken place and the amount of decomposition in the inspissated material. The desquamated epithelium provokes little reaction while the cells remain intact. When the clinical signs of "plasma cell mastitis" are present, the inflammatory tissue about the large ducts and tubules is usually extensive. Plasma cells and lymphocytes predominate with occasional foreign-body giant cells. In some instances, the microscopic picture is that of a subacute infection with numerous polymorphonuclear leukocytes invading the fat and fibrous tissue about the ducts.

Differential Diagnosis

Dilated ducts beneath the nipple must be differentiated from simple galactorrhea, from cystic disease to which the condition is closely related, and from intracystic papilloma.

In galactorrhea the leading symptom is a milky discharge which dates from the time of the last lactation and has persisted over a period of months or years. Changes in the mammary gland are not an important feature, although the distended ampullae of one or more of the lactiferous ducts may be easily palpated. With dilated ducts there are palpable changes in the nipple zone including distention of the ducts and induration of the tissues beneath the nipple, with or without retraction of the nipple. The material expressed from the nipple is usually grumous, discolored and about the consistency of putty; the patients are at or near the menopause;

the symptoms are of recent origin and do not date back to the period of lactation.

Dilated ducts differ from cystic disease in the absence of a round, distinct tumor away from the nipple, in the character of the material that can be expressed from the nipple, and in the tendency for the condition to occur in postmenopausal women who have had large families. A mild degree of infection in the perithelial tissue is common with dilated ducts and rare in cystic disease.

Dilated ducts accompanied by dark-brown discharge may be confused with intracystic papilloma. The dark discharge is often referred to as bloody by the patient or physician, although microscopic examination would show the presence of amorphous material and desquamated epithelium rather than blood. The palpation of a single tortuous ducts may give the impression of a soft intracystic papilloma and transillumination may cast a shadow. The differential diagnosis in such cases rests upon microscopic study of the character of the secretion or upon exploration.

Dilated ducts distended with lactiferous material may be a feature of residual lactation mastitis. At the menopause, on the other hand, the accumulation of inspissated material in the large ducts may be complicated by infection and in such cases the periductal mastitis is a secondary feature. From the standpoint of diagnosis, the mastitis is the dominant feature and its treatment and differentiation from mammary carcinoma is the important problem.

Prognosis

Patients with inspissated secretion in the larger ducts, not subjected to operation, usually report the disappearance of the condition within a few months to several years if infection does not supervene. There is no evidence in our cases to indicate that secretion retained in the larger ducts exerts a cancer-producing influence on the duct epithelium. This is of interest in view of the significance which has been attached to retained secretion in the experimental production of mammary cancer. Inspissated secretion is found in the acini and terminal tubules in the mammary glands of rats developing cancer in respose to overdosage with estrogens. Bagg increased the incidence of mammary cancer in lactating mice by ligation of the ducts, and has reported on the influence of repeated breeding and removal of the offspring to prevent nursing on the incidence of mammary cancer in susceptible mice. Apparently the ducts, which serve as a reservoir for milk storage between nursings in the lactating breast, are more resistant to retained secretion than the lobular structures which secrete the fluid.

Treatment

Thirty-two of the 72 cases with inspissated secretion were ultimately reported well without operation. In the remainder, one or both nipples were excised, including the surrounding zone of mammary tissue, or the breast was amputated. In all, 14 cases were treated by mastectomy, five of which were bilateral.

Most of the cases of dilated ducts beneath the nipple may be treated conservatively. Tortuous dilated ducts, 1 to several mm. in diameter, not associated with discharge of the nipple, usually require no treatment. Larger ducts distended with inspissated secretion and associated with a discharge from the nipple may be emptied in some instances by firm digital pressure or with the breast pump. When secretion is present, the patient should be instructed to wash the nipples nightly with soap and water followed by 50 per cent alcohol to avoid infection. When the surrounding tissues become indurated or inflamed, exploration to establish diagnosis is indicated. A radial incision should be employed and the distended ducts excised. The nipple should be preserved, if possible.

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6

Mastitis

The various forms of acute and chronic mastitis with abscess or sinus formation are becoming increasingly rare, since pre- and postpartal care of the nipples has reduced the incidence of puerperal

TABLE XVI

FORMS OF MASTITIS

COMMON FORMS	Cases[1]	RARE FORMS	Cases[1]
Acute Puerperal Mastitis	60	Mammary Syphilis	8
Chronic Puerperal Mastitis	64	Boeck's Sarcoid	4
Tuberculous Mastitis	34	Typhoid Mastitis	4
Plasma-Cell Mastitis	15	Fungous Infection	0

[1]The numbers indicate cases in the author's series.

mastitis. Reduction in the morbidity rate of tuberculosis has been accompanied by reduction in the incidence of tuberculous mastitis. The same is true of typhoid mastitis, a relatively rare complication of typhoid fever. Recently more attention has been directed to the nonpuerperal and nonsuppurative forms which may be confused with mammary cancer (Table XVI).

ACUTE PUERPERAL MASTITIS

Incidence

Acute mastitis arising during the first four months of lactation usually presents a characteristic clinical and pathologic picture. The incidence of the disease decreases with each successive pregnancy, more than 50 per cent of cases occurring in primiparae.

In obstetric clinics, mastitis is observed in about 2 per cent of the cases and suppurative mastitis in 0.1 to 0.5 per cent. In our records there are 60 cases of acute lactation mastitis in which tissue was excised or in which the breast was amputated. Fifty of the 60 patients were between the ages of 21 and 35, none more than 45 years. Eight patients noted symptoms when the child was 5 to 10 days old; 14, when the child was 1 month or less of age; and 13, when the child was between 2 and 4 months old. An acute abscess is rare beyond the fourth month although recurrent or late abscesses may appear in chronic lactation mastitis. In rare instances the mastitis may appear during the second half of pregnancy. A discharge from the nipple, other than milk, is uncommon. Milk mixed with pus was noted in several cases and in one case the milk was blood tinged.

Symptoms and Course

Acute puerperal mastitis is often preceded by cracked or painful nipples although some authors believe that this is not an etiologic factor but that the infection reaches the breast through the blood stream from a focus (Smith). Puerperal mastitis is usually seen between the 7th and 21st days postpartum, but may occur as late as 14th to 16th week. There is progressive induration, pain, and tenderness in the affected region and the overlying skin becomes red, hot, and tense. The patient has a fever, a leukocytosis and general malaise. If the fever, which may be as high as 105° to 106°F., persists more than 48 hours, suppuration usually follows. An area of fluctuation develops (Fig. 141), the skin becomes shiny and discolored, and incision releases pus and may disclose an abscess cavity. In its early stages the condition may be aborted by the application of ice bags. The axillary lymph nodes may or may not be enlarged. The forma-

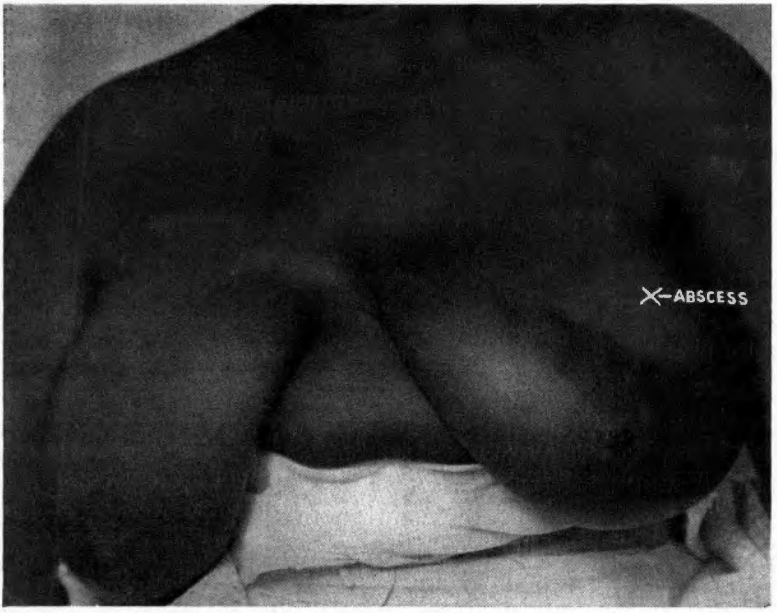

FIG. 141. Acute puerperal mastitis. A large fluctuating mass is visible.

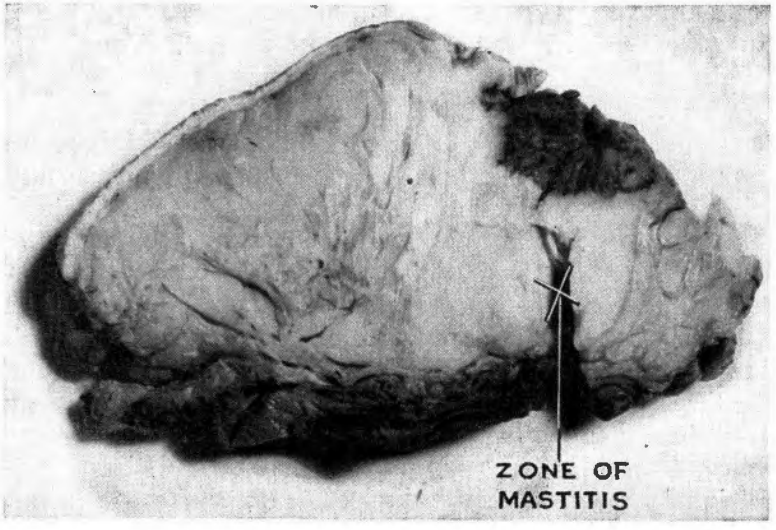

FIG. 142. Chronic puerperal mastitis. Cross section of breast showing the density of the infected tissue.

tion of an abscess and the adherence of the overlying skin may suggest a cancer developing during lactation; in other instances, the tense, inflamed character of the tissue may suggest an acute or erysipeloid carcinoma.

Acute puerperal mastitis is usually divided into three types, the subareolar, the glandular and the interstitial form. In the subareolar, the infection is confined to the region just beneath the nipple; in the glandular form one or more lobes are involved; and in the interstitial form the fat and connective tissues are involved by a diffuse cellulitis which may give rise to a retromammary abscess. The various groups of staphylococci and streptococci are the com-

FIG. 143 FIG. 144

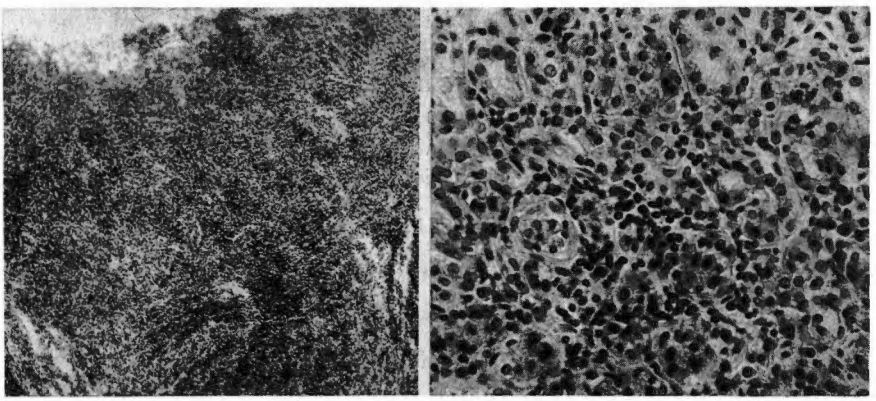

FIG. 143. Photomicrograph of zone about small abscess cavity in chronic puerperal mastitis.

FIG. 144. Photomicrograph of zone of granulation tissue invading a mammary lobule. The appearance is suggestive of carcinoma.

mon pathogenic organisms. The colon bacillus and pneumococci may be the infective agents.

Localization of the suppurative process results in abscess formation. The ragged inner walls of the cavity are covered with heavy deposits of wandering cells. All varieties of leukocytes and lymphocytes are present as well as plasma cells and monocytes. Beneath is a dense, scarred, fibrous zone. (Fig. 143.)

Treatment

If the infection is seen within the first few hours after the onset of tenderness or fever, an attempt should be made to abort it by the application of ice bags and cessation of nursing. The breast should

be supported by a tight binder. If the treatment is successful, the acute symptoms should subside in 36 hours.

Sulfathiazole should be started promptly. While a large series of cases has not been studied, the prompt and favorable response to this drug in those cases in which it has been tried to date has been encouraging.

A relatively recent and effective procedure in the management of acute puerperal mastitis is the use of roentgen therapy. If this is instituted within 24 to 48 hours after the onset of symptoms, less than 10 per cent of the cases go on to suppuration (Elward and Dodek). Should suppuration occur, applications of heat to localize the abscess are indicated, followed by incision and drainage. The incision is made over the fluctuant area, radial to the nipple. Streptococci are usually found in cases with a diffuse cellulitis, and a course of sulfonamide therapy should be given.[1]

The response to penicillin therapy in cases of puerperal mastitis is dramatic. In a recent case with a temperature of 105°, severe prostration, vomiting and delirium, the symptoms subsided and the temperature returned to normal within a period of four days on administering 30,000 units of penicillin intramuscularly every two hours, night and day. At the end of this time the mammary abscess was evacuated. It had shrunken to an exceedingly small size (from over 5 to less than 3 cm.) and the pus was sterile on culturing.

CHRONIC LACTATION MASTITIS

The symptoms and signs of mammary infection may continue after the appearance and healing of one or more abscesses or suppuration may fail to occur. In 64 cases of chronic mastitis the duration of symptoms ranged from 2 months to 28 years. Abscess formation occurred one or more times in only 28 of the 64 cases. The patients varied in age from 18 to 46 years. In 15 cases the signs of infection appeared three or more years after the last lactation. Apparently the number of lactations is not an important factor. Twelve patients had but one, 14 had two and the remainder had more than two lactations.

Suppurative Form of Chronic Mastitis

The majority of cases with chronic lactation mastitis present findings similar to the acute form but less severe. The skin is tense, red, and warm. The breast in the affected region is swollen, indurated, painful and tender. The regional lymph nodes are frequently enlarged and fever and leukocytosis are present.

Diagnosis. With such signs diagnosis is aided by the history or

1 Recently Leinzinger and Bayer treated 64 cases of puerperal mastitis with good results by the applications of ointment containing stilbestrol. The ointment was applied twice daily to a surface 5 cm. wide over the inflamed region. The quantity of milk is decreased in two or three days after starting the inunction.

scar of a previous lactation abscess or signs of abscess or sinus formation if these are present at the time of examination. In this chronic suppurative group, the infectious process differs from the acute form only in the slowness of its onset or in its delay in resolution.

In the following case mastitis had developed in the right breast 21 years previously, again 11 years later, and had recurred intermittently over a period of nine years following the birth of the last child.

A white woman, 47 years old, had 11 children. The eldest child was 26 and the youngest nine years old. The first time she had mastitis in the right breast was with the third child. At that time, 21 years ago, an indurated mass was incised. About 10 years ago there was a definite abscess in the same breast while she was nursing her tenth child. To the patient's knowledge there was no residual lump following this. Since the birth of the last child, nine years ago, the lump has appeared and disappeared repeatedly. Three weeks ago it became red and painful. Examination showed a tumor above and to the outside of the right nipple and two scars in the region below the nipple. The nipple was retracted and the entire lower hemisphere of the breast was indurated. There was a slight area of fluctuation in the mass. The mass was explored and an abscess containing blood-tinged pus was found. A simple mastectomy was performed. The patient was reported well one year later.

In the following case, multiple abscesses and a sinus formed over a period of years during which there were multiple lactations.

A colored woman, aged 41, had 15 children, the eldest 19, the youngest seven months. Abscesses developed in both breasts eight years ago, when because of fissured nipples she was unsuccessful in her attempts to nurse. The breasts healed after multiple incisions. She did not nurse the three subsequent children and no further abscesses developed, although there was galactorrhea following each of these pregnancies. Three years ago with another pregnancy (next to last), abscesses developed, ruptured, and healed spontaneously three months after delivery, although the child was not nursed. Five months after the last pregnancy, although the child was not nursed, the right breast became inflamed and tender and an abscess again ruptured spontaneously. For a period of two months following this there were repeated attacks of inflammation and swelling in both breasts, accompanied by high fever and leukocytosis. At the time of the last examination there were multiple sinuses and abscesses in both breasts. A bilateral mastectomy was performed in March, 1939. The patient was reported well two years later.

The treatment of chronic suppurative mastitis is similar to that for the acute form—heat, incision and drainage. However, it is always important to remove at the time of incision a portion of the abscess wall for biopsy. Carcinoma may develop in an area of unresolved lactation mastitis and following hot compresses ulceration of the wound may simulate abscess formation. If the infection does not respond promptly to the simple measures mentioned, the entire zone

of affected tissue should be excised and further pathologic study made. If multiple abscesses or sinuses develop, simple mastectomy is the treatment of choice if sulfonamide drugs or penicillin therapy are unsuccessful. (See Part VI.)

Nonsuppurative Mastitis or Residual Lactation Mastitis

Diagnosis. The differential diagnosis between cancer and nonsuppurative mastitis may be extremely difficult. Not only the clinical

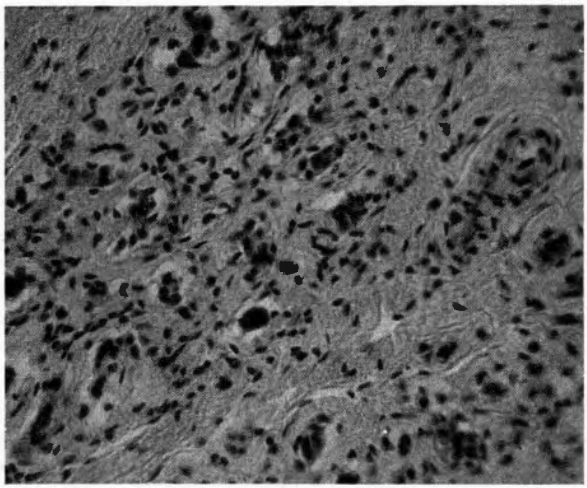

FIG. 145. Chronic nonsuppurative mastitis. Photomicrograph of distorted lobules sometimes confused with cancer.

but the gross and microscopic diagnosis may remain in doubt even after careful study (Cohn). In 11 of the 36 cases without frank pus, the inflammatory nature of the lesion was indicated by heat and redness in the overlying skin and by the systemic reactions of the patient. In the remaining 25 cases, the area of mastitis was described as a definite mass or nodule. In six of these, a local excision was performed because the benign nature of the lesion was evident on examination or at exploration. Cases 1 and 2 are illustrative:

Case 1. A woman, 29 years old, had one child two years of age. An abscess of the right breast was incised in the second month of lactation. This healed but an indurated mass remained above the nipple. Recently it increased in size and became painful. On palpation a mass 5 cm. in its longest diameter with definite edges was felt above the nipple. It was not adherent to the overlying skin. The mass was excised, its inflammatory nature recognized at frozen section and nothing further done. The patient was reported well one year later.

Case 2. A woman, 42 years old, had one child 16 years old. The right

breast had been caked during lactation. Three months ago a small nodule was felt in the right breast. This enlarged rapidly from a few millimeters to 1½ cm. in diameter. The mass was excised. Malignancy was first suspected upon microscopic examination but when additional sections were prepared the lesion was recognized as inflammatory. The patient was reported well one year later.

In the remaining 19 cases of nonsuppurative mastitis an erroneous diagnosis of malignancy was made, either on the basis of the clinical findings or upon microscopic examination. All these cases were treated by radical mastectomy, but none of them has died of cancer.

The long period of time elapsing after the last lactation, together with the absence of reddening or suppuration, makes diagnosis difficult in this group of cases. The zone of induration often is infiltrating in character and may feel like cancer. Dimpling of the skin, retraction of the nipple and palpable axillary nodes are additional misleading signs.

Pathology. At exploration the inflammatory tissue may be found infiltrating fat and fibrous tissue. The fibrous stroma is increased in amount and density in the region of the infection. Foci of friable or softened tissue may be found, and inspissated secretion distends the neighboring ducts. Microscopic examination may show residual lactation in some intact lobules. In the infected zone the lobules are invaded and partly replaced by inflammatory tissue. A few scattered acini or tubular structures remain, others are partly destroyed leaving groups of epithelial cells, without a basement membrane, imbedded in fibrous tissue and wandering cells. These groups of free epithelial cells may give the impression of infiltrating mammary cancer because of their disarrangement and because of variation in the size and staining characteristics of their nuclei produced by degeneration. The ducts in the infected region have a collar of wandering cells. Their lining cells are increased in number and are undergoing desquamation.

The treatment of the chronic nonsuppurative form presupposes surgical exploration to confirm the diagnosis. When this is established, excision of the indurated tissue is indicated.

PERIDUCTAL MASTITIS AND PLASMA-CELL MASTITIS

Periductal Mastitis

Inflammation in and about the larger mammary ducts occurs, sometimes associated with dilated ducts beneath the nipple. The patients affected are usually women who have borne several or more

FIG. 146. Photomicrograph of periductal or so-called plasma cell mastitis. Periductal inflammatory reaction.

FIG. 147. Invasion and disruption of mammary lobules.

children and who are at or near the menopause. The inflammatory signs are neither severe nor of long duration, but because of the time of life at which they occur and the tendency for retraction of the nipple and induration of the surrounding tissues, the diagnosis of cancer is sometimes made. Of 15 cases of periductal mastitis, 12 were associated with dilated ducts beneath the nipple and the remaining three were preceded by a watery or serous discharge from the nipple, of one or more years' duration.

The outstanding pathologic feature of these cases is the epithelial activity in the larger ducts and the periductal infiltration of wandering cells. The ducts are distended by desquamated epithelium or with the amorphous debris of inspissated secretion. The inflammatory exudate may be found in and around the ducts and the number of polymorphonuclear leukocytes may approach that seen with pyogenic mammary infections. More often plasma cells and lymphocytes predominate.

Plasma-Cell Mastitis

Adair, and Cutler, and others, following the pathologic description of Ewing, have established the periductal mastitis arising in association with dilated ducts beneath the nipple as a separate entity under the term plasma-cell mastitis. In the region of the nipple the lesion is characterized by redness, tenderness and induration which fans out over a small sector or triangle. Sometimes the entire breast is involved. Because of the induration and edema of the skin and retraction of the nipple, a diagnosis of carcinoma is frequently made. In rare instances, as in a case observed by the author, the area of induration and redness appears suddenly in the region of the nipple and disappears within several days without residuum. Usually, however, it is persistent and increasingly extensive or resolves slowly, leaving an indurated nodule. One of the diagnostic features is the presence of one or more tense bands or cords traversing the inflamed area (distended ducts) from which a thick dark discharge may be expressed on pressure. The axillary lymph nodes may be enlarged. A mild elevation of temperature and a leukocytosis of 15,000 to 17,000 may be present.

The important diagnostic features of plasma-cell mastitis are the sudden onset of the inflammatory signs in the region of the areola and the tendency for spontaneous regression of the inflammation with the persistence of indurated tissue. Constitutional manifestations are mild or absent.

Treatment. Although simple mastectomy has been recommended,

local excision of the indurated tissue sufficed in our cases. Moderate doses of roentgen-ray therapy (1000 roentgens in divided doses) will cause complete regression in from 10 to 20 days in some cases, and is a valuable diagnostic test.

TUBERCULOUS MASTITIS

Tuberculous mastitis produces a painless mass which enlarges slowly, ultimately breaks down and discharges pus from one or more sinuses. Young and middle-aged adults are usually affected.

Compared to the frequency of tuberculosis in other organs, the disease is extremely rare in the breast. Webster, in 1939, reviewed all of the cases reported following the first description by Sir Astley Cooper in 1829 of a "scrofulous swelling of the bosom," and could find only about 500 cases. Harrington found one case of tuberculosis in his series to every 200 cases of mammary cancer. There were 34 cases of tuberculous mastitis in our series. Nicolson and Gillespie list the following pathways of infection for mammary tuberculosis, finding retrograde extension through the lymphatics most common: (1) through the ducts, (2) through abrasions of the surface of the nipple or skin, (3) through the blood stream, (4) through the lymphatics, (5) through contiguity of tissue. Extension to the breast in our cases was usually secondary to involvement of the cervical, axillary or retrosternal lymph nodes. Kilgore and also Cutler have recorded cases in which the mammary abscess was secondary to pulmonary tuberculosis which had extended through the chest wall.

Symptoms and Course

A painless swelling is the most common symptom of onset in tuberculous mastitis, and in one-third of the cases a discharging sinus develops. Enlargement of the axillary nodes with occasional rupture or a diffuse induration of the breast, pain, and a discharge from the nipple are other symptoms of onset, in the order of frequency given. In some of our cases, swelling and a discharging sinus persisted from one to several years before the patient presented herself for treatment. The average duration is under six months, however, in those cases more recently reported (Nicolson and Gillespie).

The swelling in tuberculous mastitis may take the form of a discrete mass—the so-called nodular type—or give rise to diffuse hardening—the so-called sclerosing type. In either case the overlying skin is reddened and fixed, and the resemblance to mammary carcinoma may be quite marked.

Diagnosis

The outstanding features of the disease are its long duration, its frequent association with active pulmonary tuberculosis, its tendency

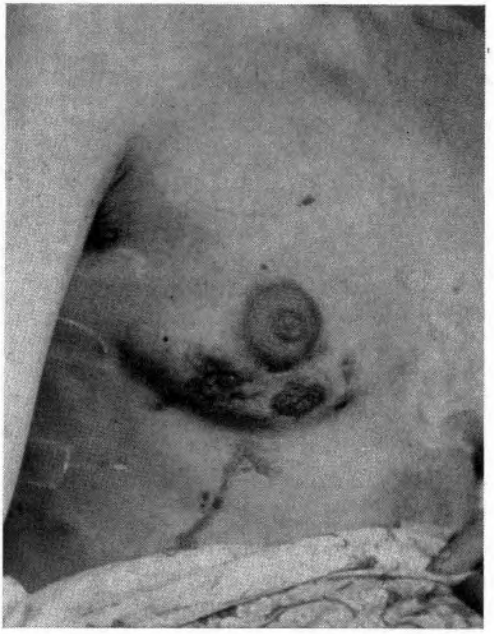

FIG. 148. Mammary tuberculosis. Appearance of the breast.

to sinus formation and the enlargement of the axillary nodes. In the absence of abscess or sinus formation, the presence of tuberculosis elsewhere in the body may suggest the correct diagnosis. Otherwise, exploration and microscopic study are necessary. Usually, caseation is present in one or more foci and in more advanced cases there are multiple, small, pus-containing cavities which may connect with the skin, chest wall or mediastinum via a sinus tract.

Pathology

The microscopic picture is characteristic. Typical tubercles with foreign-body giant cells are found replacing the glandular structures. The lobules in the affected zone are obliterated and the duct walls are replaced by necrotic fibrous tissue. The neighboring fat shows increased vascularity. (Figs. 148, 149.)

Treatment

When tuberculous mastitis is recognized in the stages where the infection is localized and a solitary mass is present, conservative exci-

sion of the involved tissue together with a zone of the surrounding normal tissue is indicated. When the axillary nodes are affected and when multiple sinuses have formed, mastectomy with removal of the axillary nodes should be performed.

If the case is extensive or of the sclerosing type, simple mastectomy is the treatment of choice. When the axillary lymph nodes are involved, excision has been our procedure, although Nicolson and Gillespie have recently suggested roentgenotherapy, a total of 1000 to 1200 roentgens given in divided doses. In all cases, hygienic measures such as those given in pulmonary tuberculosis are in order, including adequate rest, diet and heliotherapy.

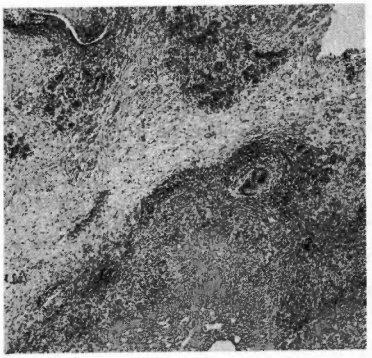

FIG. 149. Photomicrograph showing the margin of a tubercle in mammary tuberculosis.

In rare instances, tuberculous mastitis and mammary cancer may co-exist. In two of our cases mammary cancer developed in the breasts of patients with a long-standing tuberculous mastitis. In another patient, tuberculosis and metastatic mammary cancer were found co-existing in the same axillary nodes. A similar case has been reported by Hollósi.

BOECK'S SARCOID

Boeck's sarcoid is usually confined to the skin and forms multiple, sharply defined cutaneous, and subcutaneous nodules or plaques which are distributed over the face, the extremities or both. These may undergo spontaneous healing, leaving pigmented spots or scars. The lesions do not break down or ulcerate. The disease pursues a slow course. The etiology is unknown.

In rare instances a solid tumor may appear in the breast, with dimpling and adherence to the overlying skin. Increase in size occurs slowly over a period of months or years, without evidence of suppuration or other inflammatory signs. Excision and pathologic examination show a picture similar to tuberculosis, but the acid-fast bacillus cannot be demonstrated.

The author has examined four of these cases. They occurred in adult married women, aged 35 to 54 years, who had had one or more children. The Wassermann reaction was negative and in two cases the Mantoux and von Pirquet skin tests for tuberculosis were also negative. Acid-fast bacillus could not be demonstrated in the sec-

tions. In each case, the mammary tumor was small (1 to 2 cm. in diameter), painful and adherent to the skin. On excision, the growth was firm, solid, white, and without signs of caseation.

In three instances the surgeon performed radical mastectomy for cancer because of the clinical signs and the appearance of the lesion in the gross. All of these patients have survived, two beyond the six-year period, although one of these had only a simple excision. Two of the patients developed nodules on the extremities subsequent to mammary operation.

Treatment

The skin lesions respond to arsenic therapy. Those which appear rarely, as in the bones of the hands and feet and in the breast, are more difficult to treat and require excision.

SYPHILIS OF THE BREAST

The breasts may be affected by syphilis in any of the three stages. A chancre may occur on the nipple or a gumma in the glandular tissue, but secondary syphilis other than a skin rash is exceedingly rare.

FIG. 150

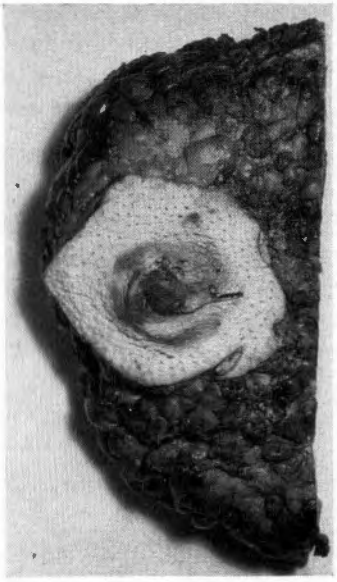

FIG. 151

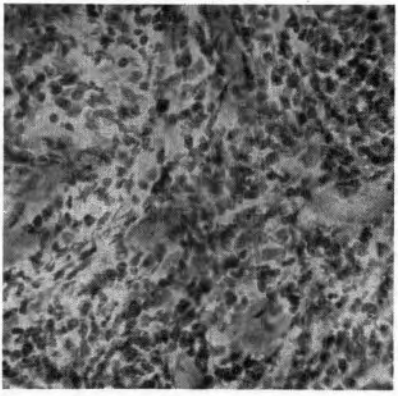

FIG. 150. Mammary syphilis. Gross specimen.
FIG. 151. Photomicrograph of a chancre of the nipple.

Chancre of the nipple was more common formerly, when wet nurses were employed and no Wassermann reaction was taken. The nurse infected the child who in turn infected the nipple of the mother. Fournier, in 1897, found that chancre of the nipple comprised 5.1 per cent of extragenital primary lesions. Chancre of the

nipple is occasionally seen in the male as well as the female. Menville has reported a case in a man, aged 72 years. The chancre produces a shallow ulceration of the nipple with raised edges. It may be mistaken for Paget's disease.

Stokes reports that he has seen acute syphilitic mastitis during the secondary period, which responded to antiluetic treatment and recurred when treatment was temporarily stopped.

Gumma of the breast is a rare complication of tertiary lues and is usually mistaken for carcinoma. Adair reported a case of mammary gumma and collected 46 similar cases from the literature. The lesion is hard, circumscribed, and painless. The axillary lymph nodes are enlarged. The gumma forms and increases in size rapidly; then fluctuation and necrosis occur. The overlying skin may be reddish or purple in color. Malherbe treated a case of gumma of the breast with iodides and mercury and with local applications of mercury ointment. The gumma disappeared, but nine years later the patient returned with mammary cancer at the site of the former syphilitic lesion.

Diagnosis and Treatment

The Wassermann reaction and, microscopically, the inflammatory character of the lesions establish the diagnosis of syphilitic lesions of the breast. There is a prompt response to antiluetic treatment.

FUNGOUS DISEASES OF THE BREAST

Mycotic infections of the breast are extremely rare. Jacobson observed one case of mammary blastomycosis and could not find any reported in the literature. Jacobson's case began with lesions of the skin of the left shoulder, followed by a board-like induration of the tissues of the left breast. The skin was composed of confluent, purplish, translucent pustules. The patient died in spite of iodide therapy.

Cheatle and Cutler state that actinomycosis may begin as a small painful lump in the breast, resembling tuberculosis or gumma. Involvement of the breast, however, is exceptionally rare. Sanford and Voelker, in describing the anatomic distribution of actinomycosis, do not report mammary involvement.

Apparently actinomycosis of the breast is more common among peasant women who work in the fields of Continental Europe. In the European literature are reports both of primary cases where there is no evidence of pulmonary or systemic involvement, and of secondary infections where the breast is involved by direct extension through the chest wall. Deaver and McFarland were able to collect 27 such cases from the literature.

In primary cases the disease enters by way of the skin through superficial abrasions or through the milk ducts. In secondary cases, there is evidence of pulmonary involvement with extension through the chest wall or by retrograde permeation of the lymphatics.

Diagnosis. The mammary lesion is usually accompanied by swelling, with retraction of the nipple and fixation of the overlying skin, simulating cancer. Sooner or later, a fistulous tract discharging the characteristic pus with sulfur granules occurs and makes diagnosis relatively simple. Prior to such abscess formation, however, microscopic study or cultures are necessary to establish the diagnosis.

Treatment. With small, early mycotic infections of the breast, excision, and iodide therapy (Lugol's solution) to the point of tolerance should be used. If the abscess cavity is large, and the lesion is primary, radical mastectomy with removal of the involved lymph nodes should be performed. The prognosis is good if the involvement is localized. In all cases, excision of the diseased tissues should be practiced if possible.

TYPHOID MASTITIS

Acute mastitis is a rare complication of typhoid fever. In 1500 cases of typhoid fever, Osler observed mastitis in only four: three during the course of the fever, and one during convalescence. The findings resemble those found in acute lactation mastitis: there is pain, induration and fluctuation with suppuration in severe cases.

PARASITIC INFESTATION OF THE MAMMARY GLAND

The term "filariasis" is applied to the disease manifestations produced by infestation of the body with the parasitic nematodes of the super-family **Filarioidea.** The larva form of this small, thread-like worm is introduced into the body by the bite of a variety of Anopheles or Aedes mosquitoes. The disease occurs in practically all warm countries and is found in the tropics throughout the world. Clinical manifestations are produced by a progressive obstruction of the lymphatic vessels of the affected part, which results in elephantiasis, usually of the scrotum or lower extremities. According to Strong, the mammary glands are affected in some cases. Elephantiasis of the mammae has been recorded in which the organ descended to the pubis. One such tumor weighed twenty-one pounds after removal. There is no satisfactory method for diagnosis of the disease in the early stages. The treatment in suspected cases is to remove the patient from the infested region to prevent reinfection. Surgical measures are indicated once

elephantiasis is established. In the breasts this consists of simple mastectomy.

Man may be parasitized by ingesting eggs of *Taenia echinococcus,* which is an intestinal parasite of dogs and cats. The liver and lungs are usually involved and other organs such as the breast (Taniana and Storace) much more rarely. A progressively enlarging cyst with encapsulated fluid and parasites develops in the infected organ. A diagnosis can be made by finding the free scolices or their scattered hooklets on microscopic examination of cyst fluid or by a positive intradermal test using such cyst fluid as an antigen. Treatment other than surgical has proved unsuccessful.

MASTITIS NEONATORUM, ADOLESCENT MASTITIS AND CYSTIC MASTITIS

The forms of so-called mastitis in infancy and in adolescence, which occur in both the male and female breast, are forms of hypertrophy, rather than inflammation and are discussed in Chap. 4. A true periductal mastitis may rarely occur in the breasts of infants who have active mammary secretion during the first few weeks of life. The inflammation usually subsides promptly when treated with hot compresses. Some of the cases of unilateral retraction of the nipple seen in young girls are related to this form of infantile mastitis. The forms of cystic mastitis are also noninflammatory and are discussed in Chap. 8 to 12, under the heading of Mammary Dysplasia.

CANCER OCCURRING IN MASTITIS

Cancer occasionally occurs beneath the scar of an incision for suppurative puerperal mastitis or in a persistent lump of residual mastitis. The time elapsing between the acute stage of mastitis and the appearance of the cancer averages 20 years. The appearance of the malignancy is accompanied by pain, a mass which enlarges rapidly, or changes in the overlying skin. In most instances such cancer pursues a fairly rapid and fatal course. A discussion of 38 cases of cancer developing in lactation mastitis is found in Chap. 20.

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7

Influence of Pregnancy and Lactation on Mammary Lesions

Pregnancy and lactation may produce relatively permanent changes in the form of the breast. The breast following lactation and weaning may remain pendulous and give rise to cosmetic complaints. With adequate nourishment adipose and fibrous tissue tend to restore the former size and contour of the organ in a matter of one to several years. In rare instances a definite gravid hypertrophy may occur at this time, leading to marked mammary asymmetry. (Fig. 152.) The treatment of these deformities of the breast have been previously discussed in Chapter 4. The influence of pregnancy and lactation on lesions of the breast is of special interest in tuberculosis, chronic cystic mastitis, benign fibro-adenoma, mammary carcinoma.

MAMMARY TUBERCULOSIS

Mammary tuberculosis becomes evident during lactation more often than during pregnancy. Kilgore has estimated that approximately one-fourth of the cases of mammary tuberculosis come under observation during the nursing period. On the other hand, many obstetricians of wide experience have never observed a case, emphasizing the fact that mammary tuberculosis is far rarer than the pulmonary form.

Symptoms and Diagnosis

Patients developing tuberculosis of the breast in the puerperium are usually less than 30 years of age. The mass in the breast enlarges

rapidly and at first is diffuse and hard, resembling cancer both in its rate of growth and in its firmness to palpation. If operated upon at this time, the gross appearance may resemble cancer, although small points of caseation are present. Later, caseation, abscess formation, and the appearance of one or more draining sinuses make clinical recognition easy.

Treatment

Because of the extent of the disease, which is masked in its earlier stages by the increased density of the gland during pregnancy and lactation, mastectomy is usually required. The axillary nodes are involved and must be removed but not the pectoral muscles. Examination of the lungs for pulmonary tuberculosis, proper diet and rest are important in these cases. The extent and character of pulmonary tuberculosis determine whether or not therapeutic abortion should be performed. The baby should not be nursed. The results obtained are favorable. The majority of the patients are alive and well 10 or more years after treatment. Kilgore reported five cases well longer than the five-year period.

MAMMARY DYSPLASIA OR CYSTIC MASTITIS

Forms of cystic mastitis or mammary dysplasia observed prior to pregnancy and lactation disappear during this period of maximum physiologic function. Kilgore was unable to find the record of a case of cystic, shotty or painful breast which came under observation during this period. The favorable influence of endocrine stimulation of the breast at this time has been previously reported by the author (Lewis and Geschickter). Solitary cysts of appreciable size; multiple small nodules, including minute cysts and papillomas in Schimmelbusch's disease or adenosis; and the tender, dense tissue of mastodynia cannot be demonstrated after mid-pregnancy, as a rule. That these lesions of the breast are eradicated rather than masked by the physiologic impetus of this period is indicated by their failure to reappear after weaning.

Breasts with tender dense tissue and multiple small shot-like nodules are frequently seen in married women complaining of sterility. Treatment of the sterility with estrogen or progesterone therapy, cauterization for endocervicitis, etc., usually results in improvement of the mammary condition, and if pregnancy follows, the last vestiges of the mammary condition disappear.

Mastodynia. Sixteen cases of mastodynia or painful breasts were followed during and after pregnancy and lactation. Two of these

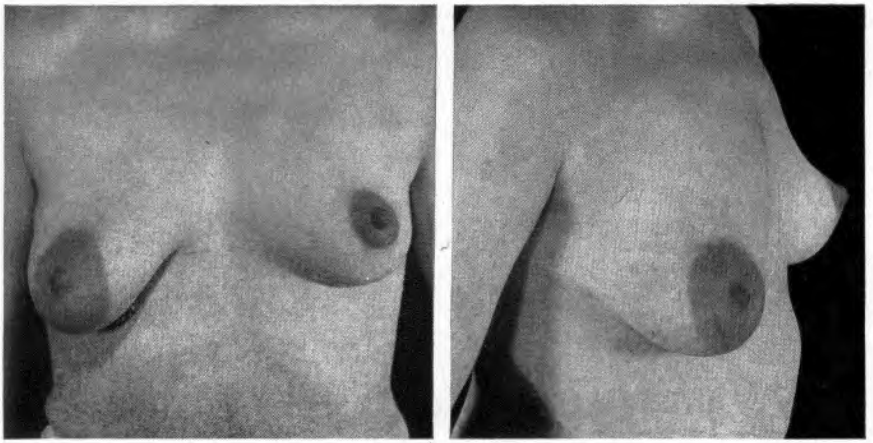

FIG. 152. Unilateral hypertrophy of the right breast occurring at the end of pregnancy and lactation.

patients who had been sterile were treated by estrogen therapy, a year or more previously. The affected tissue in the painful breasts could be identified, during the first two or three months of pregnancy, by its tenderness, but could not be distinguished on palpation as a separate mass after the sixth week because of the density of the rapidly developing gland. By mid-pregnancy symptoms of the previous mammary complaint could no longer be elicited.

Adenosis. Five cases of adenosis with multiple, small, shot-like nodules in both breasts have been followed through pregnancy and lactation. All of these patients are well except one who developed a fibro-adenoma during her second pregnancy and who had intermittent sanguineous discharge from the nipple when last heard from

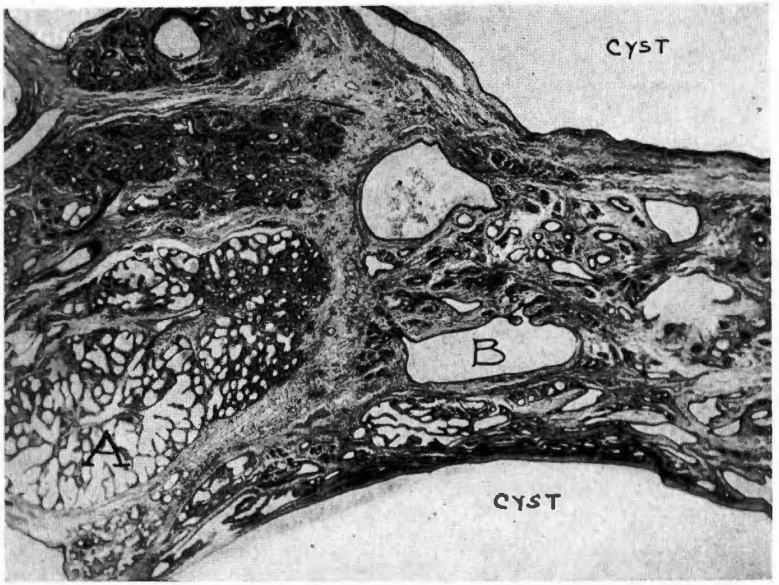

FIG. 153. Cystic change in lactating fibro-adenoma. Photomicrograph of a tumor excised in the sixth month of lactation.

(See Chap. 9). The fifth patient, who is well, had complained of sterility but became pregnant following progesterone therapy. This case has been reported elsewhere (Geschickter).

Cystic disease is seen in women toward the end of the child-bearing period and few cases have been followed during pregnancy. In two of our cases a solitary cyst disappeared during early pregnancy in one instance, and in the other, multiple cysts in both breasts disappeared following lactation.

The disappearance of the lesions of mammary dysplasia during pregnancy is apparently due to the influence of the luteal hormones

elaborated by the corpus luteum and the placenta. This is suggested by experiments on the rat's breast. If high or prolonged doses of estrogenic hormone are administered to the rat, the various changes seen in mammary dysplasia result. These changes, however, do not appear, if the ovaries are luteinized and the rats are made pseudo-pregnant by administering pregnancy urine hormone (Astwood and Geschickter).

FIBRO-ADENOMA

Diagnosis

Because of their occurrence during adolescence or during early sexual maturity, fibro-adenomas are frequently modified by subsequent pregnancy or lactation. In general, the changes in the tumor follow the changes in the surrounding mammary tissue so that the growth of the nodule is rapid during early pregnancy and the tumor may undergo secretory and cystic changes during lactation. In a young married woman the rapid growth of a pre-existing, firm, circumscribed breast nodule which has remained stationary in size since adolescence, is often sufficiently characteristic to permit a clinical diagnosis of both conditions—the existence of a fibro-adenoma and the presence of pregnancy.

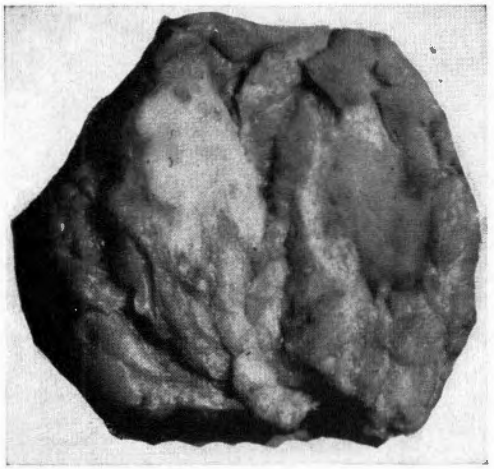

FIG. 154. Fibro-adenoma in mid-pregnancy. Gross specimen of a rapidly growing non-encapsulated tumor excised in the fifth month.

Pregnancy and Lactation Changes. Until recent years relatively little attention was devoted to the changes occurring in fibro-adenomas during pregnancy and lactation. Moran reviewed the literature in 1935 and found only 19 cases. In 1938, Geschickter and Lewis reported 33 additional cases.

Rapid enlargement of the fibro-adenoma may be observed as early as the end of the first month of pregnancy. In one case in which excision was performed during the fifth week, the nodule had already doubled in size. In two other instances marked enlargement occurred

by the sixth week. Enlargement is more rapid during the first half of pregnancy than during the second. Increase in size noted late in pregnancy usually results from secretory changes. In spite of their accelerated growth, these tumors remain encapsulated and freely movable. The overlying skin and axillary lymph nodes are not affected. Tumors of long standing with hyalinization of the connective tissue may remain refractory to pregnancy changes, and those which have responded to a previous pregnancy may remain un-

FIG. 155A

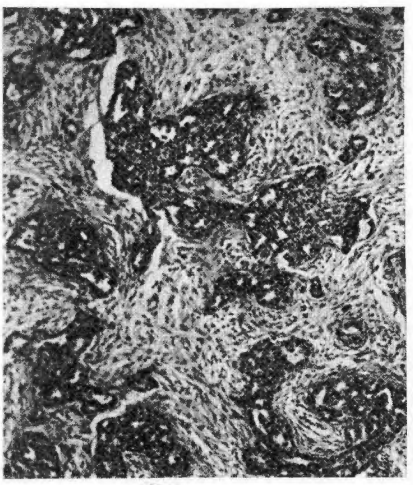

FIG. 155B

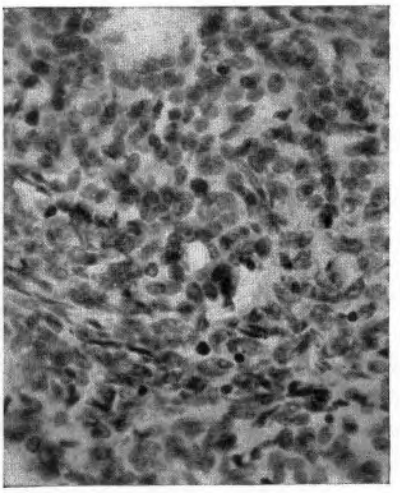

FIG. 155A. Hyperplastic changes in fibro-adenoma during pregnancy and lactation. Photomicrograph of fibro-adenoma excised in mid-pregnancy, undergoing carcinomatous change.

FIG. 155B. Photomicrograph of proliferating fibro-adenoma excised in the third month, of lactation, resembling sarcoma.

changed during subsequent gestations. Multiple fibro-adenomas in the same breast may show varying degrees of response. McFarland (1922) has reported a case of multiple fibro-adenomas removed during pregnancy. The largest tumor showed marked response, the medium-sized tumor showed some changes, but practically no hypertrophy was observed in the smallest nodule. Small fibro-adenomas which remain stationary in size during pregnancy may undergo cystic change during lactation, as in the case illustrated in Fig. 153.

The growth and cellularity of fibro-adenomas in pregnancy or lactation may lead to difficulties in diagnosis, and as a result mutilating operations may be performed under the impression that the lesion is carcinoma or sarcoma. Malignant change during pregnancy

or lactation is exceedingly rare in fibro-adenomas and occurred in only one case of the 33 studied. No similar case is known to have been reported in the literature.

In general, the microscopic changes occurring in fibro-adenomas during pregnancy correspond to those occurring in the surrounding normal breast tissue. The changes in the tumor, however, are more irregular, most pronounced at the margins, and there is a tendency for the tumor at first to exceed and later to lag behind the physiologic development in the surrounding mammary tissue (see Chap. 13).

Endocrine Role in Development

Recent studies indicate that the changes observed in fibro-adenomas and in the surrounding breast during pregnancy and lactation are the result of hormonal influence. The failure of the fibro-adenomatous tissue to respond to the same extent and in the same manner as normal breast tissue suggests that the tumor is more sensitive to certain hormones than to others.

The growth of mammary ducts and periductal fibrous tissue in both animals and human beings is stimulated by estrogen. The histology of fibro-adenomas removed at puberty is characterized by growth of ducts and stroma without evidence of lobule formation. This suggests that these neoplasms represent an increased estrogen response on the part of the tissue involved. Estrogen, which is secreted by the ovarian follicle in increased amounts at puberty, acts as a stimulant to the growth of fibro-adenomas and accounts for their frequent appearance in patients at this period. The concentration of estrogen in the blood is again greatly increased during the first third of pregnancy. Growth of the fibro-adenoma as well as of the surrounding breast results in the ramification of mammary tubules and the increase in periductal fibrous tissue in both the tumor and the normal breast. Heiman and Krehbiel noted that estrogen in combination with anterior-pituitary–like hormones increased the number of spontaneous fibro-adenomas in rats and stimulated hyperplasia of duct and fibrous tissue in the normal breast. As the growth of the tumor is maximal at the periphery, the physiologic changes of pregnancy and lactation are usually observed in these newly formed tubules at the periphery of the fibro-adenoma.

Treatment

Prompt excision of fibro-adenomas is indicated, particularly during the childbearing period, in order to avoid the difficulties in

diagnosis and treatment associated with rapidly enlarging tumors in pregnancy and lactation. Pregnancy is an added reason for promptness of treatment, rather than a reason to postpone operation.

MAMMARY CANCER

Susceptibility

Evidence that susceptibility to mammary cancer is influenced by the number of children, failure to bear children, the number of lactations, or failure to nurse is still inconclusive. Numerous studies, however, would seem to indicate that cancer of the breast is somewhat more prevalent in women without children or large families or in mothers with a history of abnormal lactation (see Chap. 17). The rapid involution of the mammary gland following abortion and following weaning indicates that the breast is capable of disposing rapidly of the increased cellularity of the glandular tissue at this time. On the other hand, the number of refractile mammary tubules and lobules in the mammary gland which microscopically do not respond to the impetus of pregnancy or lactation indicates that the beneficial effects of this period of physiologic activity are not shared uniformly by all the mammary tissue present.

Pregnancy and Lactation Effects

Regardless of opinions concerning the importance of the influence of pregnancy and lactation on susceptibility to a future mammary cancer, there is general agreement that a mammary cancer already present or arising in pregnancy or lactation is unfavorably influenced. Most of the women affected by cancer at this period are less than 40 years of age. In addition to the early age, the vascularity of the gland at this time and the intensity of endocrine influences result in an increased rate of growth and spread of cancer.

Prognosis

During Pregnancy. Fifteen cancers diagnosed during pregnancy and four noted shortly after miscarriage have been studied and, in addition, there have been 39 cases operated upon during or shortly after lactation, a total of 58 cases. None of the 15 patients operated upon during pregnancy survived the five-year period. On the other hand, 23 per cent of those in whom diagnosis and treatment took place during or shortly after lactation were well at the end of five years (the survival rate for mammary cancer in general is about 35 per cent).

TABLE XVII

MAMMARY CANCERS IN PREGNANCY AND LACTATION

RELATION TO PREGNANCY AND LACTATION	NO. OF CASES	AGES	NO. OF PREGNANCIES	EXTENT	ACUTE CANCERS	AVERAGE DURATION	RESULT
First half pregnancy	5	28–40	1 to 5	3—under 5 cm. 2—over 5 cm.	1	6.0 mo.	5—dead, 7–32 mo.
Second half pregnancy	10	26–42	8—1 to 2 2—4 to 6	4—under 5 cm. 6—over 5 cm.	1	8.6 mo.	10—dead, 1–33 mo.
After miscarriage	4	36–44	1 to 6	2—under 5 cm. 2—over 5 cm.	1	25.5 mo.	2—well, 5 yr.+ 2—dead, 1–2yr.
Less than 6 months of lactation	9	32–16	1 to 9	9—over 5 cm.	2	8.3 mo.	7—dead, 5–36 mo. 2—well over 5 yr.
6–12 months of lactation	13	21–46	1 to 10	4—under 5 cm. 9—over 5 cm.	2	7.1 mo.	3—well over 5 yr. 10—dead, 3–36 mos.
End or just after lactation	17	30–50	1 to 11	7—under 5 cm. 8—over 5 cm.	4	11.4 mo.	4—well over 5 yr. 13—dead, 6–36 mos.

In the 15 cases of cancer in pregnancy, the patients were between the ages of 25 and 42 years, the majority being primipara; five of the cases were diagnosed during the first half of pregnancy and 10 in the latter half. In most cases the duration of the cancer exceeded the duration of the pregnancy, indicating that the cancer was already present at the onset of gestation. The duration of symptoms averaged six months in the tumors observed in the first half of gestation and eight and half months in the second half. The size of the growth was between 4 and 6 cm. in diameter at the time of examination. A rapidly growing mass, pain, and changes in the skin were the

FIG. 156. Gross specimen of a diffuse carcinoma excised during pregnancy.

leading complaints. In two cases diffuse reddening of the overlying skin was present, giving the clinical picture of inflammatory cancer. Nine cases were operated upon during pregnancy and six shortly after parturition. None of these cases underwent therapeutic abortion although this was advised in two instances. All of the patients died within a period of 1 to 33 months following treatment.

During and After Lactation. Mammary cancer observed during or shortly after lactation has a better prognosis than cancer complicated by pregnancy. The same is true of cancers seen after miscarriage. Acute cancer with a rapidly fatal termination is more common at this time, however, and occurred in 8 out of 39 cases. If these acute cases are excluded, the prognosis for cancer in lactation is approximately the same as that for other forms of infiltrating mammary cancer.

Nine cases were observed during the first six months of lactation. These had an average duration of about eight months and all were over 5 cm. in diameter. Only two patients survived the five-year

period. Among 13 cancers observed between the sixth and twelfth months of lactation, the average duration of symptoms was approximately seven months. Four of these were small tumors; three patients survived the five-year period. Among 17 cases observed at the end or just after lactation the average duration of symptoms was just under one year. Seven were less than 5 cm. in diameter; four patients survived the five-year period.

In cases of mammary cancer during lactation, the baby should be weaned and the patient warned against subsequent pregnancies or sterilized.

There is no adequate explanation for the difference in prognosis between cancers treated during pregnancy and those treated during or shortly after lactation. From cases studied by the author and those reported by Taylor and Meltzer, it is evident that acute cancer may arise in either pregnancy or lactation because of the increased vascularity of the organ during this period. The unfavorable influence of pregnancy has been attributed to a calcium deficiency by Behan. The increased estrogenic stimulation of the breast at this time has also been cited as an important factor.

The estrogen content of the blood is markedly increased throughout pregnancy but during the latter half of pregnancy this is counteracted, as far as the breast is concerned, by increased amounts of luteal hormone. The estrogenic output drops a few days after parturition and is low during lactation. The unfavorable effects of estrogen on mammary cancer, which have been demonstrated experimentally, are apparently at a maximum, therefore, in the first half of gestation. A more detailed discussion of cancer in pregnancy and lactation is found in Chap. 20.

Treatment

At the present time, no permanent cure for mammary carcinoma occurring during pregnancy has been recorded. The consensus is that irradiation rather than surgery is the treatment of choice. There are insufficient data on the effects of therapeutic abortion, but to be effective it must be done prior to the last third of pregnancy.

SURGERY OF THE BREAST IN PREGNANCY AND LACTATION

Bloodgood recommended the following rules for operative technic on the breast during pregnancy or lactation:

1. The patient is prepared for anesthesia and operation as in nonpuerperal cases.
2. During lactation, the breast is emptied by nursing or by a milk pump just before operation. After operation, it is safer to stop nursing and put the baby on a formula.
3. One must remember to deal properly with the increased vascularity of the breast at this time.
4. If the patient is lactating there will be leakage of milk from the closed wound or drain. This means daily dressings with every aseptic and antiseptic precaution.
5. Since anxiety and worry interfere with lactation and with the normal course of pregnancy, the patients during this period must be handled in the most tactful and optimistic manner.
6. The most important part of treatment is promptness of action. This is especially true in pyogenic or tuberculous mastitis and malignant tumors. When the benign fibro-adenoma is growing rapidly or the galactocele is getting larger, nothing is gained by delay.

The common conditions of the breast requiring surgical intervention during pregnancy and lactation are, in their order of frequency: acute mastitis, carcinoma, fibro-adenoma, chronic infectious mastitis, tuberculosis, and galactocele. Cancers developing during this period are often of the acute type and accompanied by inflammatory signs. It is important therefore to remember DaCosta's rule that in any case of supposed mastitis persisting for more than two weeks, biopsy is indicated to rule out inflammatory cancer.

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PART III

CHRONIC CYSTIC MASTITIS OR MAMMARY DYSPLASIA

8. Mastodynia
9. Adenosis or Schimmelbusch's Disease
10. Cystic Disease
11. Endocrine Aspects of Chronic Cystic Mastitis
12. Relation of Chronic Cystic Mastitis to Cancer

ORIENTATION

The term "chronic cystic mastitis," not accurate in its strict sense, is applied to a group of benign conditions in the breast which are neither inflammatory nor truly neoplastic. The classification of the several forms of the disease and its relation to cancer have been much debated. This group of abnormalities, also termed fibrocystic disease, mastopathy or mammary dysplasia, includes painful mammary tissue of increased density (mastodynia), nodosities resulting from epithelial hyperplasia (adenosis) and cysts resulting from secretory changes (cystic disease). Recent studies indicate that these forms of mammary dysplasia result from abnormalities in the secretion of the ovarian hormones.

More than a century ago, the solitary cyst of appreciable size was described by Sir Astley Cooper. Before the present century, bilateral polycystic disease had been emphasized by Reclus and the variety marked by epithelial proliferation had been reported by Schimmelbusch. Cooper recognized the benign nature of the cysts and Brodie noted that the disease was confined to the period of the sexual life of women. Schimmelbusch suggested the possibility of malignant change in the proliferative form, known today as adenosis.

In the chapters of Part III devoted to mammary dysplasia, approximately 1200 cases have been analyzed. The forms of the disease have been separated into three groups. The incipient form—mastodynia—comprises those cases in which neither cysts nor epithelial hyperplasia are outstanding. The remaining two groups are made up of cystic disease, characterized by the formation of one or more cysts of appreciable size and adenosis characterized by the formation of minute cysts and by epithelial hyperplasia. A chapter dealing with the endocrine aspects of mammary dysplasia and another on its relation to cancer are included.

The forms of mammary dysplasia, collectively, are in the author's experience the most common mammary abnormality in women during sexual maturity. The predisposing factor to the disease is postponement or absence of the normal functions of pregnancy and lactation. The three forms of dysplasia—mastodynia, adenosis and cystic diseases—are to a certain extent inter-related. Mastodynia is often an intermittent or self-limited condition. Some cases, however, terminate in proliferative tissue or adenosis and a small number develop cysts of appreciable size. None of our adequately followed cases of mastodynia developed mammary carcinoma. Adenosis is a more per-

sistent condition than mastodynia and may terminate in the formation of multiple cysts. In 3 per cent of our cases mammary carcinoma ultimately developed. In cystic diseases, the cyst usually develops abruptly near the menopause in a previously normal breast. About 1 per cent of these patients will develop mammary carcinoma.

Cessation or diminution of the luteal function of the ovary with persistence of its estrogenic function apparently is the underlying etiologic factor in all forms of chronic cystic mastitis. The lobule is the mammary structure primarily affected. Mastodynia is characterized by partial suppression of lobule formation; adenosis, by hyperplasia of the lobular elements with various degrees of involution; and cystic disease, by dilatation of the lobules with metaplasia of the lining cells into a form of duct epithelium, which may resemble that of a sweat gland. This endocrine interpretation of the pathology of mammary dysplasia renders obsolete the inflammatory theory of its origin which gave rise to the misnomer, "chronic cystic mastitis." True mastitis whether associated with lactation or whether periductal in origin is always the result of infection by microscopic organisms that can be demonstrated by culturing. The so-called productive mastitis and adolescent mastitis of older authors are forms of hyperplasia and hypertrophy which owe their origins to physiological factors rather than to inflammation. This new knowledge forms the basis of the methods of endocrine therapy described in Chapter 11.

Two fundamental factors should govern treatment in cases of mammary dysplasia. The first is the necessity for accurate diagnosis; and the second is the statistical liability to malignant change. If the clinician can differentiate by palpation the dense tender tissue found in mastodynia and adenosis from the more definite mass of malignant tumors and if aspiration of a cyst reveals clear or cloudy fluid without evidence of blood, conservative measures are justifiable. However, if doubt exists surgical exploration and competent pathologic examination of the excised tissue are indicated.

The statistical liability to cancer in mammary dysplasia has been much discussed but only recently have accurate follow-ups on large series of cases become available. Control figures for the normal population of the same age period likewise have been compiled only recently. These data, which are presented in Chapter 12, indicate that mastodynia does not predispose to mammary carcinoma, that blue-dome cysts are followed by malignancy within 10 years in 1 per cent of the cases, or twice the normal expectancy, and that adenosis is followed by malignancy within 10 years in 3 per cent of

the cases, which is seven times the incidence for the control group. The incidence of cancer in 793 cases of mammary dysplasia in the author's series followed for an average of 10.2 years is 1.26 instead of the normal expectancy of 0.42 per cent. Only in adenosis is there a significant predisposition to malignancy, which in rare instances may justify prophylactic simple mastectomy when there are recurrent indurated nodules following a previous excision of benign proliferating epithelial tissue.

8

Mastodynia (Painful Breasts)

SYMPTOMS AND DIAGNOSIS
DIFFERENTIAL DIAGNOSIS
PATHOLOGY
CLINICAL COURSE AND PROGNOSIS
TREATMENT

Persistent pain, exacerbated in the premenstruum and referred to an indurated region of the breast which is tender to palpation, is relatively common in mature women. The tender tissue may be confined to a single sector of one breast, or both glands may be tender and granular when examined. (Figs. 157, 158.) In spite of its frequency, the clinical and pathologic features of this condition have remained ill-defined. Bloodgood described the bilateral form of painful breasts in 1922. He did not, however, emphasize the mammary pain or the form characterized by a solitary focus of tender, indurated tissue.

In 1928 Semb described the solitary form under the term "fibroadenomatosis simplex." He states "the lesion must be said to have received relatively little attention in proportion to its frequency. Clinically, it presents large or small thickenings of firm consistency in the mammary gland palpable as 'tumors' and giving grounds for excision." Pain was recognized as a prominent feature in only 13 of 27 cases studied by Semb.

In 1931 Cheatle and Cutler described a form of painful breasts under the term "mazoplasia." They called attention to the tenderness and the finely nodular surface. On histologic grounds, they believed the condition similar to the hypertrophy of normal puberty and to the lumpy postlactation breast. They state that mazoplasia is present in some degree in the breasts of all women who have borne children; although in a tabulation of 15 cases treated by them, seven were single and two were married but childless.

The present study is based on 375 cases. These cases, observed over a period of fifty years, reflect the changing conceptions of the nature

of this condition. In the earlier cases treatment varied from mastectomy to one or more excisions. No surgery was used in 240 patients observed in the past two decades. Sixty recent cases received endocrine therapy; endocrine assays on the urine were done to measure both estrogenic and corpus-luteum function in some of these.

FIG. 157

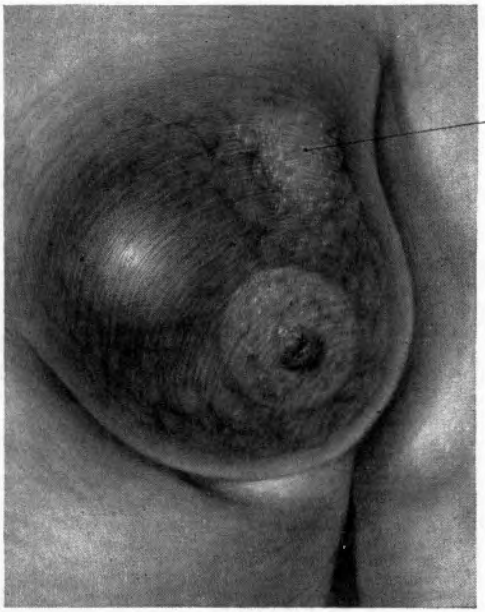


FIG. 158

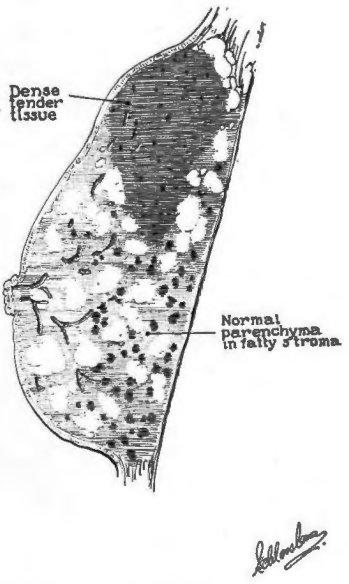


FIG. 157. Drawing to illustrate the characteristics of mastodynia on palpation. The affected tissue is raised, granular, tender, and has ill defined margins.
FIG. 158. Drawing of cross section of the same breast.

In the common form of painful breast, the mammary changes are localized and tend ultimately to regress. The breasts are of normal or of slightly increased size, and the patients affected are 30 or more years of age. In the second and smaller group, the breasts are small, the changes occur early, often in the twenties, are diffuse and bilateral. The condition once established tends to progress.

SYMPTOMS AND DIAGNOSIS

Mastodynia is characterized by pain which is gradual in onset over a period of months. The pain is worse in the premenstruum and is referred to a portion of the breast (usually the outer and upper

quadrant) which is tender, firmer, thicker, and more granular than the surrounding mammary tissue. The condition may be unilateral or bilateral and is more common between the ages of 26 and 40 years in single women or in married women who are of low fertility.

TABLE XVIII

DATA ON 375 CASES OF PAINFUL BREASTS

I—AGE

20–25	29
26–30	68
31–35	89
36–40	93
41–45	49
46–50	26
51–55	21
	375

Average Age—35 yrs.

II—MARITAL

Single	76
Married	216
Married—childless	66
Married—miscarriage (incl. 4 ectopic)	17
Married—1 child	41
Married—2 or more children	47
Married—no data	45

III—DURATION

Days	3	av. 3
Weeks	12	av. 2
Months	122	av. 4
Years	124	av. 3.4

Average Duration 21.5 mos.

IV—SYMPTOMS

Pain	355
Swelling	191
Discrete nodule	36
Discharge (all serous)	12

V—LOCATION

Bilateral	203
Unilateral	172
Upper outer quadrant	84
Mid-upper quadrant	28
Upper inner quadrant	7
Nipple zone	12
Mid-lower quadrant	14
Lower outer quadrant	6
Lower inner quadrant	5

VI—ENDOCRINE FINDINGS

Irregular menstruation	18
Difficulty nursing	18
Thyroid enlargement	3
Improved by pregnancy	15

VII—TREATMENT

No surgical treatment	282
Excisions	64
Amputations (12 bilateral)	29
	375

VIII—RESULTS

Cases Living and Well

Under 3 years	97
Over 3 years	37
Over 5 years	105
Over 10 years	106
Over 15 years	30
Followed 5 yrs.+	241

Tendency to Sterility. A study of these cases emphasizes the tendency to sterility in married women with this condition, and the frequent inability to nurse in those who have borne children. The

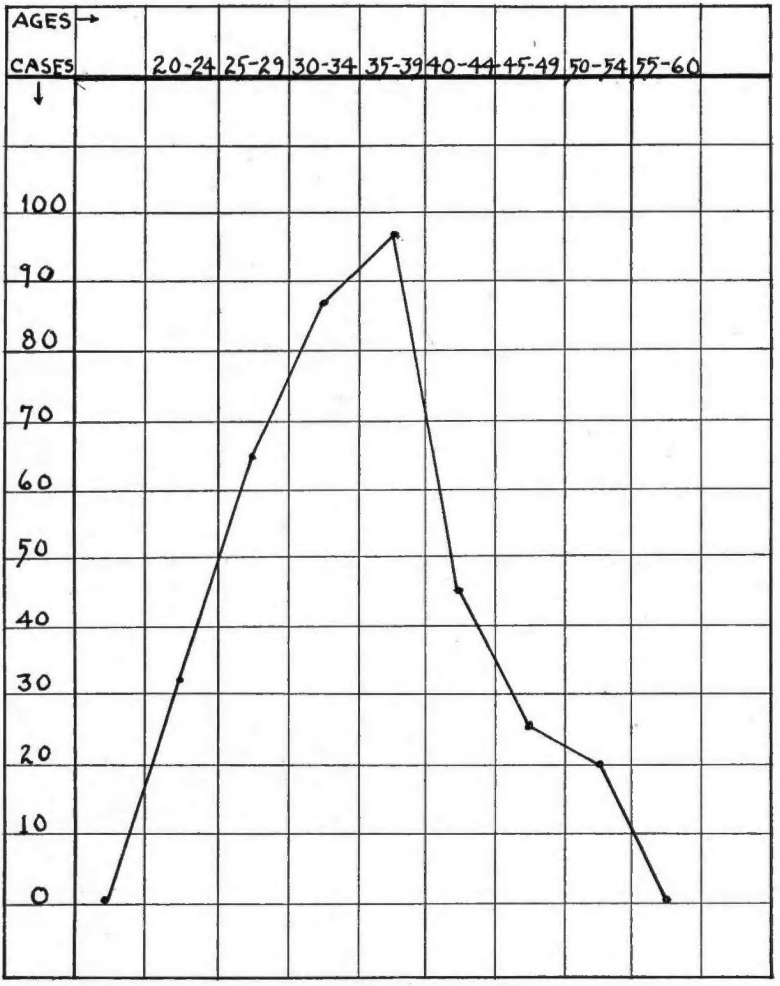


FIG. 159. Chart showing the age incidence of 375 cases of mastodynia.

condition is rare in women with large families; in the present series there were only eight patients with more than three children. The menstrual periods tend to be closer together than normal.

The average age of women with painful breasts is approximately 35 years. It was 33 years in the series of patients studied by Semb (Fig. 159). Married women predominate in the ratio of three to one, the ratio in the normal population for the corresponding ages being

approximately five to one. Data regarding pregnancy were obtained from 171 married women with this condition. Eighty-three patients (48 per cent) were childless; these included 13 who had had one or more abortions and four who had ectopic pregnancies. Of the remainder (with eight exceptions) approximately equal numbers had either one or two children (Table XVIII). Some of the married women with this complaint are more concerned with sterility than with the condition of their breasts. Endometrial biopsies, where taken, were normal. Among those who had borne children, 18 were unable to nurse because of insufficient milk.

Pain. The outstanding symptom is pain referred to a tender region in one or both breasts. Although the average duration of the symptoms for which the patients sought advice was 21.5 months, the majority stated that their breasts had been painful or sore before the menstrual period for a number of years. Usually, mammary pain and tenderness which were at first mild and premenstrual, then became more severe and prolonged, finally lasting practically throughout the entire cycle. The pain is sufficient in some cases to keep the patient awake at night and may radiate down the arm or over the shoulder to the scapular region on the affected side. The use of the arm may aggravate the pain, and fear of cancer is often aroused.

In a small group, swollen indurated tissue rather than pain was the conspicuous feature. (Cases of so-called mammary nodosity.) Some of these patients had a discrete, dense nodule excised for pathologic study in order to rule out the presence of cancer.

Lump. Approximately one-half of the patients noted a lump or swelling in the tender region. The swelling frequently varies in size, and is larger before and smaller after the periods. Sometimes the lump and symptoms disappeared for months then returned, or the swelling regressed in one breast and reappeared in the other, after an interval of months or years, a so-called disappearing tumor. Mammary pain and tenderness were usually most marked in one breast, but the condition was bilateral at the time of examination in 203 women and unilateral in 172. Thirty-three patients had noted recent mammary enlargement and 12 (4 per cent) had a serous discharge from one or both nipples. (Fig. 161.) Dimpling or fixation of the overlying skin was not noted.

Although in the majority of these cases the histories report regular menstrual periods, in 21 consecutive cases observed by the author the interval between periods, on careful questioning, was found to be 24 to 26 days in 19 cases. The histories of the entire series revealed periods at 21-day intervals in several patients and 18 had either marked irregularity or "flooding."

On examination, swollen tender tissue is palpated which has increased thickness, density or hardness. An irregular doughy mass of dense tissue may be felt. The painful tissue resembles the "caked" area in acute mastitis. The most common finding is an elevated zone, with a flat granular surface, 3 to 5 cm. in its greatest diameter, occupying the outer and upper quadrant. When mild pressure is exerted

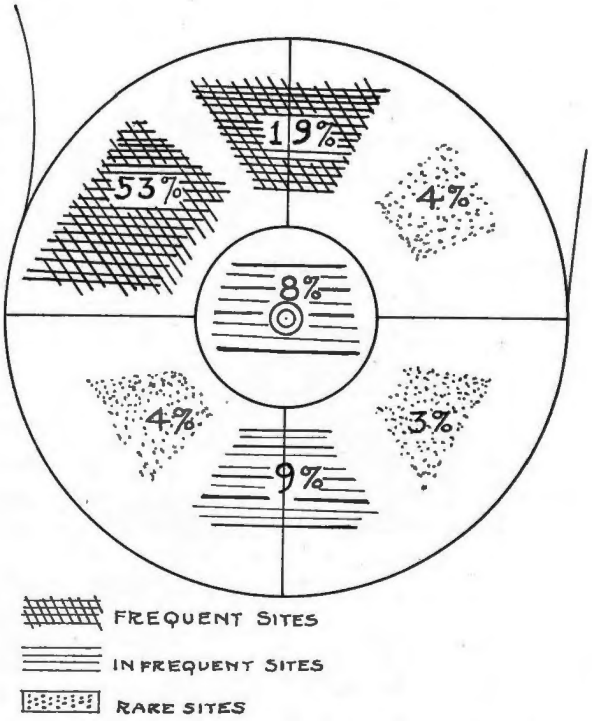


FIG. 160. Chart showing the location of the tender tissue in cases of mastodynia.

here, the patient winces. Although one or more margins of the tender tissue may be felt as a distinct disk-shaped mass, demarcation from the surrounding breast is usually absent. The region of the outer upper quadrant, of the mid-upper zone, of the mid-lower and of the central zone was affected in the order of frequency given (Fig. 160). In addition to tender dense tissue, indefinite nodularity may be palpated. These areas are coarsely granular and do not contain the definite millimeter to pea-sized nodules found in cases of adenosis or the hard distinct borders found with carcinoma. A firm, round edge of mammary tissue in the outer hemisphere can be felt when the breast is grasped between the examining fingers.

Breast Types. Women who complain of painful breasts may be separated into two groups:

In the larger group the patients are between 30 and 40 years of age. The breasts are well developed or have recently increased in size, and the tender tissue forms a swollen granular zone, in a breast which is otherwise negative to palpation. Unilateral and bilateral cases occur with about equal frequency. In these women, the disturbance in the mammary gland comes on late, after the breast has

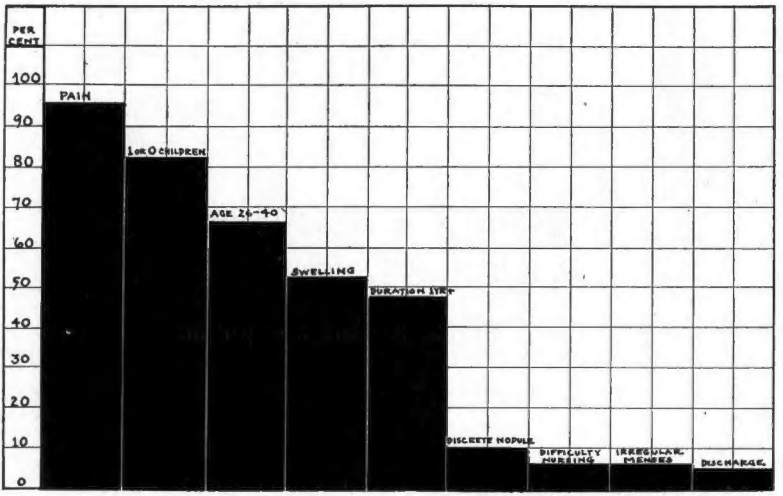


FIG. 161. Chart showing the relative frequency of various symptoms and findings in mastodynia.

achieved its full maturity, and is usually transient. This may be termed "simple mastodynia" and the mammary gland affected may be accurately described as a "swollen, granular breast" (Figs. 162-166).

In the second group, the breasts affected are smaller than normal and often unequal in size. The condition is usually bilateral. In addition to the tender, swollen tissue of which the patient complains, the entire mammary gland is found to be more compact, dense and granular than normal (Figs. 167, 168). These patients are younger (in their late twenties or early thirties), and are more often nervous or underweight. A greater percentage have menstrual disorders. The early age at which the condition becomes manifest, its bilateral character and the frequent inability of these patients to nurse, if they become pregnant, suggest a primary mammary deficiency. These small, granular breasts have either not attained their full physiologic development or have suffered dysfunction shortly after adolescence.

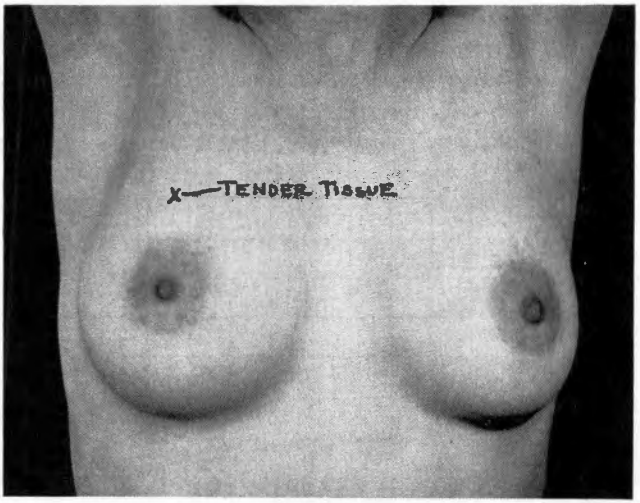


FIG. 162. Mastodynia. Photograph of patient.

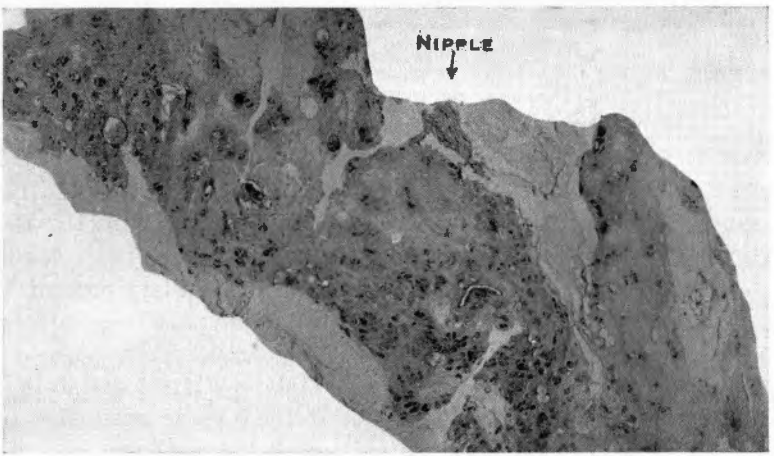


FIG. 163. Mastodynia. Cross section of breast tissue.

As they approach the menopause these patients are prone to develop the proliferative form of chronic cystic mastitis (or adenosis) which

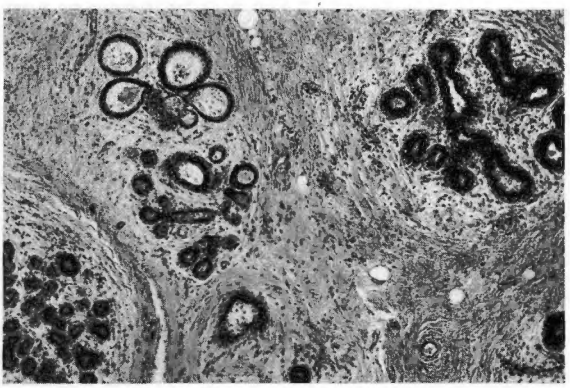


FIG. 164. Photomicrograph of typical mastodynia tissue.

FIG. 165

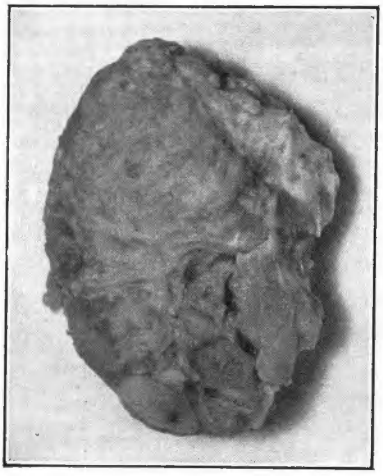


FIG. 166

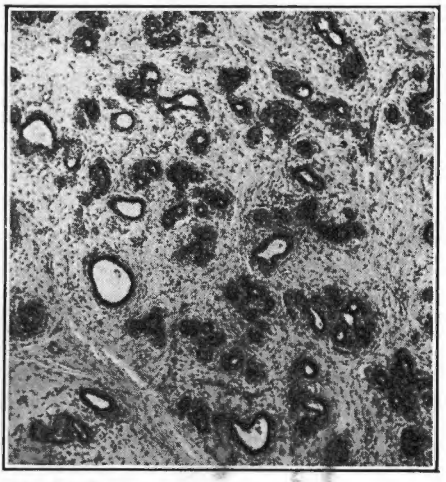


FIG. 165. Simple mastodynia. Gross specimen.
FIG. 166. Photomicrograph of swollen granular breast from a case of simple mastodynia.

was first described by Schimmelbusch. These breasts may be described as small, granular breasts, as mammary deficiency, or as an early stage of adenosis.

DIFFERENTIAL DIAGNOSIS

Mastodynia must be differentiated from pain referred to the region of the breast originating from soreness in the pectoral muscles fol-

lowing exertion; from arthritic and neuritic pains referred outward along the costal nerves which may be associated with infected teeth

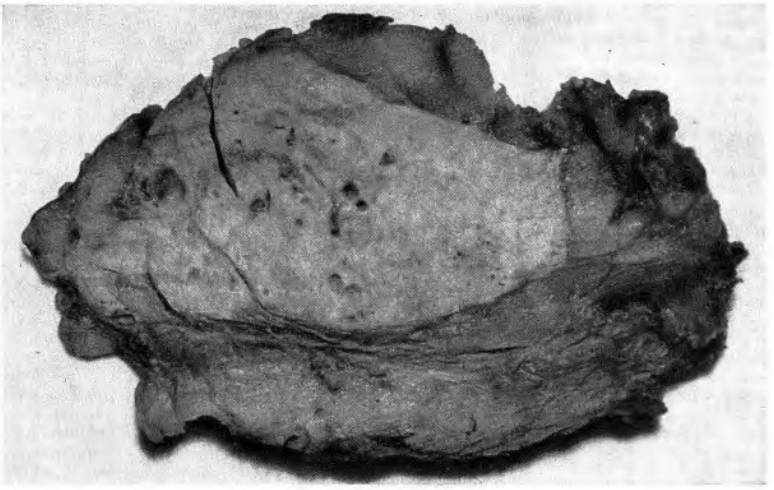


FIG. 167. Mastodynia with mammary deficiency. Gross specimen.

and tonsils; from the pain in heavy, obese breasts and from pain localized at the site of a bruise. former abscess or the scar of a previ-

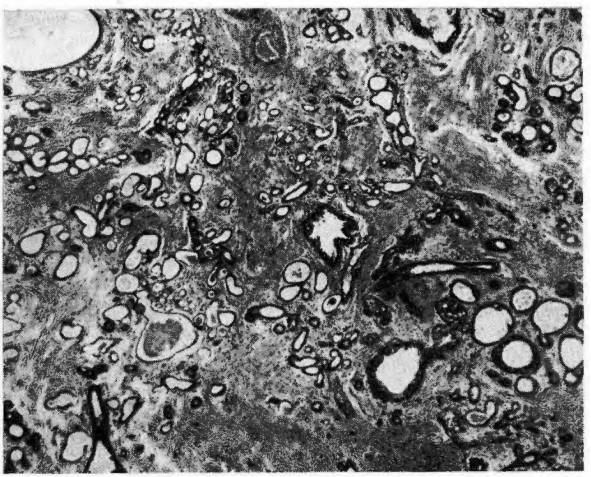


FIG. 168. Mastodynia with mammary deficiency. Photomicrograph showing transitions toward adenosis.

ous operation. In all these conditions the pain does not have the characteristic exacerbation in the premenstruum and is not localized in a dense, granular zone which is tender to palpation. This char-

acteristic tissue is likewise absent in cases of cancerphobia, in which the pain may be relieved by reassurance and psychotherapy. The pain in mastodynia, moreover, usually responds quickly to endocrine therapy with disappearance of the tender, lumpy tissue.

Fluctuation in size or sensitivity of the tender tissue during the menstrual cycle is not a reliable means to differentiate the mass from cancer, unless complete disappearance is recorded by the examining physician at one or more examinations (so-called disappearing tumor). In mastodynia the altered tissue is usually several centimeters in diameter, freely movable and forms an induration rather than a tumor. In cancer, a mass of corresponding size is more distinct on palpation, shows some fixation or attachment to the overlying skin, and it is harder and more irregular.

PATHOLOGY

The majority of cases of painful breasts in the present series were not subjected to operation. However, 64 of our early cases were treated by one or more excisions and 29 by amputations. The fear of cancer in the mind of the patient or physician, rather than the characteristics of the lump on palpation was most frequently the cause of operation. These operations have afforded opportunity for the study of the affected tissue. In the gross, the tissue is nonencapsulated, white, dense, tough and more fibrous in appearance than the surrounding glands. Numerous pink or gray, elevated points indicate persisting parenchyma. Small cysts may be present. (Figs. 165, 167.) Semb in a similar study noted thickening of the affected tissue, either local or diffuse, with a consistency firmer than normal. Bloodgood described

> a nonencapsulated area of breast tissue in which the elevated pink and grey dots representing the adenomatous lobules are more numerous than in the surrounding breast. This area resembles somewhat the fibro-adenoma but has less stroma.

On exploration it is frequently difficult, after incising the skin, to palpate the tumor which had been felt previous to operation. Both Semb and Bloodgood have commented on the absence of cysts or papillomas of appreciable size. Among his patients, Semb found three cases of fibro-adenoma complicating mastodynia.

Histologic features of mastodynia are the imperfect lobular development, and increase in periductal and intralobular stroma. The mammary tubules are surrounded by pale staining fibroblasts, often interspersed with moderate numbers of wandering cells. The lobules

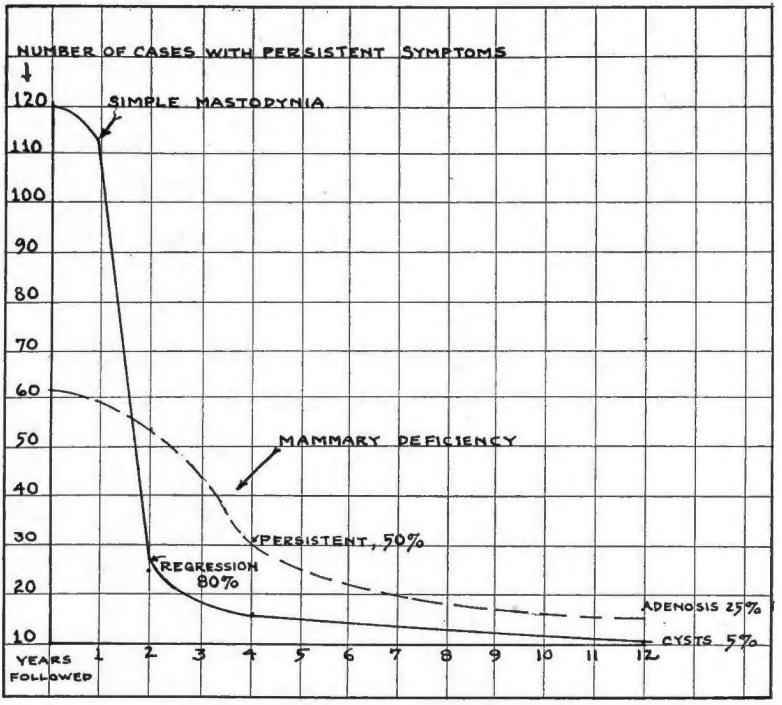


FIG. 169. Chart to show the end-results in cases of mastodynia.

FIG. 170

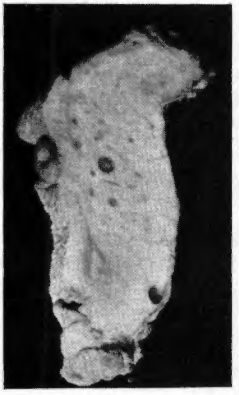


FIG. 171

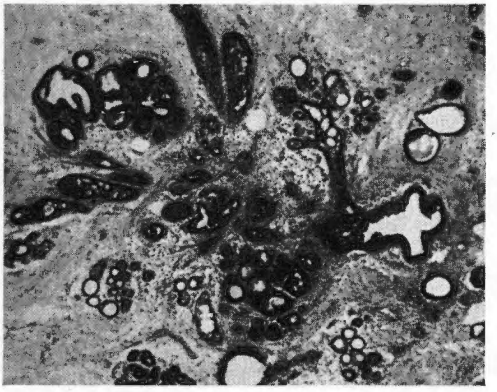


FIG. 170. A case of mastodynia terminating in adenosis. Gross specimen showing the dense, compact character of the mammary gland.
FIG. 171. Photomicrograph showing fibrosis and epithelial hyperplasia.

in the affected tissue show marked variations in size and number. They are often made up of terminal tubules with irregular sprouts and ramifications instead of regular clusters. The lining cells of the tubules may be reduplicated or the smaller ducts dilated with secretion. If epithelial proliferation is marked, the tissue resembles adenosis or Schimmelbusch's disease. If secretion and dilatation are marked, minute cysts may be formed. The tendency to epithelial proliferation is greater in those cases of mastodynia associated with mammary deficiency. Increase in the connective tissue is a constant finding, and this fibrosis may compress or obliterate the mammary lobules and form minute nonencapsulated fibro-adenomatous masses. Typical microscopic features of mastodynia and the transitional stages toward cyst formation, adenosis, and fibro-adenoma are shown in the accompanying photomicrographs. (Figs. 166, 168, 171.)

The histology of mastodynia differs from normal mammary development during adolescence with which it is sometimes confused. Although the mammary ducts are surrounded by increased amounts of connective tissue, and lobule formation is incomplete in both normal puberty and in painful breasts, there is irregular epithelial growth in the terminal tubules, dilatation of tubules and acini with increased secretion and desquamation of lining cells in mastodynia.

According to recent studies the defective lobule formation in mastodynia is associated with reduced function of the corpus luteum. Decreased amounts of luteal hormone interfere with lobular development of the breast in the premenstruum. The terminal tubules taking part in lobule formation are distorted. This distortion is apparently accentuated by repeated, interrupted and relatively increased amounts of estrogenic stimulation with successive menstrual cycles, and leads to abnormal budding and secretory activity. The endocrinology of this condition is discussed later (Chap. 11).

CLINICAL COURSE AND PROGNOSIS

The cases in the present series afforded an opportunity to study the clinical course of painful breasts and its relation to other forms of mammary pathology unmodified by treatment. In all, there were 261 cases in which operation was not advised, and in which no form of treatment was given. Thirty-five cases were treated by endocrine therapy and 93 received surgical treatment. Two hundred and forty-one cases were followed more than five years and of these 136 were followed 10 or more years.

The majority were examined and heard from repeatedly after the first examination, and in most of them the pain and tender lumps

had disappeared within two to three years without treatment. In some of the patients who had been single, the condition improved with marriage and in 15 pain and tenderness disappeared during pregnancy.

Improvement during the course of pregnancy usually is apparent by the end of the second or third month. There are exceptions. One patient, aged 29, married six years and without children, was examined in 1931 for painful breasts. In 1933, the condition was bilateral and worse although she was then three months pregnant. When examined in the fourth month of pregnancy, however, the condition had disappeared and she was well in 1938.

Although mammary pain and tenderness usually disappear spontaneously after a period of months or years, the condition may persist without marked change for 10 or more years. In such cases the trouble is usually terminated by the menopause but may persist a year or two beyond.

A patient was examined for mastodynia in 1918, at the age of 28. She was seen at regular intervals during the next 10 years during which time the pain and lumpiness diminished but did not disappear. She was examined by her family physician in 1937—nineteen years after her first examination. The breasts were not painful, but were still lumpy and slightly tender.

A patient was examined for mastodynia in 1924 at the age of 37. In 1934, the patient still had occasional pain and two years previously a tender lump had appeared but disappeared before the local surgeon could remove it. She was well in 1937.

In tracing the relationship of painful breasts to other forms of mammary dysplasia and to cancer, the patients were divided into two groups. The largest group was that of simple mastodynia in which breasts of normal size had tender, granular swellings. The smaller group comprised those cases complicated by mammary deficiency, occurring in small, granular breasts with tender areas.

Simple mastodynia (swollen granular breast) is usually a self-limited disease (none of these patients developed mammary cancer). During the period of several years when this condition is manifest, the tender masses vary in size and the patient may report spontaneous disappearance and reappearance of the painful lump. Persistent lumps tend to disappear after pregnancy or the menopause. In three cases, however, pain and tenderness persisted for 10 or more years. Thirteen patients ultimately had mastectomy performed for pain or nodularity; ten of these had been treated initially by excision. Four developed cysts.

The histories of these four cases are summarized:

Case 1. A patient was examined for mastodynia in 1922. There was a pea-sized nodule in the dense painful tissue. In 1924, she was re-examined and a cyst 1 cm. in size was found. The patient stated that this had disappeared and reappeared in the last two years. She was examined in 1932, and the cyst was no longer present. In 1934, the patient was entirely well, although no excisions had been performed.

Case 2. A patient examined in 1913 had bilateral mastodynia. Although one painful lump was excised, pain and lumpiness persisted for the next 15 years. In 1928, she was examined for bilateral mastodynia. She had been married 10 years and had had no children. At the next examination in 1936, two small cysts in one breast and one in the other were found. The patient was then 49 and was still menstruating. In 1938, the patient had passed the menopause and the cysts had disappeared.

Case 3. A third patient was examined in 1922 for painful breasts in which cysts had developed. One cyst was excised from each breast. Pain and lumps were present until 1927. The patient then passed through her menopause and was well in 1932.

Case 4. The last patient was examined for bilateral mastodynia at the age of 26, in 1921. She had varying degrees of pain and lumpiness during the next 14 years. In 1935, at the age of 41 years, she was at the menopause. A cyst 2½ cm. in diameter was found in the upper mid-zone of the right breast. Six months later the lump was one-half its size. The patient was well in 1937.

In the cases of simple mastodynia in which the tender tissue has been excised and studied histologically, the tendency for microscopic cysts to form is more frequently seen (Figs. 165, 166). Among the 589 cases of cystic disease to be discussed later, 46 (on the basis of clinical or microscopic evidence) had their origin in mastodynia. Multiple small cysts, frequently bilateral and affecting younger patients, are more often a sequel to mastodynia than solitary cysts of appreciable size occurring toward the menopause.

Mammary Deficiency. In painful breasts associated with mammary deficiency (small granular breasts) there were 83 out of 105 cases, in which no operation was advised and 22 which were treated by surgery. Sixty-nine were followed beyond the five-year period and 15 cases beyond the three-year period (Table XIX).

In mastodynia associated with mammary deficiency where no treatment was instituted, one-half of the cases were unimproved after a period of three to four years. After a period of from five to eight years only one-third had persistent mammary symptoms, and at the end of 10 to 15 years one-fourth had the signs and symptoms of adenosis or Schimmelbusch's disease (Fig. 169). Mastodynia associated with mammary deficiency is a more persistent condition than simple mastodynia and the patients affected are prone to develop adenosis.

TABLE XIX

END-RESULTS IN 241 CASES OF MASTODYNIA[1]

	NO OPERATION ADVISED	EXCISION ONLY	UNILATERAL AMPUTATION	BILATERAL AMPUTATION	TOTALS
No. of cases followed	166	50	15	10	241
Over 5 yrs.	78	20	7	—	105
Over 10 yrs.	88	30	8	10	136
Dead					
Dead of other causes[2]	3	1	—	—	4
Dead of cancer of the breast	—	1	—	—	1[3]
Unimproved					
Recurrences or persistent symptoms after 5 years	7	11	2	—	20
Developed cystic disease	2	2	—	—	4
Developed adenosis	9	3	—	—	12
Well					
Reported well after 5 yrs.	145	32	13	10	200

[1] Does not include cases treated with endocrine therapy.
[2] Heart failure, pneumonia, hepatic cancer, and tuberculosis—each 1.
[3] This patient allegedly died of mammary cancer but further investigation by her family physician failed to confirm this.

Among 47 untreated patients followed five or more years, two ultimately had mastectomy performed for the same condition. Twelve ultimately developed bilateral adenosis and 31 reported themselves completely well. Among 15 additional cases followed from three to four years, seven were well, seven had persistent symptoms (shotty and painful breasts) and one had a mastectomy performed.

Twenty-two cases surgically treated were followed (three had had bilateral, and three unilateral, amputations). One had mastectomy eight years later, and two multiple excisions. In two, excision was followed by recurrence, treated by endocrine therapy. Ten remained well following simple excision.

The follow-up studies shown in Table XIX indicate that there is a definite relationship between mastodynia and other forms of chronic cystic mastitis. They do not support the observation made by other authors that mastodynia is not related to cystic disease or Schimmelbusch's disease (Cheatle) nor are they in keeping with the theory of Semb who holds that mastodynia is a precursor of fibro-adenoma. Twelve patients in the present series ultimately developed adenosis.

TREATMENT

The therapy recommended for mastodynia has varied from the extreme of mastectomy to that of simple reassurance. In 1928 Semb stated that the dense tissue constituted grounds for excision and recommended ablation of the mammary gland with preservation of the nipple. Bloodgood stated that if the patient with mastodynia were reassured against the possibilities of cancer, she tolerated the discomfort well.

Three procedures are indicated in all cases of mastodynia before undertaking any specific form of treatment. The first is to rule out the possibility of cancer by thorough examination and by biopsy if necessary. The second is to rule out any focus of infection that may account for the pain or the mammary dysplasia. The third is to try simple reassurance against fear and worry and mechanical support of the breast by a properly fitted brassiere, if indicated. If further treatment is needed, a choice may be had between surgical procedures, medical measures such as endocrine therapy, and radiation. These methods of treatment are discussed in Chap. 12.

9

Adenosis or Schimmelbusch's Disease

(Adenocystic or Microcystic Disease)

Adenosis is characterized by the occurrence, in one or both breasts, of multiple nodules varying from a millimeter to a centimeter in size usually distributed about the periphery of the upper or outer hemisphere. The breasts affected are small, dense, and edged like a saucer when grasped in the hand. Pain and tenderness (which vary during the menstrual cycle) occur as in mastodynia. The majority of women affected are childless and are in the late thirties or early forties. These patients are often nervous, underweight, and may have irregular menstrual cycles. The mammary tissue affected contains dense fibrous tissue, numerous minute cysts and foci of epithelial proliferation. (Fig. 172.)

The pathology of this form of mammary dysplasia was first described as a diffuse papillary cystadenoma by Schimmelbusch who believed it to be precancerous. Bloodgood, in 1906, described it as the "diffuse nonencapsulated cystic adenomatous type" of chronic cystic mastitis. In 1929 he stated it was the rarest form of chronic cystic mastitis and that he was convinced that it was not a precancerous lesion. Semb described it as the microcystic form of fibroadenomatosis, Cheatle and Cutler as epithelial neoplasia, and Campbell as adenocystic disease. In a pathologic study of chronic cystic mastitis published in 1934, 100 cases of this form were described under the caption of adenosis by Lewis and Geschickter.

SYMPTOMS AND DIAGNOSIS

The peak of the age incidence in our 212 women with adenosis was between 35 and 44 years (mastodynia is most prevalent between

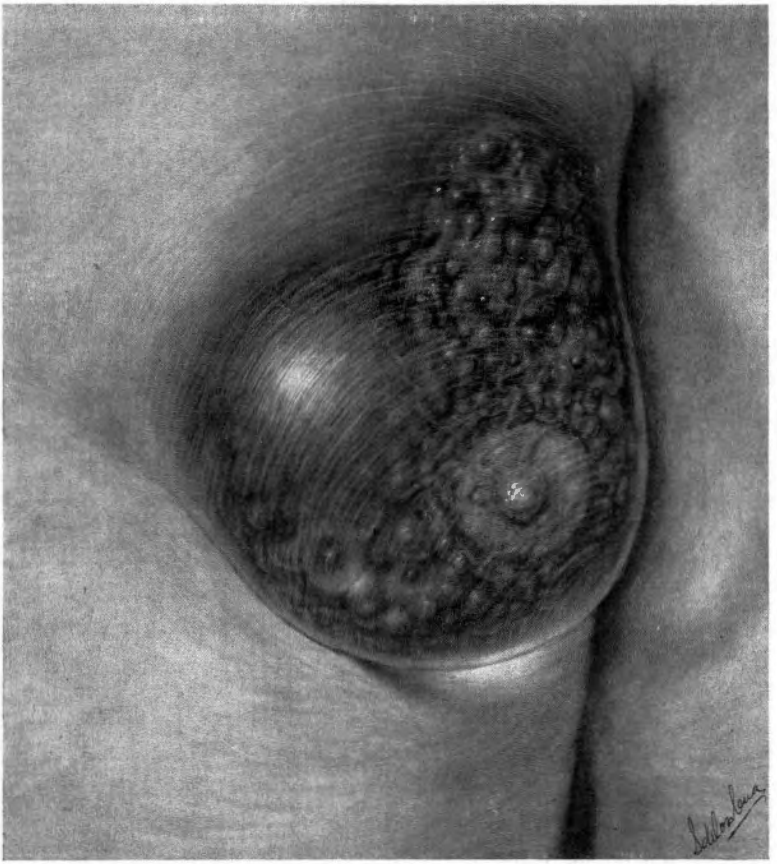


FIG. 172. Drawing to illustrate the characteristics on palpation in adenosis. The breast contains multiple shot-like nodules and has a definite edge when grasped between the fingers.

30 to 39 and cystic disease from 40 to 50 years). (Figs. 173, 191.) As in other forms of mammary dysplasia, childless women predominate; women with large families were exceptional. (Table XX.)

Late Form of Mastodynia. The low fertility among women with adenosis, the occurrence of the condition at an average age 5 years beyond that of mastodynia, and the frequency of the complaint of mammary pain suggest that many cases of adenosis are late manifestations of mastodynia.

The leading symptoms in adenosis are the discovery of a lump and the occurrence of pain and tenderness. In approximately two-thirds of the cases, the patient was aware of a nodule or thickened portion of the gland and in one-third pain was a conspicuous feature.

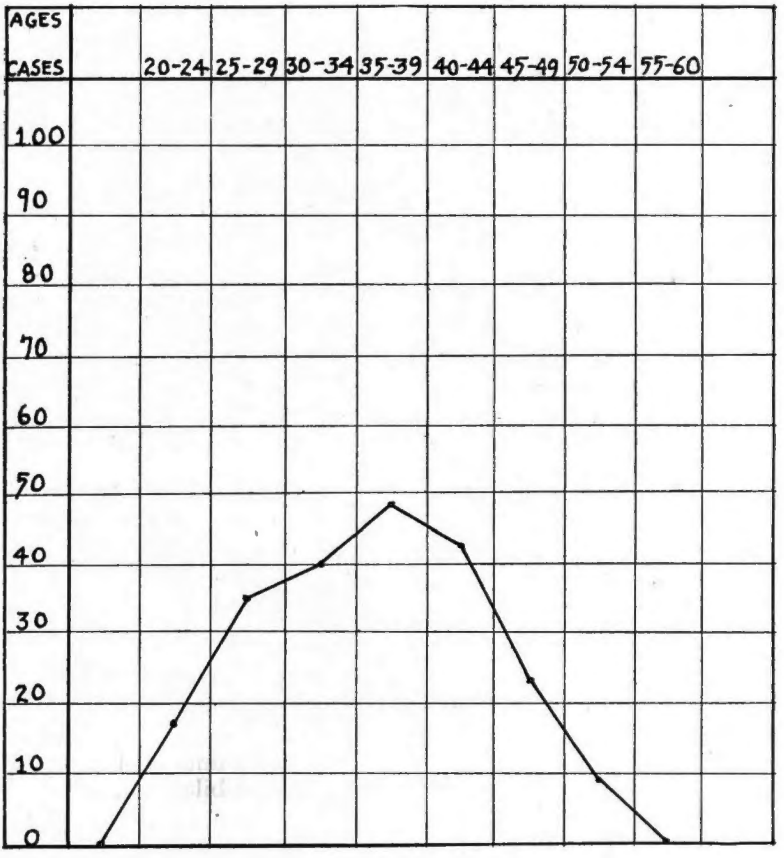


FIG. 173. Chart showing the age distribution in 212 cases of adenosis.

Exacerbation of pain in the premenstruum or the history of disappearance and recurrence of the lump is a common finding. The average duration of symptoms in all cases was 21 months. Sixty-five cases had had symptoms over a period of one or more years (averaging four years). (Table XX.)

Endocrine Make-Up. Patients with adenosis usually have a characteristic endocrine status. They are underweight or undersized. Several weighed between 85 and 90 pounds and not a few less than 100 pounds. Women of average size often complained of recent loss

TABLE XX

DATA ON 212 CASES OF ADENOSIS

I—AGE

21–25	18
26–30	34
31–35	40
36–40	48
41–45	42
46–50	22
51+	8
	212

II—MARITAL

Single	90
Married	101
No data	21
Married—childless	22
Miscarriages	6
Married—1 child	15
Married—2 children	23
Married—3 or more children	13
Married—no data	22

III—DURATION OF SYMPTOMS

Days	3
Weeks	9
Months	104 average 4.7
Years	65 average 4
No data	31
	212

Average duration 21 months

IV—SYMPTOMS

Pain	70
Tumor	142
Discharge (9 bloody)	14
Retracted nipple	9

V—LOCATION

Bilateral	122
Unilateral	90
Diffuse	53
O.U.Q.	57
Nipple zone	26
L.O.Q.	11
U.I.Q.	7
L.I.Q.	5
No data	53

VI—ENDOCRINE FINDINGS

Severe menstrual disturbance	11
Thyroid disturbance	15
Unable to nurse	12
Sterile	11

VII—TREATMENT

No operation	91
Excision	62
Amputation-unilateral	51
Amputation-bilateral	8

VIII—END-RESULTS

			Cancer of Breast
No operation—followed	5 yrs.	45	3 cases
	10 yrs.	34	
Excision —followed	5 yrs.	27	2 cases
	10 yrs.	29	
Amputation —followed	5 yrs.	20	1 case
	10 yrs.	29	
Amputation —followed bilateral	10 yrs.	8	
		192	

of weight. A feeling of nervousness or excitability having its onset prior to or during the development of the mammary lesion is noted in some instances. Such patients have an anxious expression, weep easily, and are apprehensive concerning the relation of their condition to cancer. (Fig. 174.) The menstrual periods are usually closer together than the average, the cycles being 21 to 26 days. Sterility or an inability to nurse the child from one or both breasts was noted in approximately 10 per cent of the histories. Enlargement of the thyroid gland, thyroid adenoma, or hyperthyroidism was noted in 15 cases. Marked menstrual disturbance was noted in 11 cases; two had endometrial hyperplasia. (Fig. 175.)

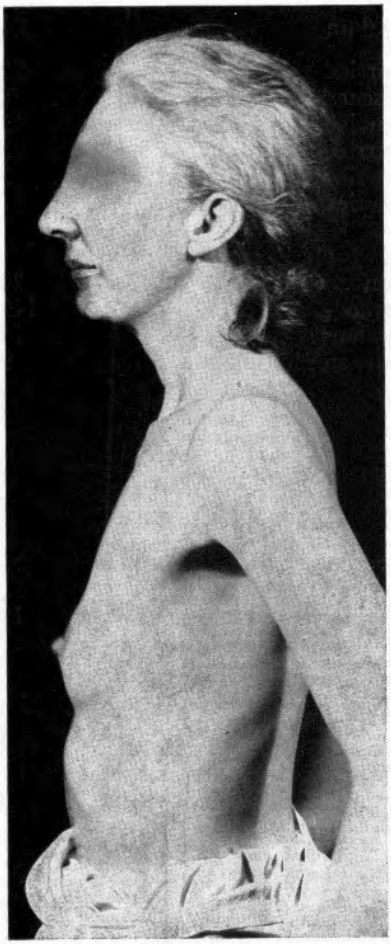


FIG. 174. Photograph of a patient with adenosis showing the small size of the mammary gland.

Breast Size. Adenosis is seen most frequently in breasts of moderate or small size. The tendency to underdevelopment is usually definite. The adipose tissue is diminished in amount and the irregular contour of the underlying mammary tissue has a characteristic, uneven and nodular surface (Fig. 176). Dimpling or attachment to the overlying skin is unusual and in such cases biopsy should be performed. A noticeable difference in the size of the two breasts is common. Tenderness is frequently elicited when the dense portion of the gland in the outer and upper quadrant is grasped between the thumb and fingers of the examining hand. The affected breasts transilluminate poorly. A serous or bloody discharge was expressed from the nipple in 14 cases.

Palpation Findings. There are three outstanding features on palpation: (1) the finding of elevated, dense, tender tissue similar to that in mastodynia; (2) the occurrence of multiple nodules; and (3) the palpation of an "edge" at the periphery of the breast. (Fig. 172.)

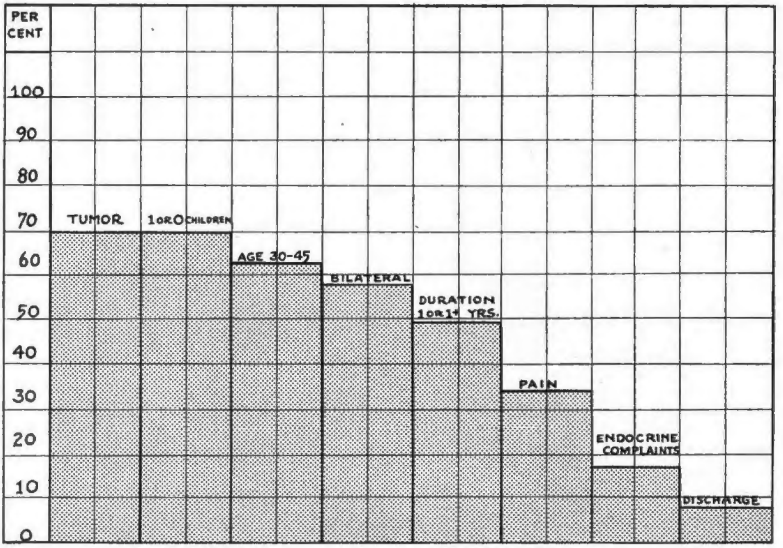


FIG. 175. Chart showing the relative frequency of symptoms and findings in adenosis.

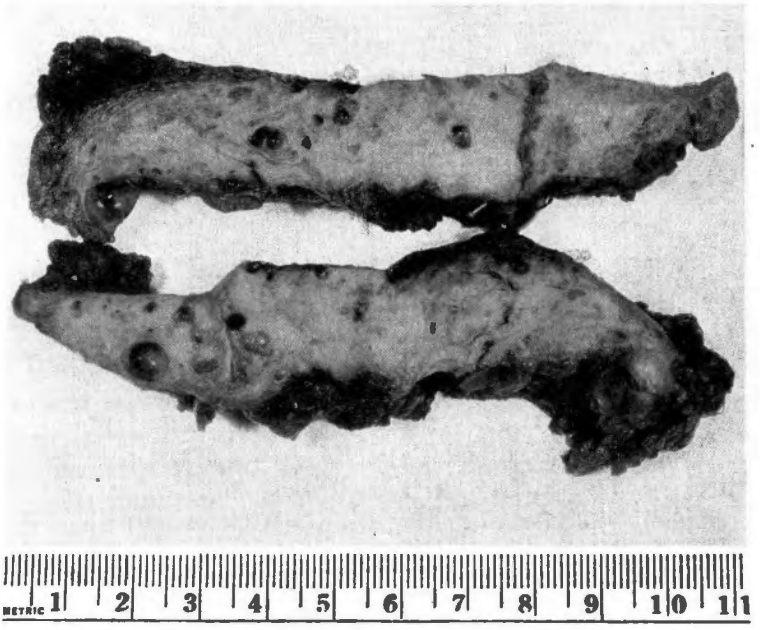


FIG. 176. The mammary structure in adenosis. The gross specimen shows the multiplicity of small cysts, discrete nodules and dense fibrous tissue.

The swollen, elevated tissue in adenosis is often similar to the "caking" or induration found in mastodynia. In many cases, however, this elevated tissue is more firm on palpation. Although it does not have the definite edge or the fixation of malignancy, its degree of

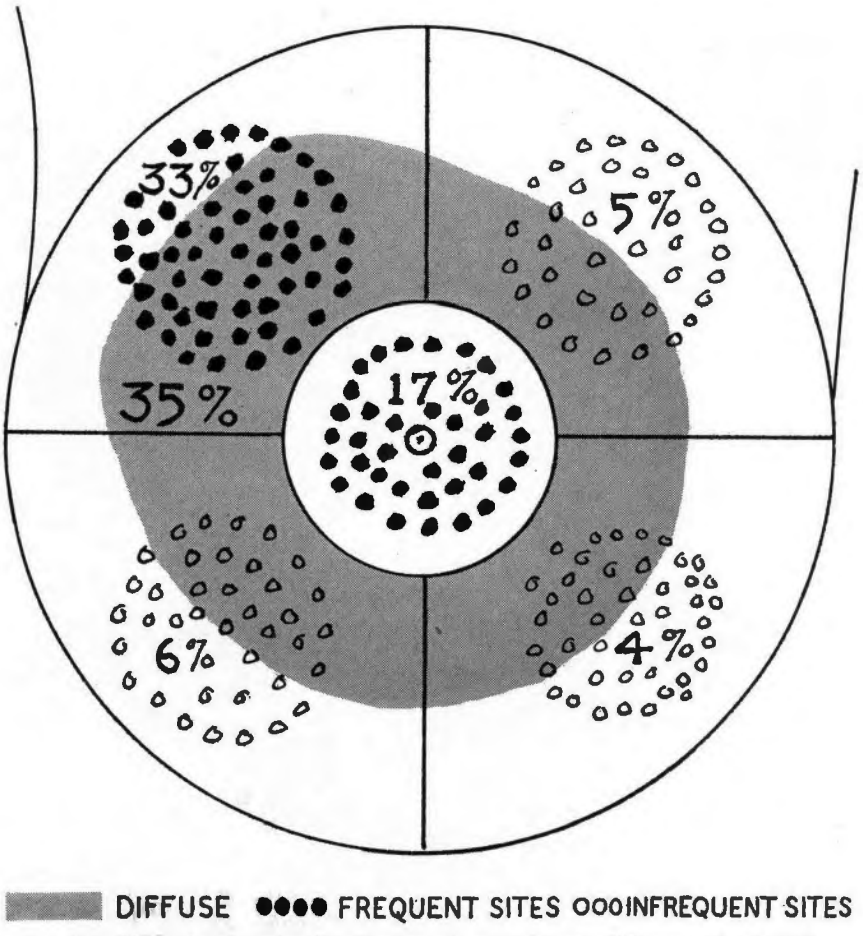


FIG. 177. Chart showing the distribution of nodularity in 212 cases of adenosis.

hardness may suggest cancer. This was remarked upon repeatedly in the histories. The surface of this elevated and indurated tissue is often coarsely nodular and may contain one or more small cysts. Variation of the size and density of the induration from one menstrual cycle to the next may occur as in mastodynia.

The occurrence of small multiple nodules has been much emphasized. These numerous small nodules found in the upper or outer hemisphere of the mammary gland have led to such descriptive terms as "shotty breasts," "the feeling of a bag of shot" and "palpat-

ing a bean bag." The size of the nodules varies from 1 or 2 mm. to 1 or 1.5 cm. The larger nodules are cystic, being round, dense and freely movable. (Fig. 178.)

Bloodgood and Semb have emphasized the saucer or liver-like edge palpated when the breasts are lifted and allowed to slip between the fingers. This characteristic edge is best felt along the outer and upper margins.

In the majority of cases of adenosis both breasts are affected (122 of 212 cases). Bloodgood believed that if both breasts are carefully palpated, bilateral disease would always be found. He stated that prior to 1921 notes on the opposite breast were not made with sufficient care in his series to pick up this bilaterality. A review of the records in the present series of cases, which include those of Bloodgood, bears out this statement.

The multiple shot-like nodules in both breasts may be inconspicuous or absent in late cases of adenosis, however. In such instances, where the disease is apparently undergoing involution, one or more cysts 0.5 to 1 cm. in diameter may affect a single indurated sector.

Changes in the region of the nipple are sometimes noted. These included dilated ducts beneath the nipple, intermittent retraction and a sanguineous discharge.

DIFFERENTIAL DIAGNOSIS

The clinical features of adenosis are in need of special emphasis since, in the past, the conception of the disease has rested almost entirely upon histologic interpretations. From the pathologic standpoint, the presence of cysts has led to the interpretation of adenosis as a phase of cystic disease. The presence of epithelial hyperplasia, on the other hand, has led to its inclusion among the precancerous lesions, while some cases have been classed as low-grade cancer.

Adenosis is the most chronic and also the most severe form of chronic cystic mastitis. Because adenosis is often superimposed upon a persisting mastodynia and since it is complicated by the occurrence of multiple small cysts or sometimes by one or more cysts of appreciable size it may embrace the other two forms of mammary dysplasia. This relationship of adenosis to mastodynia and cystic disease is also confirmed by microscopic studies. Tissue excised from cases of mastodynia may show small foci of adenosis and similar findings may occur in tissue excised in some cases of cystic disease (see Chaps. 8 and 10).

Adenosis is distinguished from the other forms of mammary dysplasia by the small size and multiplicity of the lesions, by the density of the gland, and by the endocrine status of the patient. In

simple mastodynia there is swollen doughy or dense tissue, but multiple definite nodules (pea-sized or slightly larger) are not present, and the breasts do not have a definite edge. In cystic disease the breasts are normal in size, often adipose, transilluminate well and there is usually but a single cyst, several centimeters in diameter; the patients are at or near the menopause; the cyst makes its appearance abruptly and the patient's breasts and general health are otherwise normal. The close relationship between the small painful breast (mammary deficiency) and adenosis makes the separation of the two conditions a matter of secondary importance. The more definite character of the nodules and the saucer-like mammary edge in adenosis are distinguishing features.

The differentiation of adenosis from benign intracystic papilloma and from mammary cancer may require biopsy. The frequency with which adenosis affects both breasts, however, aids in diagnosis. Benign intracystic papilloma most often occurs in women at or past the menopause. The lesion is beneath the nipple or areola, most often solitary and accompanied by a discharge of blood in 50 per cent of the cases. In adenosis the nodules are multiple and at the periphery. The patients are younger, in their late thirties or early forties. A sanguineous discharge from the nipple is less frequent and is more often brownish, the color of inspissated rather than fresh blood. There is a definite overlap between the two conditions, however, and small intraductal papillomas may occur in advanced cases of adenosis. Thus, on pathologic examination, 15 per cent of the benign intracystic papillomas reported by Hart contained multiple small foci of papillomas and were cases of adenosis complicated by papillary hyperplasia (see Chap. 14). Benign intracystic papillomas of appreciable size are less frequently multicentric in origin.

The solitary, indurated, fixed lesion of mammary carcinoma is easily distinguished by palpation from the shot-like nodularity of the breasts in adenosis. Forms of comedo carcinoma may infiltrate one or more ducts, however, and in their early stages the growth is palpated as a group of nodules rather than as a solitary lesion. The nodularity in such cases is harder and, because of the atrophy of the overlying fat, nearer to the examining finger than in adenosis. When definite, indurated nodules are palpated just beneath the skin, in a case of adenosis, biopsy is indicated to rule out cancer. The incidence of mammary cancer complicating adenosis is between 2 and 3 per cent.

PATHOLOGY

In adenosis the pathologic process is diffuse. A single quadrant or hemisphere usually shows more advanced changes than the remainder

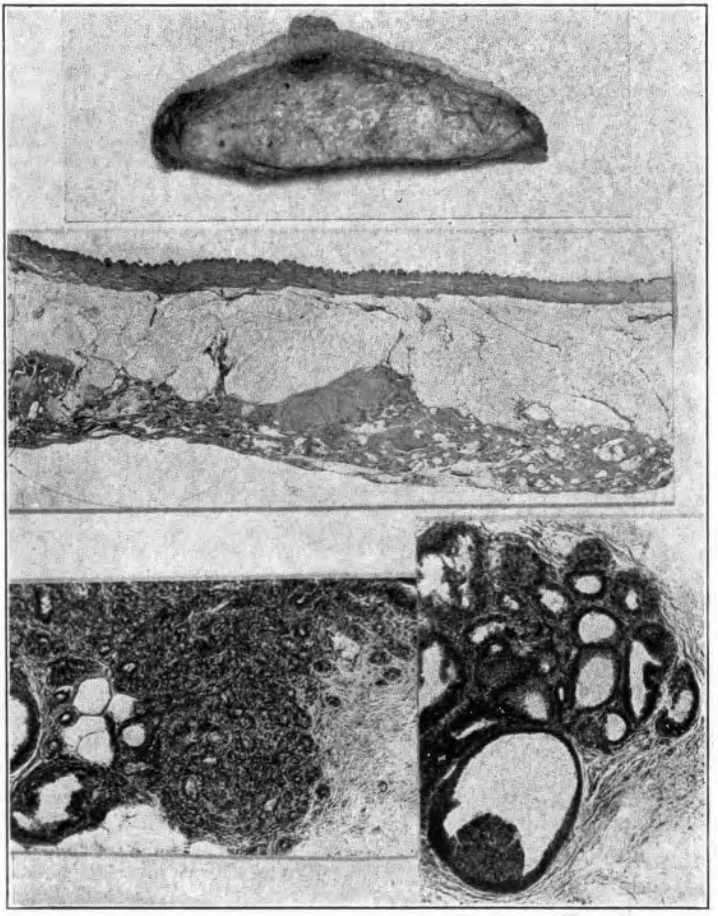
of the gland, but in many cases all portions of the breast are equally involved. The mammary tissue has an increased fibrous consistency and cuts with difficulty. Adipose tissue is diminished. The par-

FIG. 178

FIG. 179

FIG. 181

FIG. 180



FIGS. 178-181. Specimen, cross section and photomicrograph from a typical case of adenosis. The mammary tissue is dense, glistening and tough, the cross section shows an accumulation of small cysts toward the periphery, and the photomicrographs show minute intracystic papillomas and non-encapsulated epithelium proliferation in the lobules.

enchyma is riddled with small cysts, minute adenomas and papillomas and large dilated ducts may be found. (Fig. 176.)

The salient microscopic features (Figs. 178-181) are:

1. Epithelial proliferation in the terminal mammary tubules with the formation of multiple small intraductal adenomas and papillomas —intraductal hyperplasia.

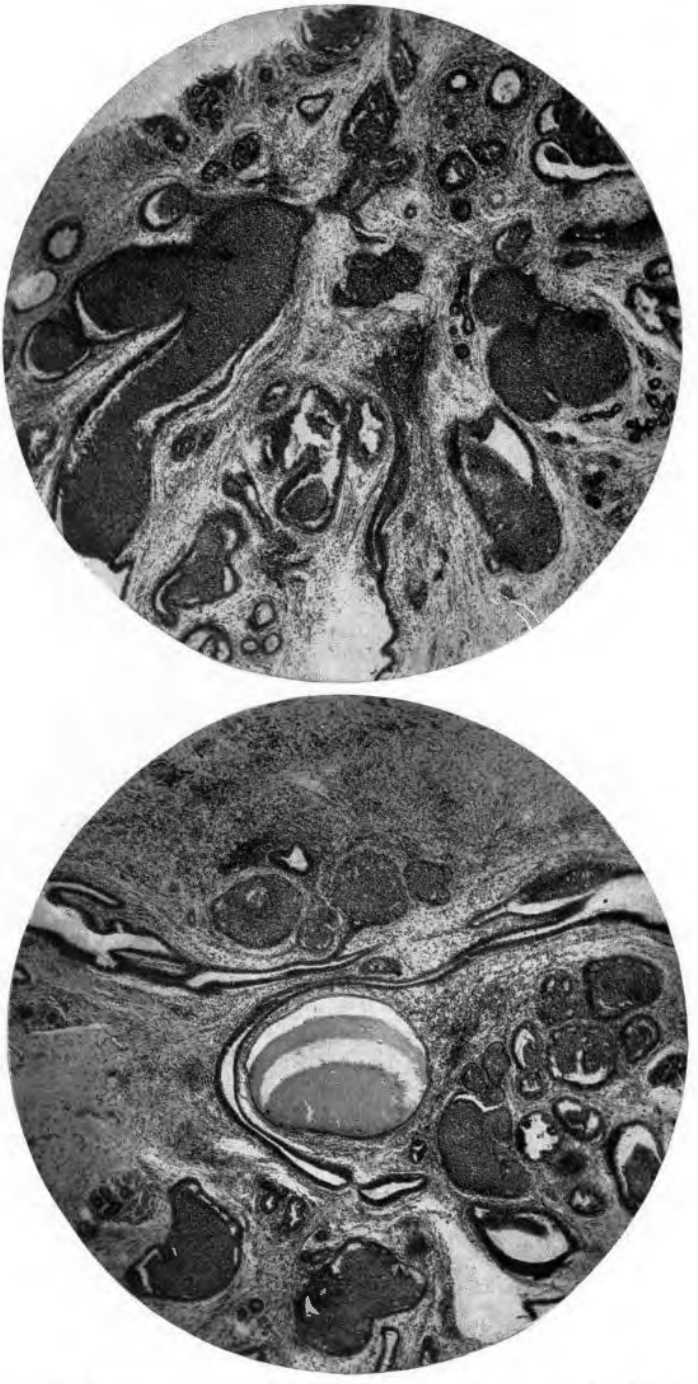


FIG. 182. Duct adenoma occurring in adenosis. Photomicrographs showing intraductal epithelial proliferation in adenosis, which must be differentiated from duct cancer.

2. A disorderly proliferation of acinar elements which invade the surrounding stroma, so-called "epithelial spilling."

3. Dilatation of terminal tubules or acini with the formation of minute cysts—microcystic disease.

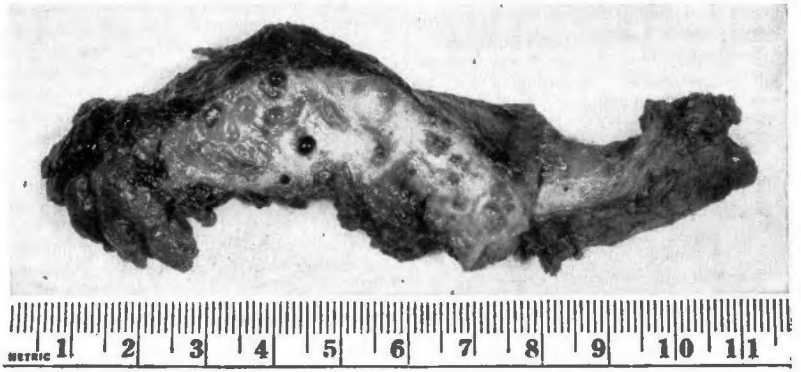


FIG. 183. Pathologic changes in adenosis. Gross specimen showing minute cysts.

4. Increase in the periductal and perilobular stroma—diffuse fibrosis.

The intraductal hyperplasia and epithelial spilling observed under the microscope account for the frequency with which radical meas-

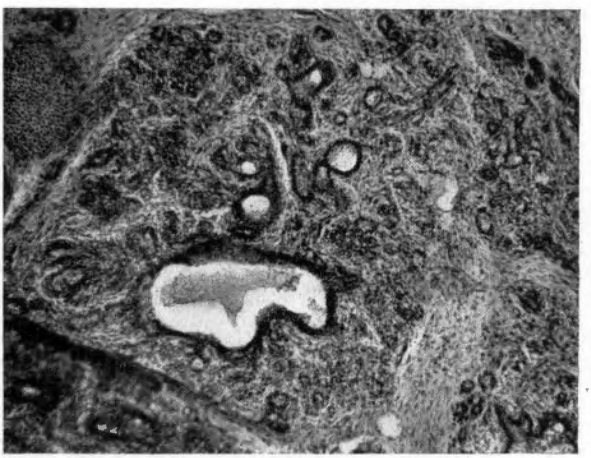


FIG. 184. Pathologic changes in adenosis. Photomicrograph showing "epithelial spilling."

ures have been adopted for the treatment of the disease. The growth of the hyperplastic epithelium within the lumen of the tubules resembles comedo or duct cancer (Fig. 182). On the other hand the

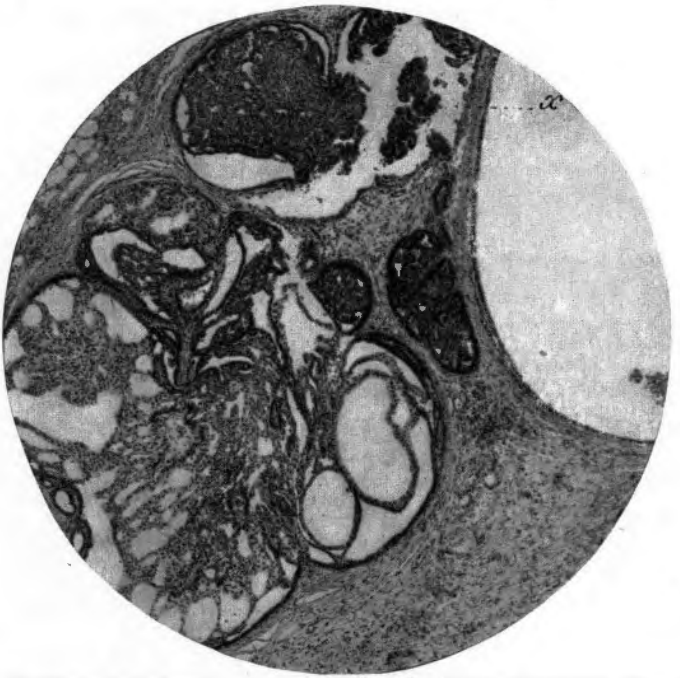


FIG. 185. Papillary intraductal growth in adenosis. Photomicrograph from the wall of a small cyst.

FIG. 186. High power from the area marked "X" in Fig. 185.

epithelial sprouts ramifying from the ends of the tubules into the surrounding stroma mimic the invasiveness of scirrhous cancer (Fig. 184). Such epithelial proliferation has been regarded as true neoplasia by certain authors, and interpreted either as precancerous or early carcinoma. In many of the atypical lobules this hyperplasia is more apparent than real, and represents a collapse of

FIG. 187 FIG. 188

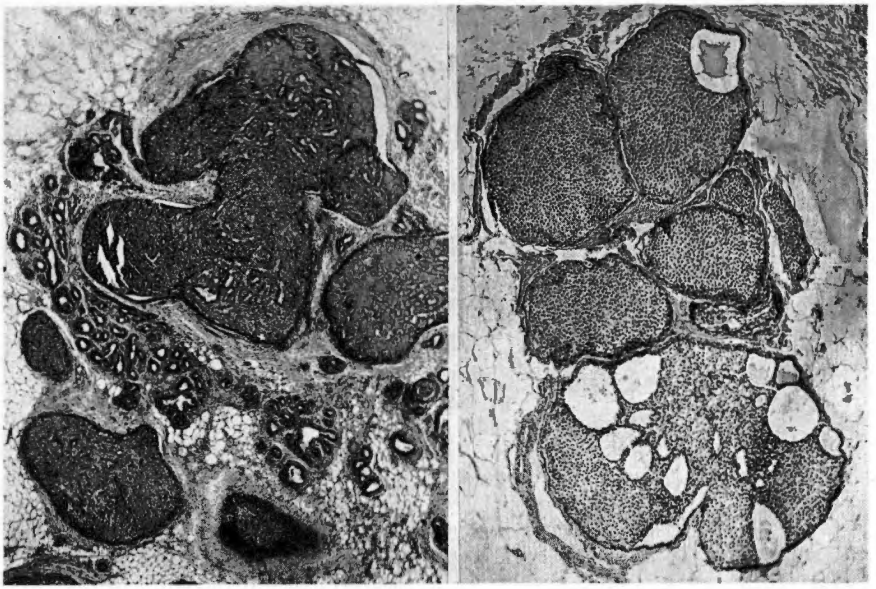


FIG. 187. Comparison of adenosis with comedo carcinoma. Photomicrograph showing the benign intraductal cells of adenosis. (× 300).
FIG. 188. Photomicrograph of the malignant intraductal cells in comedo cancer. (× 300).

the acinar and tubular structures, accompanied by atrophy of the intralobular connective tissue.

Properly prepared sections are essential to differentiate adenosis from carcinoma and diagnosis must be made from the appearance of the cells under high power. In carcinoma, the cells are larger, and their nuclei are more prominent, with vesicular or hyperchromatic features and frequent mitotic figures. The cancer cells grow en masse, lining or filling the ducts and tubules; or solid islands infiltrate the stroma. Minute papillomas within the cancerous tissue are unusual, whereas in adenosis such papillary structures are the rule within the zone of maximum proliferation. In adenosis, the epithelial spilling consists of cells which are identical with those lining the tubules and

acini, while in carcinoma the infiltrating cells have definitelv malignant features (Figs. 185, 186).

The distinction between comedo carcinoma occurring in mammary tissue affected also by adenosis and a case of simple adenosis may present unusual difficulties because of the numerous microscopic gradations between the two. In comedo carcinoma, the cancer cells lining the ducts form large rings surrounding areas of central necrosis, whereas in adenosis the plugs of proliferating tissue are smaller, solid,

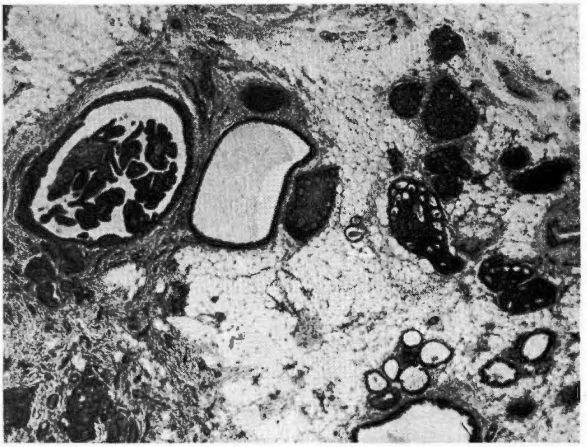


FIG. 189. Adenosis associated with early comedo cancer. Note the epithelial infiltration in the lower left hand corner.

and contain epithelial cells without malignant features (Figs. 187-189).

CLINICAL COURSE AND PROGNOSIS

One of the features distinguishing adenosis from early mammary cancer, with which it is sometimes confused, is the response of the disease to pregnancy and lactation. Cancer is adversely influenced, whereas the effects on adenosis are beneficial. The relationship of the two diseases to the menopause is also quite different. In the years following the menopause, the probability of cancer complicating involutional changes in the normal breast steadily increases. On the other hand, in the gland affected by adenosis the time of the menopause itself is the period of maximal danger and postmenopausal involution decreases the probabilities of cancer.

In cases followed during pregnancy and lactation, disappearance of the nodularity and tenderness occurs after mid-pregnancy and the breasts are normal to palpation during lactation. That these bene-

ficial effects are real and not merely masked by the increased paren chyma is indicated by a number of cases in which breasts, previously the seat of adenosis, have been found negative at examination a year or more after childbirth.

Of 212 cases of adenosis, 192 cases were followed more than five years and, of these, 100 were followed for more than 10 years. The clinical course of the disease may be adequately judged in these cases since the majority were treated conservatively. In the entire group, mammary carcinoma developed in six instances. In the remainder of the cases with few exceptions there was ultimate regression of the disease.

In tabulating the follow-up reports, the patients were separated into four groups: (1) those not treated surgically; (2) patients treated by excision; (3) patients treated by unilateral amputation; and (4) those treated by bilateral amputation (Table XXI).

TABLE XXI

END-RESULTS IN 192 CASES OF ADENOSIS

	NO OPERATION ADVISED	EXCISION ONLY	UNILATERAL AMPUTATION	BILATERAL AMPUTATION	TOTALS
No. of cases followed	79	56	49	8	192
Over 5 years	45	27	20	—	92
Over 10 years	34	29	29	8	100
Dead of other causes	0	2	6	3	11
Cancer of the breast	3	2	1	—	6
Recurrence					
Recurrence or persistent symptoms after 5 years	24[1]	10	8	—	42[1]
Amputation performed for recurrence	1	3	3	—	7
Well					
Reported well over 5 years	61	39	31	5	136
	77%[2]	72%	72%	100%	

[1] Includes 10 cases with recurrent or persistent symptoms at the end of five years but reported well thereafter.

[2] Per cent well, excluding death from other causes.

Among 93 cases of adenosis in which operation was not advised at the first examination, 79 were traced beyond the five-year period. Twenty-four had persistent symptoms 5 to 11 years after the first examination, but 10 of these were ultimately well. Five patients were

treated finally by one or more excisions and one by mastectomy. Three developed cancer of the breast (which was fatal in 2 cases) and none died of other causes. In all, 61 patients were well after five years and of these 34 were well more than 10 years.

Among the patients primarily treated by excision, 56 were followed beyond the five-year period. Ten of these patients who had had one or more excisions returned within this period with further trouble in the same or opposite breast and received no further treatment. Three had unilateral amputations during this period. Two patients died of mammary carcinoma and two of other causes. In all, 39 of 56 patients treated by excision remained well beyond the five-year period and of these 26 were well more than ten years.

Among 49 patients treated by unilateral amputation and followed for more than five years, amputation of the remaining breast was performed in three cases, two to six years afterwards. Eight additional cases ultimately returned for symptoms in the opposite breast. Five of these were followed without further treatment and were ultimately well. A sixth case had persistent symptoms in the opposite breast and in two cases local excisions were performed on the opposite breast. Six cases continued well for more than five years, but ultimately died of causes other than cancer. One developed cancer of the opposite breast. In all, 31 patients treated by unilateral amputation remained well beyond the five-year period.

There were 8 cases treated by bilateral amputation who were followed beyond the 10-year period. Both breasts were amputated either simultaneously or within a few weeks. All of these patients remained well; three of them ultimately died of causes other than cancer.

These results indicate that operations other than bilateral mastectomy do not significantly affect the clinical course of adenosis. The percentage of cases well after five years was 77 per cent for those not operated upon, 72 per cent for those treated by excision and 72 per cent for those treated by unilateral amputation. Where the condition is undergoing cystic involution and one or more cysts of 1 to 2 cm. in size occur in a single sector, local excision may prove effective. The disease, however, runs a protracted and persistent course and affects diffusely one or both breasts. In the cases of adenosis adequately traced, the mean age of the patients at the time of examination was 37.2 years and the mean age of the patients reporting well was 45.7 years. Since the average duration of symptoms was 1.8 years it may be stated that adenosis usually runs its entire clinical course within a period of 10 years.

In 192 cases of adenosis adequately followed, only six developed

mammary carcinoma, histologically verified in five of the latter. Of these five verified cases, one patient was 45 years old when adenosis was found at examination and cancer was discovered six years later at the age of 51 when the patient was passing through the menopause. In the other four cases the patients were between the ages of 35 and 40 when examined for adenosis and the cancers developed within a period of from two to seven years; all four of the patients were 42 years old when the cancers developed. No verified case of cancer complicating adenosis developed after the patient had passed through the menopause.

Of 79 untreated patients who were followed more than five years, three developed mammary carcinoma. In 56 patients treated by excision and followed, two developed mammary cancer, an incidence of about 4 per cent in each group. Of 49 patients treated by unilateral amputation and followed more than five years, one developed cancer of the opposite breast, an incidence of about 2 per cent. Unilateral amputation, as would be expected, reduced the incidence of mammary cancer in adenosis by 50 per cent and bilateral amputation reduced it to zero.

TREATMENT

Multiple definite or indefinite tumors in one or both breasts, a characteristic edge to the mammary gland on palpation and a painful indurated area are present in the majority of adenosis cases. Among 62 cases treated by excision, nodular tissue containing "shot like" masses led to exploration in 22 cases, and in 21 cases indurated tissue, elevated and disk-like in character and sometimes described "as hard as cancer," was explored. A solitary nodule 1 cm. or more in diameter, which proved to be a cyst or polycystic tissue composed of minute cysts was excised in 9 cases; a palpable papilloma was explored in 5; and in the remaining cases, the decision to operate was influenced by intermittent retraction of the nipple or sanguineous discharge. (Table XXII.)

With few exceptions, among the 59 cases treated by mastectomy (bilateral in 8 instances), amputation was performed either because the epithelial proliferation was interpreted as precancerous or because the presence of carcinoma was suspected. In the few exceptional cases, the extensive involvement of the breast led to amputation.

Only if the presence of cancer can be excluded with certainty, can conservative treatment be tried. These are cases where a clinical diagnosis of adenosis can be made from the endocrine status of the

TABLE XXII

CHARACTER OF THE LESION LEADING TO OPERATION IN ADENOSIS

Multiple shot-like tumors	22 cases
Indurated tissue	21 cases
Solitary cysts or polycystic tissue	9 cases
Small intracystic papilloma	5 cases
Intermittent retraction of the nipple	3 cases
Sanguineous discharge	2 cases
Total	62 cases

patient, the finding of a shotty breast with a definite edge, and multiple indefinite nodules with or without a dense, elevated, tender area which varies with the menstrual cycle. Exploration is indicated where a definite nodule larger and more distinct than the others can be palpated whether in the form of a cyst or of a papilloma with or without a bloody discharge or an intermittent retraction of the nipple. Radical surgery is not indicated, if the excised tissue, when submitted to competent pathologic examination, is diagnosed benign. Amputation of the breast to protect against the possible development of cancer is not justified on the basis of the follow-up statistics in the author's opinion. The removal of one breast does not protect against involvement of the other breast by the disease. On the other hand, if the pathologic interpretation is difficult and the lesion is classed as borderline, radical operation for cancer should be performed. A further discussion of various modes of therapy is found in Chap. 12.

10

Cystic Disease

In cystic disease, one or more cysts, a centimeter or more in diameter, form in the breasts at or near the menopause (Fig. 190). At operation the intact cyst has a thin blue dome and contains serous or cloudy fluid. The cavity has a smooth glistening lining and is without bloody or papillomatous contents. The breasts affected are of fair size and contain increased amounts of fibrous or fatty tissue. A solitary cyst is the most common benign mammary lesion at the cancer age, and its differentiation from cancer is at times a difficult problem.

Although a century has elapsed since Sir Astley Cooper described this lesion, and several decades since Bloodgood repeatedly emphasized its outstanding features, a tendency persists among pathologists to merge this clinically distinct disease with other histologic varieties of mammary dysplasia.

CLINICAL FEATURES

Solitary Cysts

Age Incidence. An analysis of our 589 cases of cystic disease shows the peak of age incidence to be between 41 and 45 years (Fig. 191). A solitary cyst of macroscopic size did not occur in subjects younger than 23 years; and even when the condition developed after the menopause, a history of trouble with the breasts prior to the change of life was usually obtained. Only four elderly patients (from 64 to 75 years) had cysts. In the histories of 73 cases it was reported that

the patient had recently passed the menopause or had noted characteristic alterations in the menstrual periods. The average age of these patients was 46.3 years.

Relation to Childbearing. In cystic disease, childless women pre-

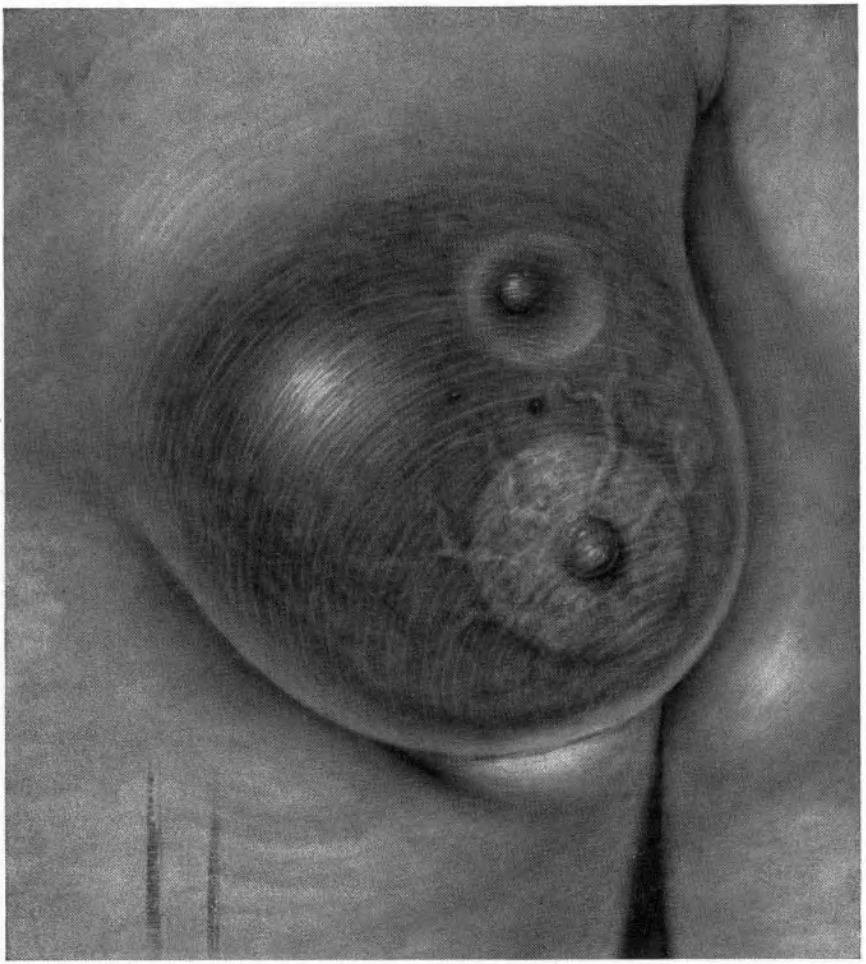


FIG. 190. Drawing to illustrate the characteristics on palpation of cystic disease. A tense, spherical, movable tumor is felt in an adipose breast.

dominate in a ratio of approximately three to two. Of 196 parous women, 74 women had borne one child and 122 had borne two or more children. In women with children, the average age of the youngest child was 10 years when the cyst made its appearance and with few exceptions four or more years had elapsed since the last pregnancy.[1]

[1] A pre-existing fibro-adenoma may undergo cystic changes during lactation in some instances.

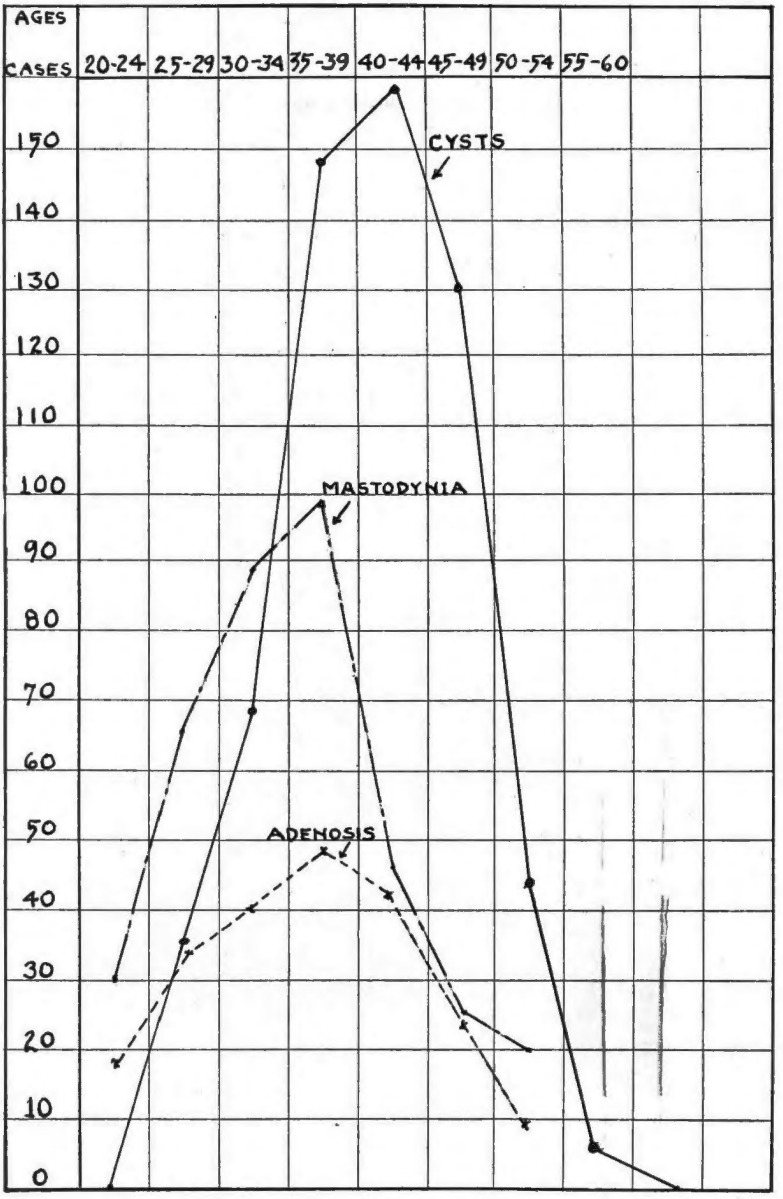


FIG. 191. The age incidence of cystic disease compared with other forms of mammary dysplasia.

Few patients with cystic disease have difficulties associated with menstruation or childbearing. Twenty-eight patients reported one or more miscarriages. Twenty-nine patients had difficulty in nursing because of insufficient milk, but this was relatively more frequent among women with multiple cysts than among those with solitary tumors. The majority of menstrual irregularities were those associated with the onset of the menopause. In only nine patients was there a record of irregular menstruation in younger women, consisting of functional or intermenstrual bleeding. Operations for cystic

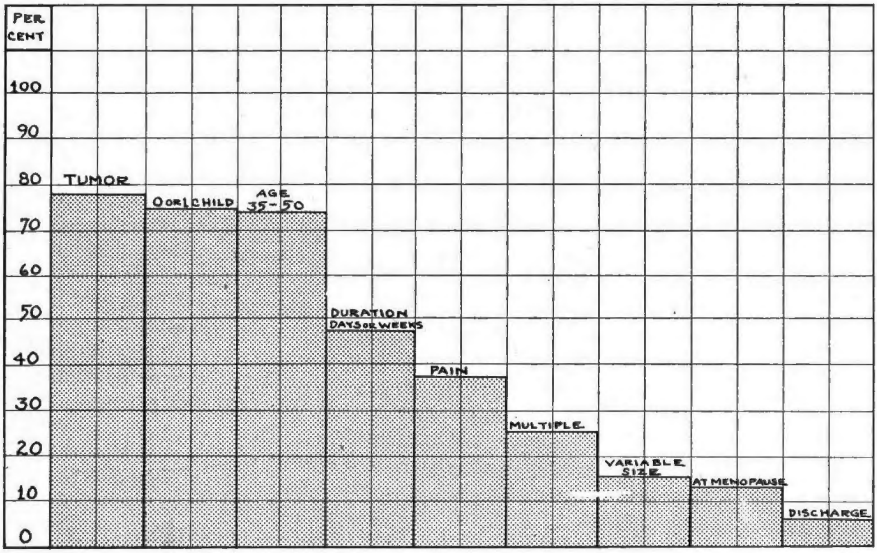


FIG. 192. Chart showing the frequency of symptoms, and findings in cystic disease.

ovarian tumors were recorded in eight patients and one of these was reported as a granulosa-cell tumor. In approximately 2 per cent of the patients, hysterectomy had been performed for myomas. The only important etiologic factors which stand out in a review of the histories are the number of childless women affected and the relatively large number of women who were approaching or at the menopause.

Although several cysts may develop over a period of years in the same patient, but a single cyst was present at the time of examination in the majority. Both breasts were affected in 11 per cent of the cases and multiple cysts at the first examination were noted in 26 per cent.

Symptoms. Cysts often make their appearance abruptly. The dura-

TABLE XXIII

DATA ON 589 CASES OF CYSTIC DISEASE

I—AGE

26–30	36
31–35	69
36–40	149
41–45	158
46–50	130
51–55	43
Over 55	4
	589

II—MARITAL

Single	201
Married—childless	106
Married—1 child	74
Married—2 or more children	122
Married—no data	86
	589

III—DURATION

Days	72	average 6
Weeks	196	average 3
Months	213	average 3.8
Years	86	average 2.6
No data	22	
	589	average 2.5 mos.

IV—SYMPTOMS

	Cases
Tumor only	359
Pain or sensitivity only	129
Pain and tumor	101
	589
Nipple discharge	32
Variable size (incl. 45 disappearing tumors)	89
At menopause (av. age 46.3)	73
Unable to nurse	29

V—LOCATION

	Cases	
Multiple (incl. 77 bilateral)	179	
Solitary (distributed as below)	410	589
Outer upper quadrant	196	
Upper mid-zone	92	
Upper inner quadrant	48	
Nipple zone	28	
Lower outer quadrant	25	
Lower mid-zone	13	
Lower inner quadrant	8	

VI—SIZE

(410 Solitary Cysts)

1 cm.	12
1½ cm.	38
2 cm.	65
2½ cm.	116
3 cm.	83
3½ cm.	53
4-6 cm.	43

VII—OPERATIONS

None	36
Aspiration	11
Excision	432
Amputation (12 bilateral)	110
	589

VIII—RESULTS

Well	No Therapy	Excision	Amputation
5– years	15	137	50
5+ years	21	165	19
10+ years	11	126	41
Mammary cancer	—	4	—

tion of symptoms was in terms of days or weeks in 268 women as compared to 299 who had observed symptoms for a period of months or years. The average duration of symptoms was 2.5 months (excluding 86 patients who had noted symptoms for a year or more). The chief complaint was the discovery of a lump, although 40 per cent

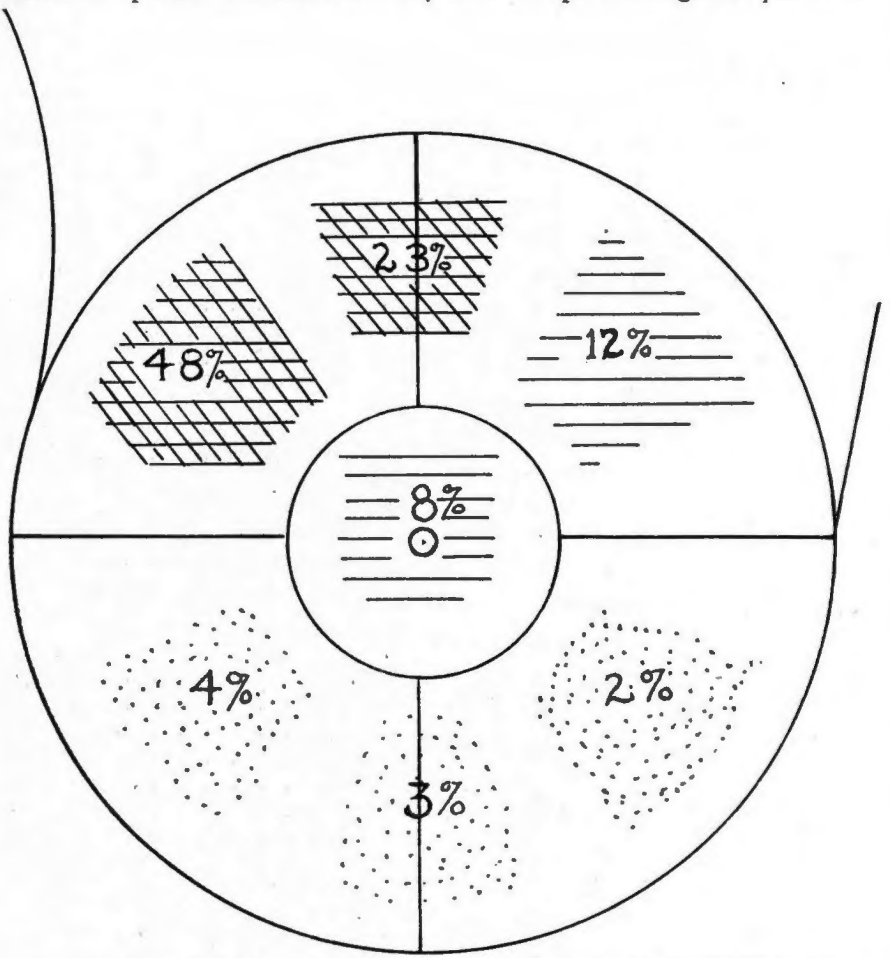


FIG. 193. Chart showing the location of 410 solitary cysts. The cross-hatched lines show the most frequent sites, the parallel lines less frequent sites, and the dotted areas the rare locations.

of the patients had noticed mild pain, soreness, a burning or sticking sensation, or merely sensitivity at the site of the cyst in addition. A serous or milky discharge from the nipple was noted in 32 cases. (Fig. 192.)

In patients who had been aware of a tumor in their breasts over

a period of months, variation in the size of the mass was frequently noted. In 45 patients the tumor had appeared and spontaneously disappeared. Because of the history of such regression, operation was sometimes postponed and in eight cases disappearance of the mass under observation made treatment unnecessary. No subsequent recurrences were noted when these eight patients were followed during the next five to 15 years.

The breasts affected by cystic disease are usually of fair size or adipose. They transilluminate readily. Rarely a cyst of appreciable size may be found in a small, dense breast complicating adenosis. The tumor when palpated is round, smooth, tense and freely movable. (Fig. 190.) In about one-third of the cases fluctuation can be made out by pressure applied alternately with the index finger of either hand. The cyst transmits light well, and upon aspiration (which is readily performed) a cloudy, milk-like fluid is obtained. At times the cyst is situated in a dense fibrous zone of breast, and in such instances the fibrous wall is thick, and the tumor may palpate like cancer. When one or more cysts have appeared and spontaneously disappeared, a residual fibrosis may be found or such a zone of increased density may precede the formation of other cysts.

Cysts are usually found away from the periphery of the breast, toward the mid-zones. The upper hemisphere is more often affected than the lower in the ratio of six to one, and the outer upper quadrant, the mid-upper zone, and the mid-outer zone were affected in the order of frequency given (Fig. 193). The most frequently reported diameter of the cyst was approximately 2.5 cm. In 78 per cent of the cases the diameter was estimated on palpation to be from 2 to 3.5 cm. In thin-walled cysts, the diameter determined after excision was usually about 1 cm. less, and in thick-walled cysts the cavity was about 3 cm. less. The cystic character of the tumor in such cases is difficult to determine before excision unless successful aspiration is performed (Figs. 194, 195, 197, 198).

Multiple Cysts—Polycystic Disease

Where a solitary cyst is palpated in the breast, several cysts 1 to 2 mm. in diameter or microscopic in size may be found in the surrounding tissue. Multiple cysts of appreciable size, however, are less frequent.

In the cases studied, 179 patients had more than one cyst when first examined and in 77 of these both breasts were affected. These cases of multiple cysts are distinguished from microcystic disease or adenosis by the following features: The cysts are larger, 2 to 4

FIG. 194

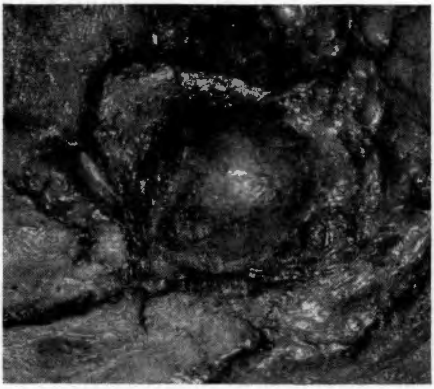


FIG. 195

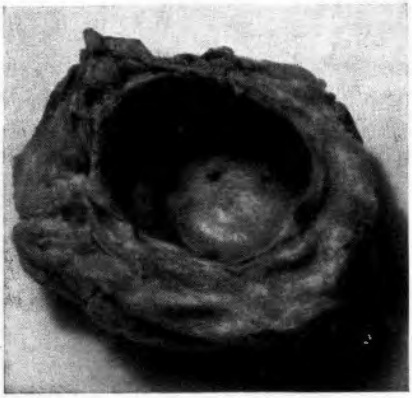


FIG. 194. The blue dome cyst of Bloodgood (see also Fig. 196, frontispiece). The appearance of an unopened cyst.
FIG. 195. Cross section of an opened cyst.
FIG. 197

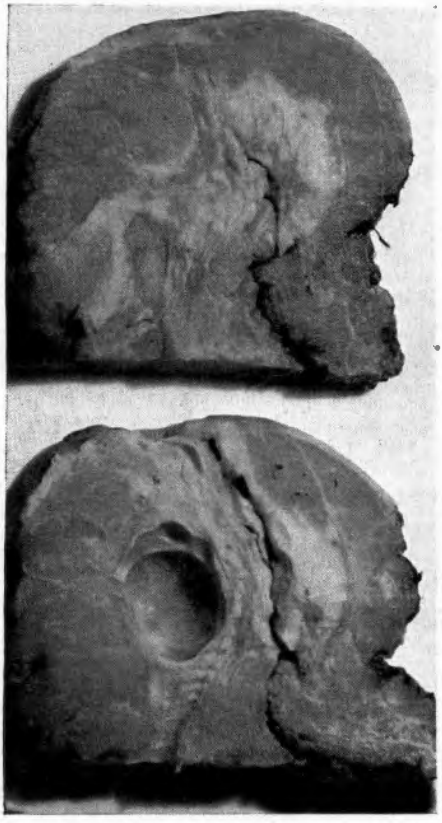


FIG. 198

FIG. 197. A thick-walled cyst which palpated like cancer. Gross specimen.
FIG. 198. Photomicrograph of the cyst wall.

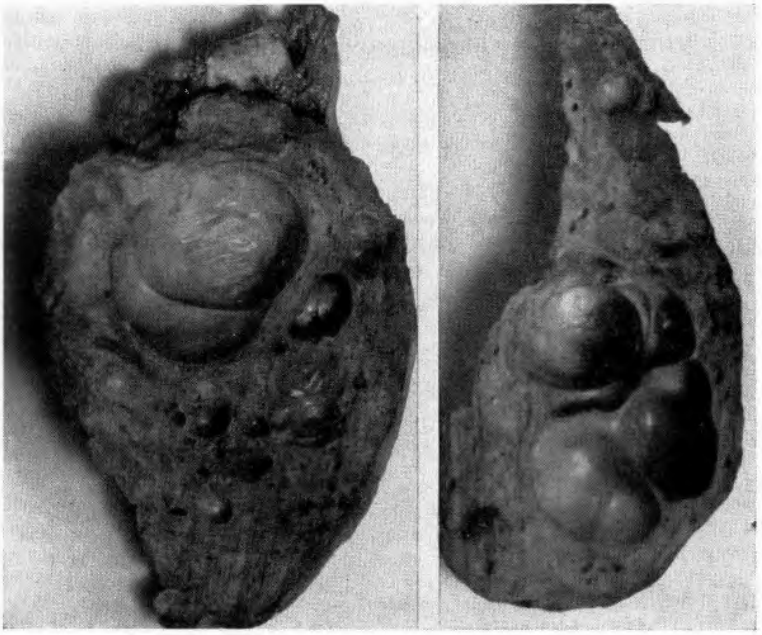


FIG. 199. Polycystic disease. Gross specimens.

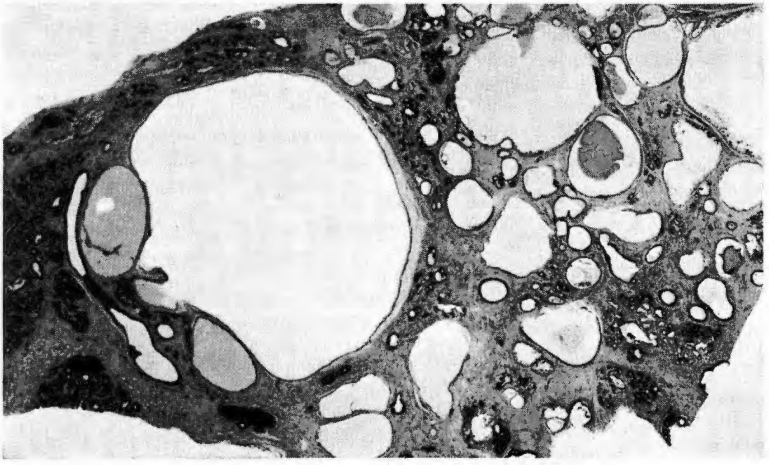


FIG. 200. Polycystic disease. Photomicrograph showing the multiplicity of cysts.

cm. in diameter, are fewer in number (usually only several cysts are palpable) and the breasts do not have the minute shot-like nodules, dense painful areas or saucer-like edges. There were 23 cases in which the condition could be characterized as polycystic and both breasts contained many cysts, 1 to 2 cm. in diameter or larger (Figs. 199, 200). As a rule these patients were younger than those with one or several cysts and the history of the cases suggested a relationship to mastodynia or adenosis.

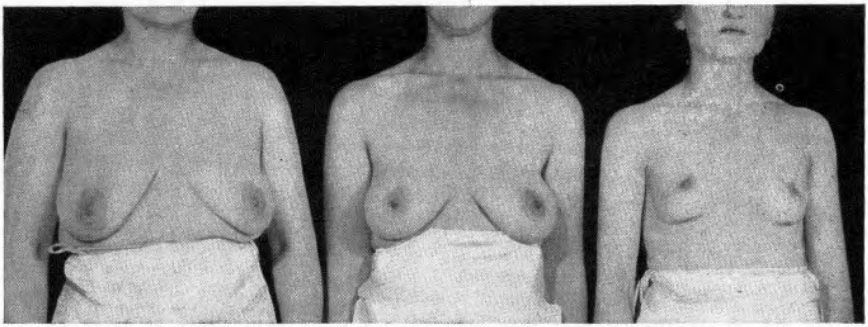


FIG. 201. Three sisters with cystic disease. The eldest sister on the left had four children and had 1 cyst at the age of 44 successfully treated by operation. The sister in the middle aged 42 had 1 child and had 2 large cysts which recurred after repeated aspirations and which were excised. The youngest sister, on the right, at the age of 33 was childless and had had repeated excisions for multiple cysts (20 to 30) in both breasts.

In the cases with multiple cysts, the peak of age incidence is between 36 and 40 years, the average duration of symptoms is 14 months as compared to 2.5 months for solitary cysts, and the condition has a greater tendency to persist or to recur. Forty-five patients had two or more operations and, of these, 12 had three or more. (Fig. 201.) Sixty-three of the patients were treated by mastectomy and six of these had bilateral amputations.

If the 38 cases of solitary cysts, in which additional cysts subsequently developed, and the 37 cases of solitary cysts with a history of a previous disappearing tumor are added to the 179 cases having multiple cysts at the first examination, one has 254 of 589 cases (43 per cent) with multiple cysts. Both breasts were affected in 118 patients. This tendency to multiplicity and to bilateral mammary involvement suggests an underlying endocrine disturbance.

DIFFERENTIAL DIAGNOSIS

Cystic disease is usually differentiated with ease from other conditions of the breast by palpation, transillumination and aspiration.

The tumor is tense, smooth, rounded and freely movable and slips easily from under the examining fingers. Both the breast and the tumor transilluminate well. The majority of cysts project into the fat overlying the breast and are readily aspirated, yielding a cloudy or serous fluid. The tumor has usually appeared abruptly without a previous history of pain or nodularity. When a thick fibrous wall surrounds a cyst buried deep in mammary tissue, diagnosis is difficult; and aspiration may prove unsuccessful because the dense fibrous wall is pushed aside rather than penetrated by the aspirating needle. In such instances exploration is indicated. When the excised cyst is bisected, the presence of a smooth lining enclosing cloudy fluid permits diagnosis from the gross specimen.

If the patient is beyond the menopause and the history of a previous cyst is not obtained, the probabilities favor a diagnosis of carci noma although the tumor may be round and freely movable.

The presence of several suspected cysts in one or both breasts does not rule out the possibility of mammary carcinoma unless the individual cysts are successfully aspirated and the characteristic serous or cloudy fluid is obtained. Bloody fluid obtained on aspiration suggests a papilloma or cancer A few red blood cells may be found under the microscope when a simple cyst is aspirated, indicating that a vessel has been penetrated during the aspiration.

PATHOLOGY

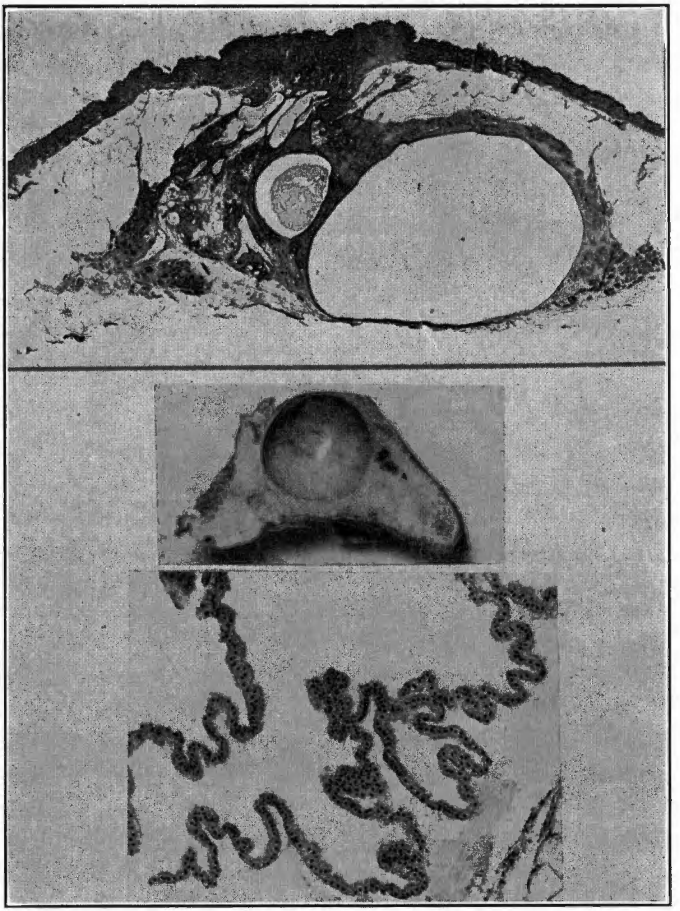
When exposed at operation the mammary cyst has a tense, thin wall with a bluish tint (Fig. 194). The blue dome which loses its color when the cyst is opened has been described by Bloodgood. Serous or cloudy fluid is contained within a cavity with a smooth and glistening wall. While the upper surface of the cyst is embedded in fat, the remainder of the circumference is embedded, as a rule, in dense fibrous tissue. Multiple dilatations of the ducts and several minute cysts may be seen in the adjacent mammary tissue. Usually, the cyst occurs in a mammary gland which is undergoing involutional changes. There is progressive hyalinization of the neighboring connective tissue and increased amounts of fat (Figs. 202-204).

Microscopically, changes are found in both lobules and ducts, in the epithelium lining these structures and in the surrounding fibrous tissue. The lobules are small, irregular and undergoing dilatation or regression. This involution, in which the number of acini are diminished and those remaining are dilated or cystic, is found also in the breasts of normal women of the same age (according to autopsy studies described in Chap. 1). It is more conspicuous, however, in

FIG. 202

FIG. 203

FIG. 204



FIGS. 202, 203, 204. The pathology of cystic disease. The cross section above shows the central location of the large cysts, the dilated ducts beneath the nipple, and the fatty involution in the surrounding breast tissue. Below are the gross and the microscopic appearance of the cyst lining.

women with cystic disease. The adjoining tubules are also dilated and may contain secretion. Occasionally small foci of epithelial proliferation resembling the tissue in adenosis may be found.

The lining epithelium of the cyst is often replaced by fibrous tissue. Persistent epithelium may be cuboidal or columnar, containing increased amounts of eosin-staining cytoplasm (Fig. 204). Desquamated and degenerating epithelium is found in the lumina of the

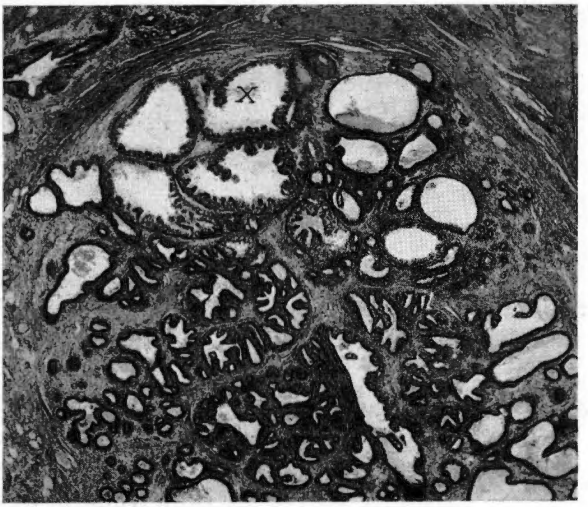


FIG. 205. Pale epithelium in cystic disease. The photomicrograph shows at the top of the lobule (x) so-called sweat-gland epithelium lining several acini.

adjoining tubules and ducts. In some of the smaller tubules and acinar structures the epithelium assumes a characteristic "sweat-gland" appearance (Fig. 205). Many interpretations have been placed upon this pale-staining epithelium. Some authors (Dawson) have interpreted this as metaplasia, others as persisting structures related to the sweat glands (Lee, et al.) and some as incomplete or imperfect lactation. In experiments performed by the author, this pale epithelium has been found in the mammary lobules of the rat and monkey after prolonged estrogenic stimulation. It must be looked upon, therefore, as a physiologic change, rather than as true metaplasia or as sweat gland in origin. It is the result of an intense and premature ripening in which the acinar elements are converted into duct-like epithelium.

The breasts affected in cystic disease are poor in lobular structures and rich in fibrous tissue. Increased amounts of connective tissue are found as a rule. The epithelial structures in the neighborhood of the cyst are obliterated by dense sclerotic fibrous tissue or

surrounded by increased amounts of young periductal connective tissue. In general these pathologic changes are an exaggeration of a phase of involution found in normal women at or near the menopause (see Chap. 1).

Cysts with papilloma projecting into the cavity (intracystic papilloma) or with walls formed by cancerous tissue (cancer cysts) are not the result of the pathologic process involved in cystic disease. Intracystic papillomas and cancer cysts occur after the menopause and affect more often the large ducts near the nipple. The epithelial proliferation in both conditions has distinctive features. Simple cysts occur prior to or during the menopause and affect the smaller ducts and terminal tubules. In cysts of long standing the epithelial lining is replaced by fibrous tissue.

CLINICAL COURSE AND PROGNOSIS

In the majority of cases of cystic disease there is but one cyst of appreciable size occurring at or near the menopause. The breast affected is undergoing cystic involution and the disease is self-limited. Spontaneous regression prior to treatment was noted in 7.5 per cent of the cases. When aspiration only was employed as a method of treatment, the cysts refilled or additional cysts occurred in two-thirds of the cases. In 432 cases treated by excision, one or more cysts subsequently appeared in the same or opposite breast in 67 cases. (15 per cent.) In 116 of these cases the initial excision was for the removal of two or more cysts. The percentage of cases in which cysts made their appearance following unilateral amputation was approximately the same (16 out of 110 cases), although amputation was more often performed for multiple cysts. Among a total of 387 cases followed for more than five years, four developed mammary carcinoma (approximately 1 per cent) (Table XXIV). In nearly every instance where further trouble developed in the mammary gland, the subsequent condition proved to be another cyst.

The present study therefore indicates that women treated by excision for cystic disease remain free from further mammary disorders in 84 per cent of the cases, develop additional cysts in 15 per cent and mammary cancer in 1 per cent of the cases. In those cases where the condition is recurrent, the time interval between the initial treatment and the appearance of another cyst is between six months and four years in 80 per cent of the cases. Nearly all patients were ultimately reported well within less than 10 years of the first examination. There were but two cases in the present series where a

TABLE XXIV

END-RESULTS IN 387 CASES OF CYSTIC DISEASE FOLLOWED MORE THAN 5 YEARS

1—No operation advised[1] (32 cases)	Well over 5 years	21 cases
	Well over 10 years	11 cases
	Mammary cancer	—
2—Excision only[2] (295 cases)	Well over 5 years	165 cases
	Well over 10 years	126 cases
	Mammary cancer	4 cases
3—Unilateral amputation[3] (51 cases)	Well over 5 years	19 cases
	Well over 10 years	32 cases
	Mammary cancer	—
4—Bilateral amputation (9 cases)	Well over 10 years	9 cases

[1] Includes three cases treated by aspiration and eight cases which had tumors which disappeared spontaneously before the advised operation could be performed.

[2] Sixty-one of these patients had additional cysts (recurrent disease). Twenty-one were ultimately well without further treatment; 28 had a second or third excision and 12 a unilateral amputation but all of them were ultimately reported well beyond the five-year period.

[3] Sixteen of these patients were treated for cysts developing in the opposite breast but were ultimately reported well beyond the five-year period.

second cyst appeared ten years after excision and one case where the interval was 11 years (Table XXV).

TABLE XXV

THE INTERVAL BETWEEN OPERATION AND THE APPEARANCE OF ADDITIONAL CYSTS

In 83 Recurrent Cases[1] of Cystic Disease

INTERVAL YEARS	EXCISION NO. OF CASES	AMPUTATION NO. OF CASES	TOTAL
0–1	7	2	9
1	13	3	16
2	15	4	19
3	10	3	13
4	7	3	10
5	3	1	4
6	4	0	4
7	1	0	1
8	2	0	2
9	2	0	2
10	2	0	2
11	1	0	1
	67	16	83

[1] There were 37 additional cases with simple cysts who gave a history of a disappearing tumor, bringing the total of recurrent cases to 120.

The disappearance of the cyst may be as abrupt as its appearance and in eight cases arrangements made for operation were cancelled

because of such spontaneous disappearance. These patients remained well without further treatment.

In 23 cases in the present series, where a previous cyst had been removed and the patient was seen because of one or more additional cysts, the diagnosis of recurrent cystic disease was made on the basis of the history and clinical findings and no further operation was advised. Twenty-one of these 23 cases were ultimately reported well without further operation. The cysts disappeared within seven months to seven years and the patients remained well thereafter. In two patients the cysts were still palpable at the last examination, one at the end of two years and the other at the end of three years. It is interesting that in this series the first patient with cystic disease to be treated by simple excision was also the first in whom a second cyst was allowed to regress without operation: in a woman, 37 years old, a cyst was excised in 1897 and a second cyst formed in 1898 and ultimately disappeared; the patient was well in 1932, 35 years after her operation. Spontaneous regression is the rule during pregnancy, and in the few cases where the cysts have persisted, the cysts disappeared during or subsequent to lactation.

TREATMENT

The majority of cases of cystic disease have a single palpable nodule in the breast and are in the cancer age. Local excision permits pathologic verification of the diagnosis and in 85 per cent of the cases additional cysts do not occur after such treatment. While aspiration confirms the diagnosis of cystic disease, the cyst often refills. In the author's experience irradiation of the breast or ovaries is not beneficial. Cysts usually do not respond well to endocrine therapy. A solitary cyst therefore is best treated by simple excision. Amputation of one breast does not prevent the appearance of cysts in the opposite breast and the incidence of mammary carcinoma in these patients (1 per cent) does not justify bilateral amputation.

In cases where a single cyst has been previously excised and additional cysts appear, or in cases with multiple cysts or polycystic disease, aspiration may be used to verify the cystic nature of the tumors. In such cases repeated observations and attempts to control the condition by endocrine therapy are justifiable. The decision presupposes accurate diagnosis and should never be made without the examination of the breast by a thoroughly experienced consultant. If the patient is beyond the menopause when additional cysts have made their appearance, the presence of a single recurrent

nodule greatly increases the likelihood of cancer. A second excision is indicated in such instances.

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11

Endocrine Aspects of Chronic Cystic Mastitis

As we have described in the preceding chapters, chronic cystic mastitis or mammary dysplasia comprises three groups of cases: mild or early cases with painful dense mammary tissue (mastodynia); cases with more persistent and definite nodularity (adenosis, or Schimmelbusch's disease); and a third group of cases characterized by the development of one or more cysts of appreciable size (cystic disease).

GENERAL PHYSIOLOGY

The endocrinology of mammary dysplasia is intimately associated with the physiology of lobule formation. In mastodynia, lobule formation is partially suppressed and many of the terminal tubules show irregular and decreased numbers of sprouts and increased periductal stroma. In adenosis, epithelial proliferation within or infiltrating beyond the ends of the tubules replaces normal lobule formation; sometimes minute cysts and papillomas are formed. In

cystic disease the normal lobules have undergone involution and some are replaced by large cysts developing in the end-buds of the terminal tubules.

Mammary dysplasia is practically confined to cyclic women. It does not occur during normal puberty, for, at this period, lobule formation has not yet begun; and it is not seen in the male breast, where lobule formation is absent. It is rarely observed after the menopause when the lobular structures have disappeared as a result of senile involution.

Normal pregnancy and mammary dysplasia are incompatible. Mammary dysplasia is not found in women who have recently borne children and is rare at any time in women with large families. The stimulus to normal lobule formation is most intense during pregnancy and mammary dysplasia existing prior to pregnancy undergoes regression at this time.

The clinical history in cases of mammary dysplasia suggests that the condition is dependent upon ovarian dysfunction. In mastodynia, the menstrual periods may be closer together than normal, the cycles being 25 or 26 days or less. This is often true of the cycle which precedes an attack of pain and swelling in the affected breast. There is also a relatively high percentage of sterility in married women with this condition. In adenosis, the menstrual periods are usually irregular. Many of these patients are approaching the menopause and have the characteristic symptoms of nervous instability. Thyroid disturbances and functional uterine bleeding may accompany this condition. In cystic disease, the menstrual cycles have usually been normal during the preceding years but the patient at the time is approaching or passing through the menopause and one or more periods may be missed.

TABLE XXVI

SALIENT ENDOCRINE FEATURES OF MAMMARY DYSPLASIA

1. *All forms show distorted lobules.*
   a. Mastodynia shows suppression of lobules
   b. Adenosis shows hyperplastic lobules
   c. Cystic disease shows dilated lobules
2. *The disease occurs in cyclic women.*
   a. It is not found in the male breast
   b. It is not found in adolescence
   c. It is incompatible with pregnancy
3. *Irregularity of the menstrual cycle is common.*
   a. In mastodynia the periods are close together
   b. In adenosis the cycle is irregular
   c. Cystic disease occurs at the menopause

While most observers agree that mammary dysplasia is an expression of ovarian dysfunction in cyclic women, there is less agreement on the exact nature of the endocrine disturbance. Taylor found a high incidence of menstrual disorders and cystic ovaries and concluded that the condition was associated with ovarian dysfunction in some cases. Hormonal assays on the urine led him to conclude that a simple excess or lack of estrogenic or gonadotropic hormone was not the underlying cause. Friedman and his co-workers came to similar conclusions. It must be emphasized, however, that endocrine assays on isolated collections of urine are unsatisfactory and total collections of the urine daily through one or more cycles are necessary to study these cases adequately. Moreover, the endocrine picture is incomplete unless it includes determinations of corpus-luteum function, which can be studied by measuring pregnandiol excretion.[1] In reviewing the experiments of Taylor, Bucher and Geschickter, and himself, Nathanson concludes that excretion studies are slightly suggestive of a hormonal imbalance, as the etiologic factor in adenofibrosis (mastodynia and adenosis).

Determinations based upon methods of extraction for total estrogens show that the normal urinary excretion during a menstrual cycle varies between 10 and 60 rat units per 24 hours of output; the total for a normal cycle is between 400 and 600 rat units (4000 to 6000 international units) (Frank, Mazer, Friedman et al., Smith and co-workers, Chap. 2).

The corpus-luteum function during the menstrual cycle has been measured by determining the quantity of pregnandiol in the urine. Following ovulation, values varying from 2 to 10 mg. per 24 hours are obtained. The total for a complete cycle is between 15 and 60 mg., depending upon the method of extraction (Browne and Venning; Stover and Pratt; Hamblen, Ashley and Baptist).

OVARIAN FUNCTION IN MAMMARY DYSPLASIA

Estrogen and Pregnandiol Excretion in the Urine

Pregnandiol determinations were carried out on the urine in seven cases of mastodynia, five cases of adenosis and four cases with cystic disease. Four normal controls were included to which were added three cases of arrested mammary dysplasia, one each of mastodynia, adenosis, and cystic disease. Estrogen determinations were made in 12 of the 23 subjects. The method of assaying estrogen and pregnandiol on the same specimen of urine is given in the foot-

[1] Pregnandiol, a metabolic end-product of the corpus-luteum hormone was first demonstrated to be an index of luteal function by Venning and Browne.

TABLE XXVII

ESTROGEN- AND PREGNANDIOL-EXCRETION DETERMINATIONS

PATIENT	AGE	CYCLE	PREG-NANDIOL	ESTRO-GEN	REMARKS
			Normal Individuals		
		days	*mg.*	R.U.	
Gos.	33	28	49.6	500	Normal (entire cycle)
Tut.	24	25	58.5	—	Normal
Wil.	23	28	25.6	826	Infected nipple
See.	25	27	40.0	—	Normal
Hun.	30	39	37.0	624	Arrested mastodynia—2 mo.
Sim.	34	25	36.7	—	Arrested adenosis—5 mo.
Wei.	33	26	26.2	302	Arrested cystic disease—21 mo.
			Mastodynia		
Lev.	28	24	13.2	—	Bilateral
Mah.	27	25	10.5	—	Unilateral
Fir.	28	23	14.6	—	Unilateral
Cut.	34	23	6.7	—	Bilateral
Had.	33	27	9.1	447	Bilateral
McC.	33	27	14.5	368	Unilateral
Sch.	28	23	10.6	—	Bilateral
			Adenosis		
Shep.	42	40	12.8	400	Bilateral
How.	38	25	12.6	260	Bilateral
Ang.	37	36	10.8	—	Bilateral
Flu.	27	28	10.9	1752	Bilateral—previous period 31 days
Pet.	46	22	12.4	—	Bilateral
			Cystic Disease		
Zin.	42	23	3.3	80	Bilateral—after cyst developed
Lut.	41	27	4.9	305	Unilateral—after cyst developed
Prin.	43	26	55.6	2085	Unilateral—1 mo. before cyst developed
Gos.	34	28	22.8	—	Unilateral—1 mo. before cyst developed

note.[1] All of the urine was collected from the tenth day of the cycle until the next period. Individual assays were run on 48-hour collections. The results are shown in Table XXVII. Among the seven patients placed in the normal group, the pregnandiol values ranged from 25.6 to 58.5 mg. per cycle, and averaged 30.1 mg. Four of these patients had estrogen determinations, ranging from 302 to 826 rat units per cycle. These values for normal patients correspond with those reported in the literature.

The pregnandiol determinations were low in all of the cases of mastodynia. The average in the seven cases was 11.3 mg. Two of these patients had estrogen determinations which were within normal limits.

The assays for pregnandiol in the cases of adenosis were similar to those found in mastodynia, averaging 11.9 mg. Three of the patients had estrogen determinations; one of these was high, 1752 rat units.

Two cases of cystic disease were assayed after the cysts had developed. The pregnandiol values were extremely low, 3.3 and 4.9 mg. One case of cystic disease was assayed the month before the cyst developed. This patient was studied because two sisters had cystic disease (Fig. 201). There was a normal pregnandiol determination (55.6 mg.) and abnormally high estrogen excretion (a total of 2085 rat units). The following month the patient developed a cyst.

The endocrine determinations in mastodynia and in adenosis are similar. In both of these groups of patients, the pregnandiol values are low, averaging 11.6 mg. per cycle as compared to 30.1 for the controls. Estrogen values may be normal. These cases may be looked upon, therefore, either as having a corpus-luteum deficiency or as having a relative hyperestrinism. (Figs. 206-209.) Adenosis may be regarded as a more advanced stage of mastodynia. Nearly all patients with adenosis give a history of painful breasts. While the majority of cases with mastodynia, when followed for a period of five to 10 years, show spontaneous regressions, a small group develops adenosis during such a period of time (Chap. 8).

The endocrine disturbance in cystic disease cannot be analyzed from the few assays performed to date. (Figs. 210, 211.) When these assays are taken in conjunction with the animal experiments reported below, it seems probable that the cysts result from an intense or unopposed estrogenic stimulus. The period of stimulation may

[1] The estrogen and pregnandiol determinations are both made on the same 48-hour specimen of urine. The total specimen is acidified to pH_8 and incubated, and then extracted with butanol. The separation of estrogen and pregnandiol from the butanol extract is discussed by Bucher and Geschickter. The pregnandiol is determined by gravimetric analysis. The estrogen determinations were made by acidifying a sodium hydroxide filtrate after precipitating the pregnandiol. This acidified solution of estrogen was extracted with ether, taken up in oil, and assayed on castrated female rats.

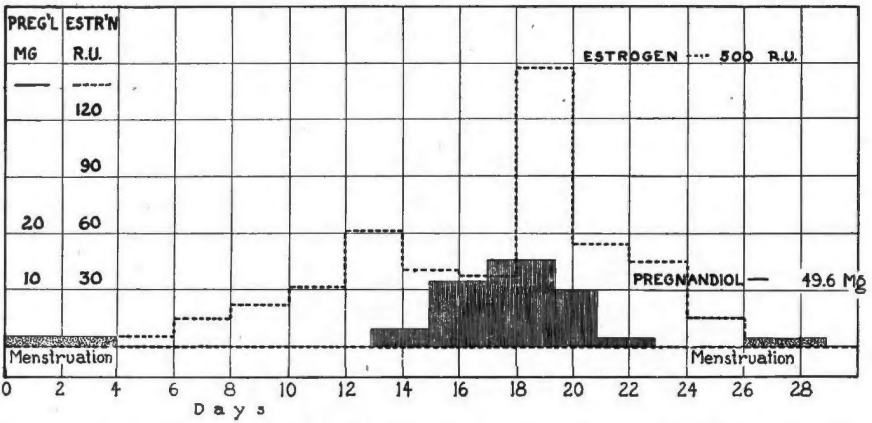

FIG. 206. Endocrine assays in normal cyclic women. Chart showing the urinary excretion of pregnandiol and estrogen in the normal cycle.

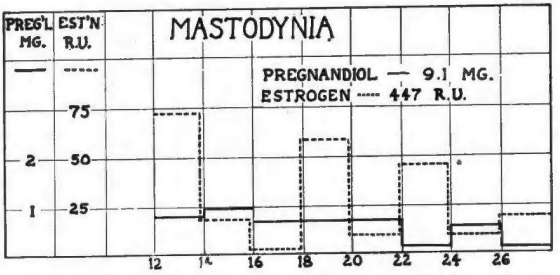

FIG. 207. Endocrine assays in mastodynia. Chart showing the urinary excretion of pregnandiol and estrogen in mastodynia.

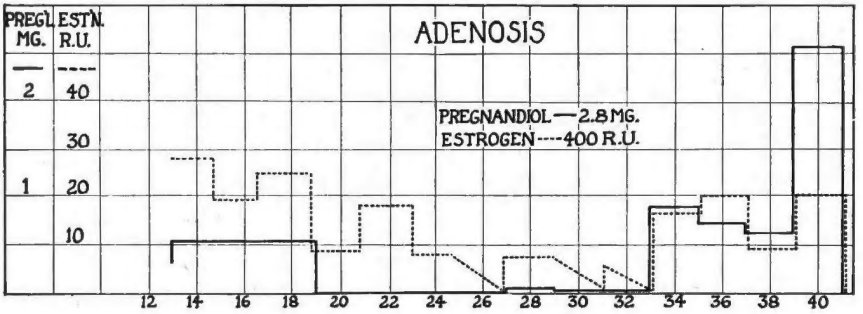

FIG. 208. Endocrine assays in adenosis. Chart showing decreased pregnandiol excretion and prolongation of the cycle in a case of adenosis.

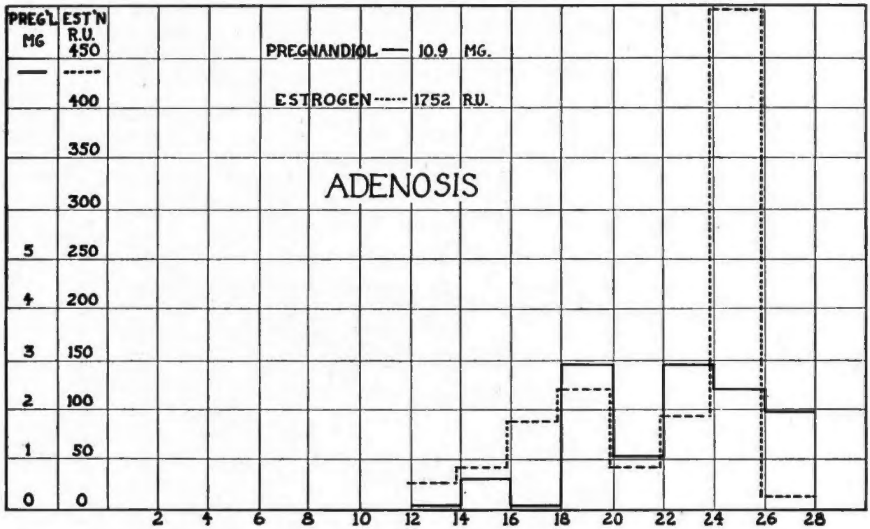

FIG. 209. Endocrine assays in adenosis. Chart showing decreased pregnandiol and high estrogen values in a case of adenosis.

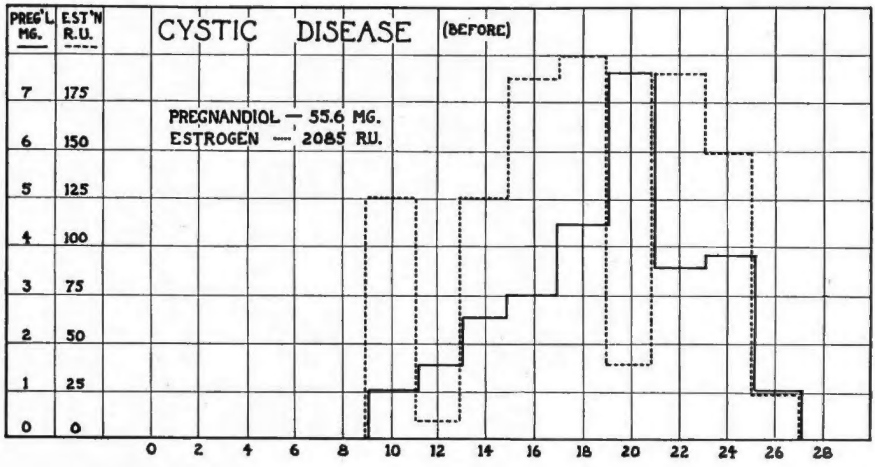

FIG. 210. Endocrine assays in cystic disease. Chart showing high estrogen and normal pregnandiol before development of the cyst.

be relatively brief, a matter of a few weeks, and the withdrawal of the stimulus (fall in estrogen level) followed by secretory activity may play a role in the development of some of the larger cysts.

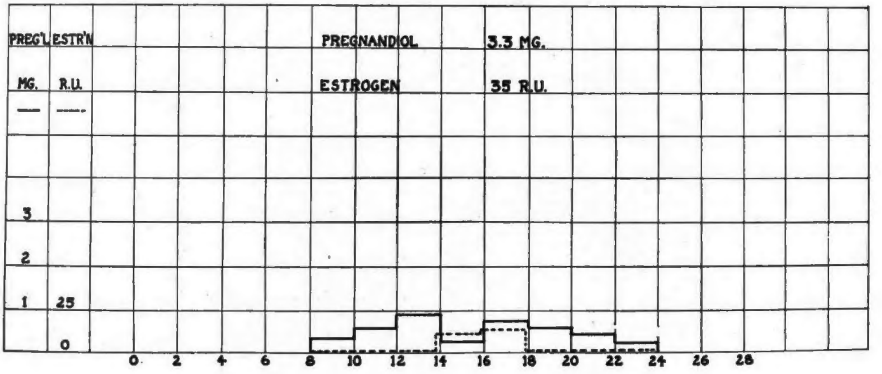

FIG. 211. Endocrine assays in cystic disease. Chart showing diminished pregnandiol and estrogen excretion after cyst formation.

Experimental Production of Mammary Dysplasia

A number of workers have reported pathologic changes in the mammary glands of animals including cystic changes and adenocarcinoma resulting from prolonged overstimulation with estrogen. (Lacassagne, Bonser, Gardner, Smith, et al., and Geschickter.)

Burrows found that continuous treatment of mice with estrogen caused cysts and hyperplasia which he considered analogous to chronic cystic mastitis in human beings. MacDonald observed epithelial proliferation and dilatation of ducts in rabbits treated for three months with estrogen and cystic changes of the mammary glands of rats have been previously reported by Astwood and Geschickter.

By varying the dosage of estrogen and its method of administration and by combining this with other hormones which produce lobule formation, various pathologic changes can be produced in the rat which simulate chronic cystic mastitis in the human breast. The variety of endocrine methods that can be employed and the range of pathologic changes make it difficult to be certain that the method of experimentation parallels the etiologic factors which produce the disease in patients.

Estrogen in physiologic doses in the rat produces rapid extension of the duct tree, similar to the marked growth observed in the human female during adolescence. The outstanding difference is that the

fibrous stroma of the rat breast is sparse and is less sensitive to estrogenic stimulation.

The diffuse lobule formation of pregnancy cannot be produced in the castrated rat by estrogen alone although with moderate dosage in intact animals, luteinization of the ovaries occurs and the breast resembles that of early pregnancy. The extent of growth in the mammary tree with strong physiologic doses of estrogen (2.5 to 10 gamma of estrone daily) has definite limitations. After six to eight weeks, size at the upper limits of normal for mature virgin females may be produced in young castrated female rats.

In the rat, as in the human breast, normal lobules are dependent upon the proper ratio of estrogen and luteal hormones; the proportion is one unit of progesterone and 5 gamma of estrone. The synthetic male hormone, testosterone propionate, in the ratio of 1 mg. to 4 gamma of estrone may be substituted for progesterone.[1]

MASTODYNIA AND ADENOSIS RESULTING FROM ESTROGEN ALONE

If maximum physiologic doses of estrone (2.5 to 5 gamma) are administered to female rats daily for long periods, the mammary gland fails to increase in size but shows abnormalities of the duct tree. Under the microscope, a pathologic change similar to that seen in mastodynia occurs in 45 to 90 days and later (300 to 380 days) the changes characteristic of adenosis are seen. That such changes may be produced, the rats are not castrated until after the first two weeks, thereby permitting lobular budding (in response to luteinization of the ovaries). After castration, the changes of mammary dysplasia are produced with estrogen alone. The degree of fibrosis accompanying the lobular irregularities is quite marked. (Figs. 212-216.)

On the basis of these experiments it may be concluded that in the human breast, mastodynia and later adenosis may follow after a few months of estrogenic stimulation alone, the estrogen occurring in amounts within normal limits, and acting upon a gland that has achieved full size and lobular development. Such estrogenic stimulation in the absence of luteal function may occur in adult women who have had inflammatory pelvic disease, or in cases of sterility with anovulatory cycles, or in women approaching the menopause. The etiologic factor is a moderate but absolute hyperestrinism.

[1] The synthetic hormone, testosterone propionate, is closely allied in its formula to hormones present in the corpus luteum of pregnancy and can be substituted for them in the experimental production of mammary lobules in the rat and monkey. The sensitivity of the mammary gland to this otherwise masculinizing hormone is also shown in the normal adult male rat where lobule formation approaches that seen during early pregnancy in the female.

Mastodynia or adenosis may also occur as a result of a relative hyperestrinism in women with increased or normal estrogenic output in the presence of low corpus-luteum function as shown above by urinary assays. This is undoubtedly the way in which the disease develops in the majority of cases.[1] This is also demonstrated by a second group of experiments performed on rats.

FIG. 212 FIG. 213

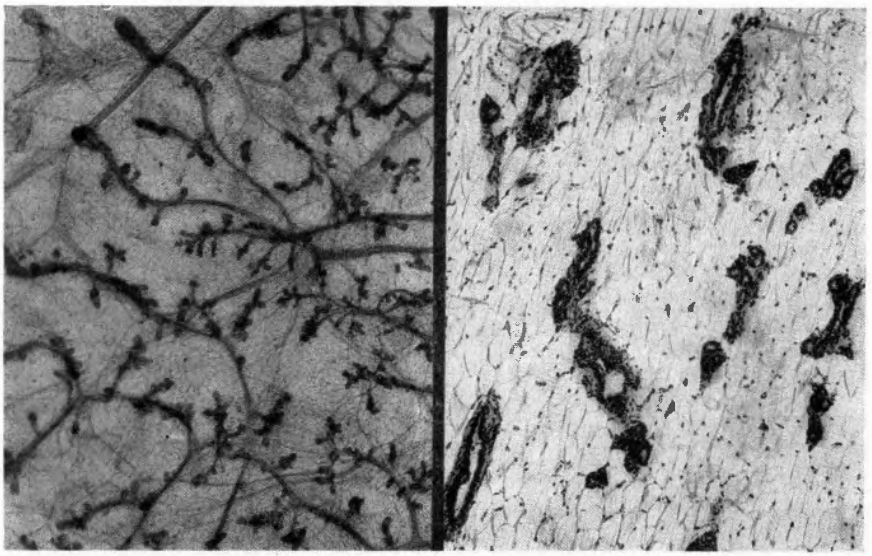

FIG. 212. The normal structure of the mammary gland of the rat. Whole mount showing mammary ducts without lobules at puberty.
FIG. 213. The microscopic appearance of the gland in early adolescence.

MASTODYNIA AND ADENOSIS RESULTING FROM ESTROGEN-PROGESTERONE IMBALANCE

Microscopic changes simulating mastodynia and adenosis may be produced in the rat's breasts by combining injections of estrone with testosterone or progesterone. If, instead of the normal lobule-producing ratio of hormones, larger doses of estrone are given, or more minute amounts of testosterone, irregular epithelial proliferation appears and changes like those of mastodynia and adenosis result.

A group of female rats, 21 days old, were castrated and were given either 10 or 20 gamma of estrone in oil injected daily together with

[1] Cases of mammary dysplasia in which corpus-luteum function is entirely absent must be relatively rare. That they do occur is illustrated by the presence of adenosis in patients with functional uterine bleeding where corpus-luteum function (as measured by pregnandiol excretion) is zero (Seegar).

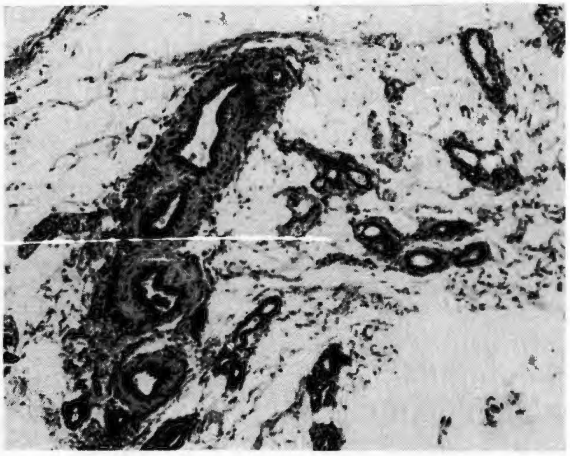

FIG. 214. Mastodynia followed by adenosis in the mammary gland of the rat in response to long physiologic doses of estrogen. Photomicrograph showing mastodynia after 45 days of treatment with 5 gamma estrone daily. (The rat was castrated two weeks after onset of treatment.)

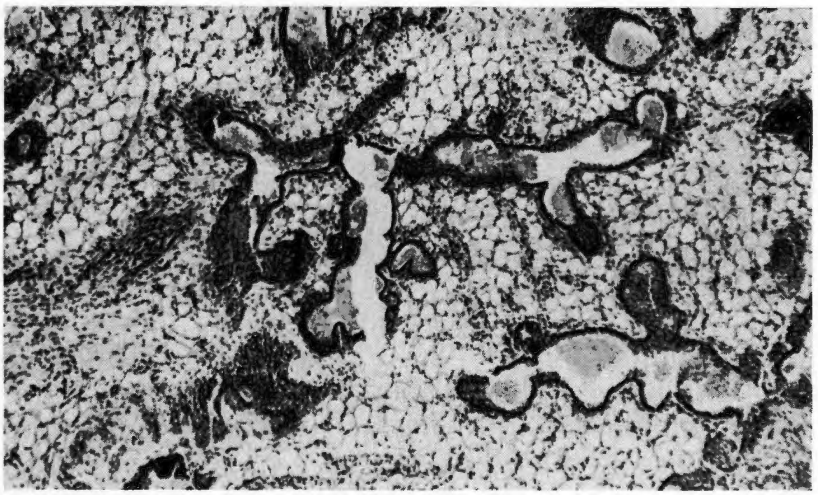

FIG. 215. Photomicrograph showing adenosis after 322 days of treatment with 5 gamma estrone daily in the same rat shown in Fig. 214.

small or decreasing doses of testosterone varying from 5 to 0.25 mg. for a period of five to six weeks. (Figs. 217, 218.) Instead of normal lobule formation, irregular epithelial proliferation in the end-buds and cystic dilatation of the terminal tubules were produced, simulating mastodynia or early adenosis. The same type of pathologic change was attained by varying this experiment. In another group of rats, females were castrated on the 72d day. Two hundred gamma of estrone were injected daily for 42 days and then 0.5 mg. daily of

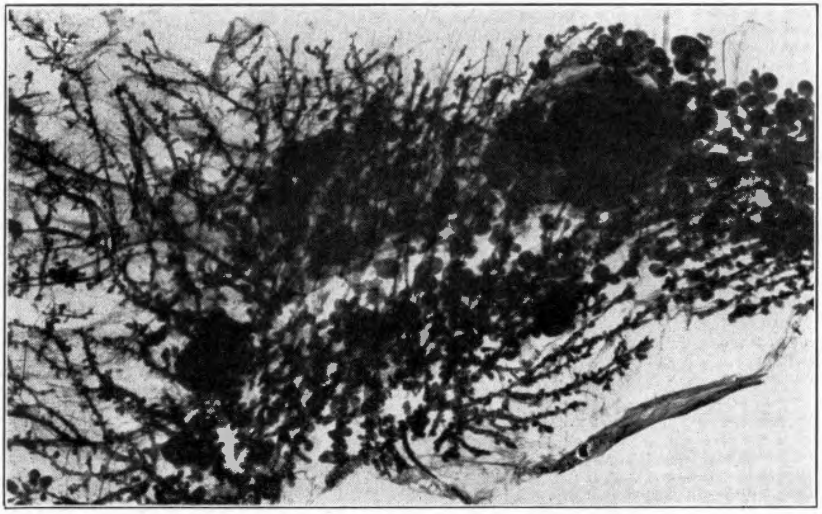

FIG. 216. Adenosis in the mammary gland of the rat. Whole mount showing adenosis after prolonged treatment with estrogen.

testosterone for an equal length of time. This sequence of injections was then repeated for like periods of time. The typical pathologic changes of adenosis were thus produced. In another variation of this experiment intact females one month of age received five pellets of crystalline estrone totalling 15 mg. and at the same time only a 3 mg. pellet of testosterone. The breasts removed at the end of 1½ month and 8 months respectively showed mastodynia followed by typical adenosis. A more detailed discussion of these experiments is given in Chapter 33.

These experiments suggest that pathologic changes of mastodynia or adenosis in women result from imbalanced ovarian function in which varying intensities of estrogenic stimulation are improperly balanced by low or deficient outputs of luteal hormone. As stated above, it seems likely from the urinary assays performed on patients that the largest group of cases of mastodynia and adenosis occur in

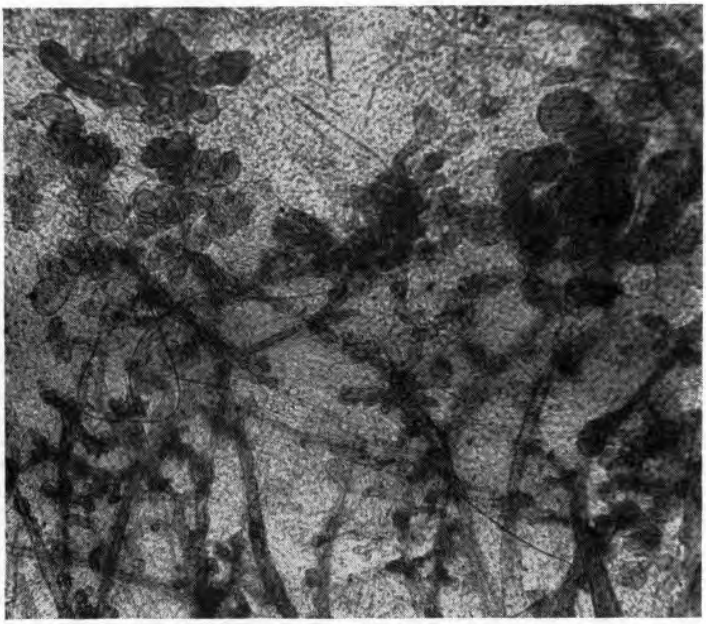

FIG. 217. Mastodynia in the rat in response to combined treatment with estrogen and testosterone. Mastodynia after 57 days of treatment (100 gamma estrone, 0.5 mg. testosterone propionate—given in sequence).

FIG. 218A FIG. 218B

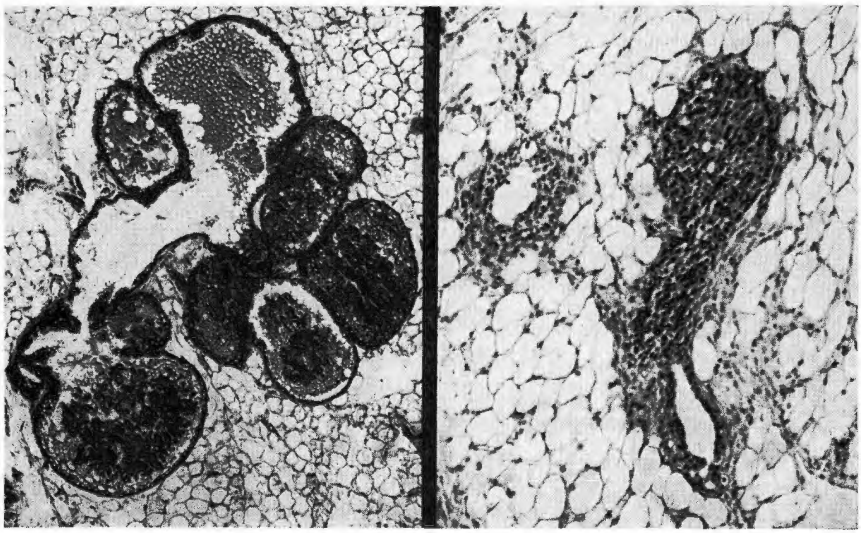

FIG. 218. Adenosis in the mammary gland of the rat after estrone (50 gamma daily) and testosterone propionate (1 mg. daily) given in sequence during 122 days. The photomicrographs show (A) cystadenoma and (B) duct adenoma.

women with normal or increased estrogenic output but with subnormal corpus-luteum function. It is significant to note in the experiments described above, that even with extremely high estrogen dosage (200 gamma in oil daily or 15 mg. of crystalline material implanted as pellets), small amounts of testosterone (a substitute for the luteal hormone) prevented the formation of large cysts and instead produced lobular irregularity, fibrosis and dilatation of the terminal tubules. In other words, mastodynia or adenosis, rather than cystic disease, was produced.

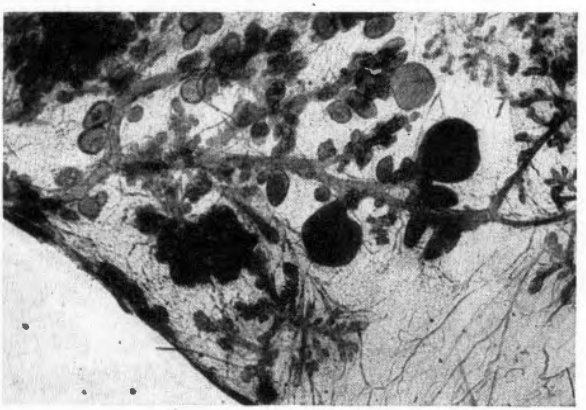

FIG. 219. Whole mount showing the appearance of the gland in Fig. 218.

CYSTIC DISEASE RESULTING FROM INTENSE ESTROGENIC STIMULATION

Extremely high doses of estrogen (100 to 200 gamma of estrone daily) fail to produce rapid extension of the duct tree in young castrated rats. Instead, normal growth is stunted and within two weeks the dwarfed duct tree shows distortion and widening with irregular club-shaped twigs. With further administration of these high doses, large cysts resembling those found in patients with cystic disease are produced. These are seen within a period of three to four weeks after the onset of the experiment if the specimens are taken four to five days after stopping the estrogen injections.

Cysts may also be produced when pellets of estrone or other estrogens are implanted in castrated rats. Here there is a gradual but continuous absorption of the hormone so that increasingly high concentrations are reached. Under these conditions many cysts of various sizes appear within two to three months (Figs. 220, 221).

These experiments indicate that human cystic disease is the result of high estrogenic stimulation partially or totally unopposed by

corpus-luteum function. The rapid development of large cysts with interrupted high doses of estrogen corresponds with the clinical history of the disease. In patients, large cysts usually make their appearance abruptly near the menopause when estrogenic output may be high and when corpus-luteum function is absent. The rapid appearance of the cysts with high interrupted doses suggests that a fall in

FIG. 220. Large cysts produced in the mammary gland of a castrated female rat after 6 weeks treatment with 100 gamma of estrone daily (whole mount).

the level of the estrogenic hormone may contribute to the rapid development of the cyst. This is verified by the rapid development of large cysts after the withdrawal of the estrogenic stimulation.[1]

ENDOCRINE VARIATIONS IN MAMMARY DYSPLASIA

If clinical and experimental knowledge is combined, it is possible to subdivide the patients with chronic cystic mastitis into several endocrine groups. (Table XXVIII.)

Types

Women with mastodynia fall into two major groups. In one group the ovarian estrogenic function is high so that there is a relative

[1] To insure complete withdrawal of estrogen, some of the animals in this experiment were adrenalectomized.

TABLE XXVIII

VARIETIES OF MAMMARY DYSPLASIA AND THEIR ETIOLOGIC FACTORS

DIAGNOSIS	CLINICAL VARIETY	URINARY ASSAY	EXPERIMENTAL PRODUCTION (in castrated female rat)	ETIOLOGY
Mastodynia followed by Adenosis	a. Sterile women b. Pelvic inflammatory disease c. Approaching menopause Breasts variable in size Menses scanty and close together	Normal estrogen; absent or extremely low pregnandiol	*Mastodynia* 5 to 10γ estrone daily for 1 to 3 months *Adenosis* 5 to 10γ estrone daily 300 to 400 days	Moderate but absolute hyperestrinism for brief or longer periods
Mastodynia	Fertile women in child-bearing period but not recently pregnant; highly sexed; breasts well-developed; normal periods	High estrogen; moderately low pregnandiol	200γ of estrone daily or estrone pellets with low doses of progestin or testosterone 40 to 60 days	Extreme but relative hyperestrinism for relatively short periods
Adenosis	Young childless women; small dwarfed breasts; periods widely spaced	High estrogen output; low pregnandiol	200γ of estrone daily or estrone pellets with low doses of progestin or testosterone 100 to 300 days	Extreme but relative hyperestrinism for long periods
Adenosis preceded by Mastodynia	Women in late thirties or early forties; childless or no recent pregnancies; breasts show loss of fat, lumpy definite edge with adenosis; periods irregular	Normal estrogen; low or extremely low pregnandiol	20 to 50γ of estrone daily with decreasing doses of testosterone for 40 or more days 20 to 50γ of estrone daily for over 100 days with an interval of testosterone injections of 1 to several weeks	Prolonged moderate relative hyperestrinism
Solitary Cyst	Women at the menopause; breast adipose; periods may be missed or far apart	High estrogen; very low or absent pregnandiol	100 to 200γ estrone daily for 3 to 4 weeks. Then withdrawal of estrone	Extreme or absolute but temporary hyperestrinism
Polycystic Disease	Previous history of mastodynia or adenosis with onset in younger age groups; breasts small; periods irregular	High or moderately high estrogen; low or absent pregnandiol	Implantation of estrone pellets for over 4 months; 200γ of estrone daily for over 4 months with insignificant doses of testosterone	Extreme hyperestrinism of long standing

γ = gamma

corpus-luteum deficiency. The corpus-luteum activity which approaches normal for cyclic women fails to supply an adequate balance because these women refrain from having an adequate number of children. In the other group, the corpus-luteum output is abnormally low in the presence of normal estrogens; these women are frequently sterile and may have had pelvic inflammatory disease; or

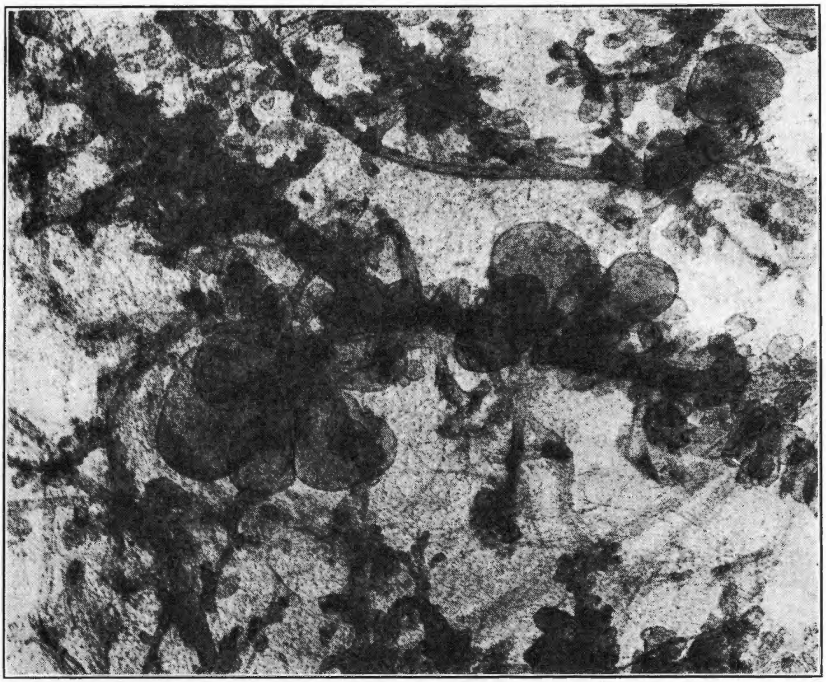

FIG. 221. Multiple small cysts in the mammary gland of the rat in response to prolonged treatment with high doses of estrogen (whole mount).

the declining corpus-luteum function may herald an approaching menopause.

Cases of adenosis also fall into two groups. One of these comprises cases of primary mammary deficiency in which the growth of the breast is stunted by high estrogenic stimulation in adolescence and early sexual maturity. These women have small breasts and may develop a relatively advanced stage of the disease in the twenties and early thirties. They have an increased susceptibility to mammary cancer. In the other larger group of adenosis, the disease represents a more advanced stage of mastodynia and comes on in the late thirties or early forties. Here there is a prolonged and moderate relative hyperestrinism due to low corpus-luteum function over a period of years, but estrogen secretion is normal.

Cystic disease also may be of two types. The solitary cyst that is most common appears at the menopause and is due to a temporarily high estrogenic output, unopposed by adequate corpus-luteum func-

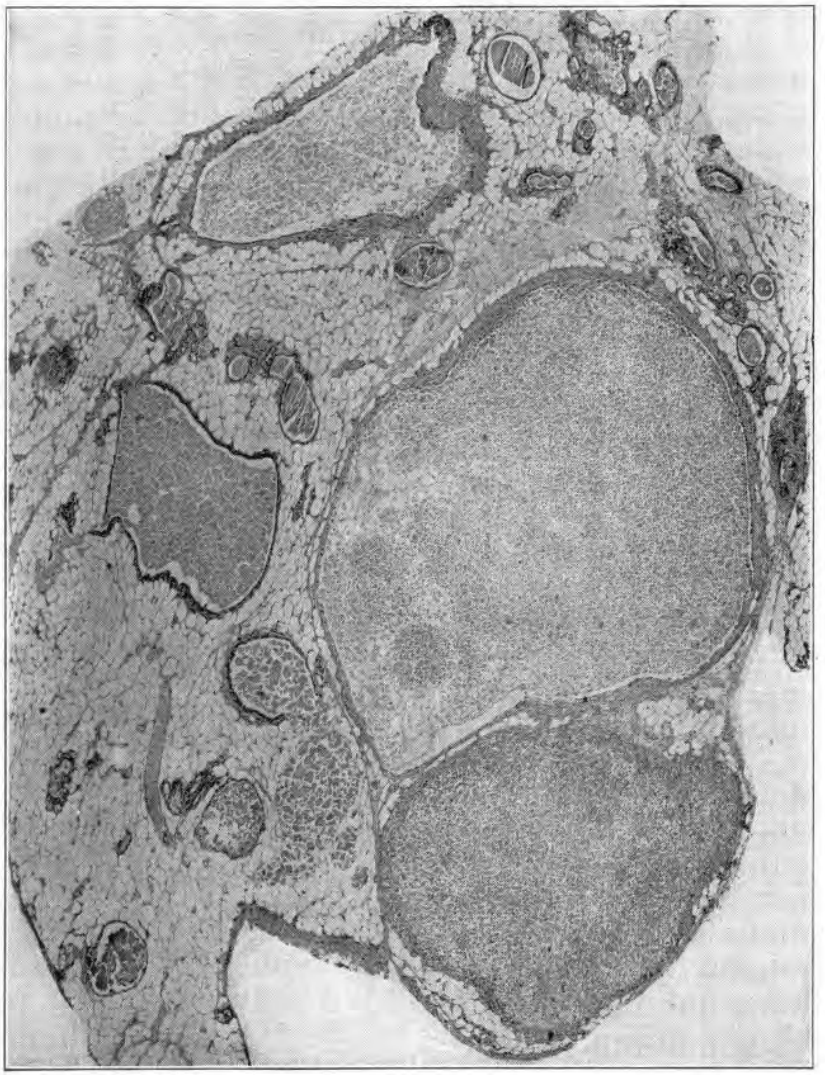

FIG. 222. Microscopic appearance of cysts shown in Figure 221.

tion. The other form of cystic disease is that which occurs late in adenosis as its end stage or following mastodynia; it is due to a prolonged but moderate hyperestrinism. These women usually have multiple small cysts.

In the last analysis, all forms of mammary dysplasia are the result of hyperestrinism of varying degrees, either relative or absolute.

ENDOCRINE THERAPY IN MAMMARY DYSPLASIA

The conclusion that the various forms of mammary dysplasia result from ovarian dysfunction has led to attempts to control the disease with endocrine therapy. The largest number of cases has been treated with estrogen, presupposing an ovarian deficiency. The results of estrogen therapy in cases of chronic cystic mastitis have been reported by Dahl-Iverson, Lewis and Geschickter, Taylor and others. The male sex hormone (testosterone propionate) has been advocated by those who believe that its use counteracts estrogen, and that hyperestrinism (an ovarian hyperfunction) may be a factor (Loesser, Atkins). Since the majority of cases of mammary dysplasia show a deficiency in corpus-luteum secretion, as measured by pregnandiol studies on the urine, progesterone is a logical form of treatment and has been used by the author in a series of more than 60 cases.

Limitations

Endocrine therapy in mammary dysplasia has definite limitations. Accurate clinical recognition of the disease and its subvarieties is essential. If the various forms including mastodynia, adenosis, and cystic disease cannot be distinguished one from the other and doubt concerning the presence of cancer exists, exploration should be performed. When the condition is bilateral or recurrent endocrine therapy may be used after its nature has been histologically verified. Among 89 patients referred for endocrine therapy, four doubtful patients were explored and found to have cancer, although the referring physician was convinced on clinical examination that the lesion was benign. In view of this experience it seems unwise for the general practitioner to administer this form of treatment without consultation to confirm his diagnosis.

Mammary dysplasia is the result of ovarian dysfunction, and the pituitary gland regulates ovarian function. Chronic infection may inhibit the pituitary (Rowe) and for this reason it is important to search for and eliminate foci of infection such as endocervicitis, rectal fistulae, upper respiratory infections, etc., in cases of mammary dysplasia before undertaking endocrine therapy.

Worry, fear of cancer, and depressive states may accentuate symptoms referable to the mammary gland and in rare instances may be a factor in the endocrine derangement of the patient. This aspect

should not be neglected and reassurance, mild sedatives and encouragement should be tried.

Objections

An objection advanced against the conservative treatment of cystic mastitis is that the lesion is precancerous. This opinion has not been substantiated in regard to mastodynia or cystic disease.

In cases of adenosis followed for five years the incidence of mammary cancer is 3 per cent as compared to 0.42 per cent for normal individuals. (See Chap. 12.) This objection has weight when estrogen is used, since mammary carcinoma in rats and mice follows large doses of estrogen. This does not apply, however, to the use of progesterone or testosterone which has been shown experimentally to be antagonistic to estrogen as regards the breast.

Two additional objections may be raised against endocrine therapy. First: the results are not permanent. While the symptoms regress, recurrence in a period of two or more years is common. Second: spontaneous remission occurs frequently in mammary dysplasia and eventual disappearance of the disease is often observed in the absence of treatment.

In unilateral mastodynia (summarized in Chap. 8), of 166 cases 19 patients had persistent symptoms five to eleven years after the first examination. Five were ultimately treated with one or more excisions, and one by amputation. In the author's opinion, endocrine therapy (progesterone injections) is indicated in this group for the relief of symptoms. However, any definite nodule which is regarded as suspicious should be treated by excision and studied microscopically.

In cystic disease, in which a definite solitary nodule is the rule, excision permits pathologic verification of the diagnosis and in the majority of the cases additional cysts do not form. Aspiration also may be used to confirm the diagnosis and in more than one-third of the cases so treated, the cysts do not refill. In these cases, endocrine therapy may be helpful to prevent recurrence after aspiration or excision.

Mastodynia

Estrogen Therapy. Since reliable preparations of progesterone and testosterone have become available this form of endocrine therapy is not advisable. The author treated 19 cases of mastodynia with estrogen therapy between 1934 and 1936. One milligram of estrone twice weekly (10,000 international units) was given for three weeks between two menstrual periods. Following menstruation the patients

received the same dose once weekly until the second period.[1] After this, a single injection was given in the premenstruum each month or the estrogen was administered by mouth (2,000 international units daily) to complete six months of treatment. This is nearly always a successful method of treatment for painful breasts. The injections must be given frequently during the first month of treatment, and once or twice weekly during the second month. THEREAFTER, IT IS IMPORTANT TO DIMINISH THE DOSE WHEN RELIEF OF SYMPTOMS IS OBTAINED. The symptoms have the tendency to recur at the end of eighteen months to two years in approximately half the cases. In three cases no relief of symptoms was obtained. (These were apparently patients with a high estrogenic output.)

Since the majority of the patients with mastodynia have a relative hyperestrinism, the injection of additional amounts of estrogen appears illogical. On the basis of the experimental results, adenosis and, later, multiple cysts should result if high doses of estrogen are given frequently over a period of many months. However, with continued estrogen injections in physiologic amounts, atrophy follows mastodynia before adenosis or cysts form. The treatment is largely empirical, but the fact remains that satisfactory results may be obtained by short courses of treatment. The most logical explanation for this is that advanced recently by Astwood. He has been able to demonstrate in animals and in patients that estrogens during the latter part of the cycle may prolong the life of the corpus luteum, and thus an increased luteal function offsets the effects of estrogen. Hamblen, Cuyler and Axelson have confirmed this by doing pregnandiol determinations on patients following intermenstrual administration of estrogens. Dosages as great as 15,000 rat units every two days from the sixth to the fourteenth days of the menstrual cycle failed to depress corpus-luteum function; on the contrary an accentuation of the progestational phenomena occurred in some cases. In animal experiments, physiologic doses of estrogens may enhance luteinization of the ovaries and produce lobule formation in the breast. Estrogen therapy when successful may act by increasing corpus-luteum function. Hence it is important not to give large doses and this precaution should be observed when using the stronger estradiol or stilbestrol preparations.

Progesterone Therapy. This is the preferred treatment. Fifteen cases of mastodynia were treated with progesterone. The hormone was administered in oil, intramuscularly in doses of 5 mg. twice weekly for the last two weeks of one or two consecutive menstrual cycles. The total dose varied from 20 to 40 mg. The majority of these were childless women and eight were married but sterile. The

[1] The injections are never given during menstruation.

symptoms of pain, nodularity and tenderness in one or both breasts had been present for a year or more prior to treatment. Six of the 15 patients were treated for recurrence following previous estrogen therapy. Two of the patients had pregnandiol determinations on the urine prior to progesterone therapy. These were low, 13.2 mg. and 14.5 mg. per cycle (normal 26.2 to 58.5 per cycle, Bucher and Geschickter). One of the patients successfully treated had pregnandiol determinations on the urine following progesterone therapy. The determination was normal, 37.0 mg. per cycle.

All but two of the patients showed improvement. Those successfully treated remained well two or more years after which time three had recurrent symptoms. The improvement following 30 mg. of progesterone therapy in one case lasted only two months; this case was controlled subsequently by the injection of 5 mg. once a week.

Male Sex Hormone Therapy. A small group of cases with mastodynia has been treated with the male sex hormone. Testosterone propionate in doses of 25 mg. twice weekly are used. The results are satisfactory if the treatment is maintained for several months. Atkins has reported good results with more intensive therapy which may produce masculinizing effects. The local application of testosterone ointment nightly for two months has proved beneficial in some of the author's cases.

Adenosis

Estrogen Therapy. Since most cases of adenosis begin as mastodynia, many features are common to both. The tender, swollen, and dense tissue present in mastodynia also occurs in adenosis. Adenosis, however, is a more advanced and persistent condition and responds less readily to endocrine treatment. Estrogen therapy is not advised because of the relation of this form of chronic cystic mastitis to cancer, and because, in the rat, cancer ultimately follows continuous high doses of estrogen. These patients already have a relative hyperestrinism of long standing and the result of repeated courses of estrogenic therapy, which is to convert the disease into areas of fibrosis and cyst formation, may overreach the mark and carry the disease into precancerous or cancerous changes. Moreover, recurrence was observed in 15 to 20 months in 50 per cent of the cases of adenosis treated with estrogen by the author prior to 1937. For this reason the use of estrogen has been discontinued in favor of progesterone (corpus-luteum therapy).

Progesterone Therapy. Ten patients with adenosis have been treated with progesterone. The hormone was administered in the same fashion as in the cases with mastodynia. The total dose ranged from 20 to 60 mg. over one to two cycles. The symptoms had been

present for one to four years prior to treatment. Two of the patients were treated for recurrence following estrogen therapy several years previously.

Pregnandiol and estrogen determination were made before progesterone therapy in two cases. Both of these had low pregnandiol values (12.8 and 10.9 mg.); one had high, the other normal, estrogen values. One patient had a normal pregnandiol excretion (36.7 mg.) following therapy. Symptomatic relief was obtained in all cases, but the small discrete nodules may persist for six or more months after treatment. These are usually small cysts 0.5 to 1 cm. in diameter which may be successfully aspirated with a 22-gauge needle and locked-barrel syringe.

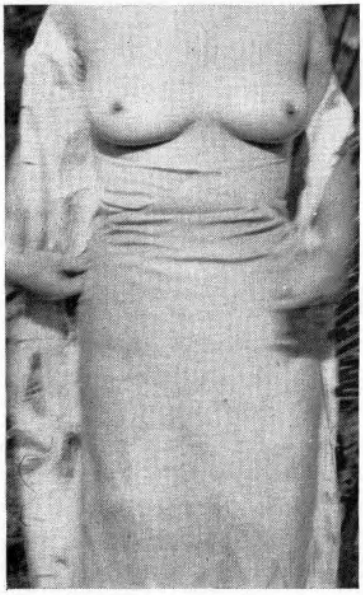

FIG. 223. Case of adenosis successfully treated by estrogen therapy. The size of the breast is practically doubled after a series of courses of treatment between 1937 and 1942.

Other Hormones. In five cases of adenosis treated in 1934 and 1935, injections of lactogenic substance were combined with estrogen, apparently with good results. Among the more successfully treated cases was a woman, 40 years old, who had advanced bilateral adenosis; she was treated with estrogen and lactogenic hormones in August and September, 1934, remained well until 1937. Since that time she has been taking a course of estrogen each year and is well in January, 1942. The breasts, which are entirely free from pain and nodularity, are about twice the size they were in 1934. (Fig. 223.) This method of therapy was discontinued when active preparations were no longer available, but this material is again obtainable (Prolactin, Schering). Testosterone injections have also been discontinued since beneficial results were not observed in the five cases where it was tried. Recently, however, beneficial results have been observed in several cases where local applications of ointment containing 2 mg. testosterone propionate per gram (Perandren, Ciba) have been used.

Cystic Disease

In general, striking results in cystic disease are difficult to obtain by any form of endocrine therapy.

The cysts usually remain stationary in size during the course of

treatment, whether estrogen or progesterone is given. In one case each treated by estrogen, progesterone or testosterone, the cysts had disappeared after a period of several months. This may have occurred spontaneously. In recent cases it has been the author's practice to aspirate the cyst and then to give progesterone therapy in order to prevent recurrence. In one out of ten cases thus treated, multiple cysts recurred in both breasts one year after the treatment was discontinued. The other cases have remained well for two to four years.

Summary of Endocrine Therapy in Chronic Cystic Mastitis

In the author's experience, beneficial endocrine therapy in chronic cystic mastitis depends on stimulating or adding to luteal function. Experimentally, the formation of lobules in the breast in response to luteal stimulation prevents the appearance of the various forms of mammary dysplasia or tends to correct the condition once formed. In the human breast these beneficial results are best demonstrated by the disappearance of various forms of chronic cystic mastitis during pregnancy. (See Chap. 7.) Endocrine therapy should not be tried unless an accurate diagnosis has been established and biopsy should be done in doubtful cases. The elimination of foci of infection, reassurance against the fear of cancer, and the use of an uplift brassiere in mastodynia should be the initial forms of treatment in verified cases.

Progesterone (corpus-luteum therapy) injected intramuscularly in 5 mg. doses twice weekly for the last two weeks of two successive menstrual cycles is satisfactory endocrine therapy in cases of mastodynia and of adenosis and may be used to prevent recurrence following aspiration or excision in cystic disease. Short courses of estrogen given by injection or orally may be used in cases of mastodynia if care is taken to guard against overtreatment. Testosterone has been advocated by some observers but relatively high doses which may produce masculinizing effects are required unless the hormone is applied locally as an ointment.

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12

Relation of Chronic Cystic Mastitis to Cancer

The prevalence and high mortality rate of mammary cancer have stimulated a search for etiologic factors and precancerous changes which might provide an opportunity to prevent the disease. The abnormalities in mammary dysplasia have been regarded by numerous investigators as a probable basis for mammary carcinoma. The list of authors who subscribe to such a view is a long one and includes such names as Billroth, Aschoff, Ewing, Konjetzny, MacCarthy, Semb and numerous others. Schimmelbusch stated that three of 43 patients with adenosis subsequently developed cancer of the breast. Rodman found cancer associated with chronic cystic mastitis in 15.5 per cent of 100 cases, and according to Cheatle and Cutler approximately 20 per cent of all mammary cancers have their onset in the changes of chronic cystic mastitis. Two recent studies have led to opposing conclusions. Campbell (1934) reported that the two conditions were unrelated and Warren (1940) concluded that patients with chronic cystic mastitis show a definite predisposition to mammary cancer.

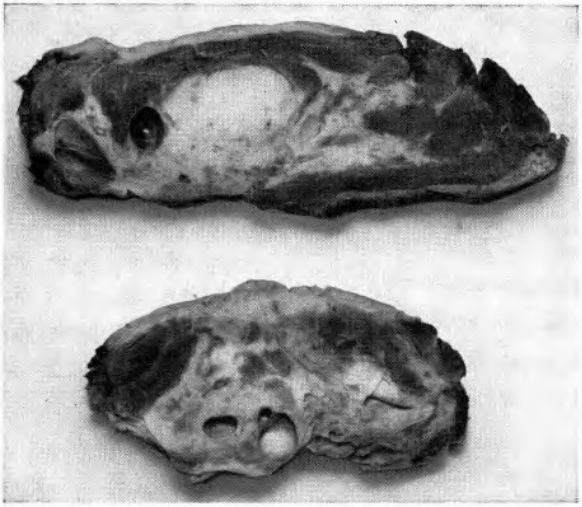


FIG. 224. Cystic disease and mammary carcinoma occurring simultaneously. The gross specimen shows a large mammary carcinoma and several cysts in the same breast.

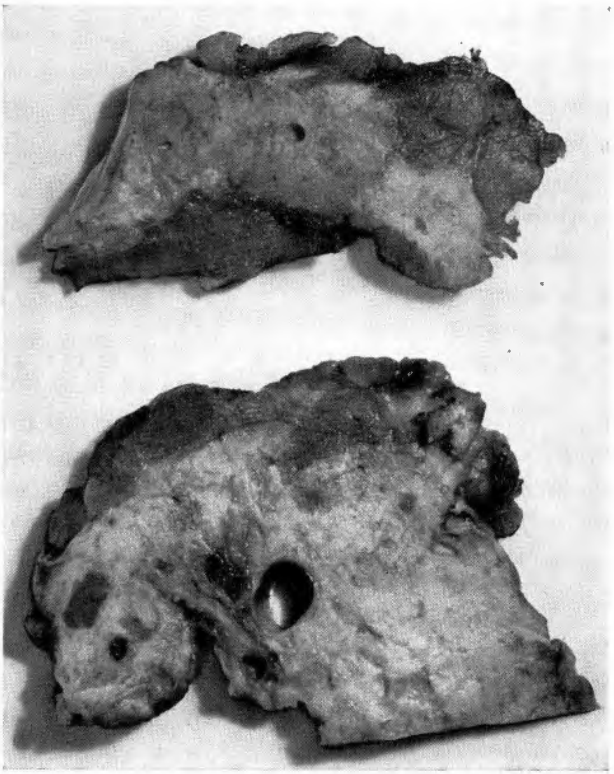


FIG. 225. Cancer occurring in adenosis. The gross specimen shows the dense fibrous tissue of adenosis undergoing cystic involution.

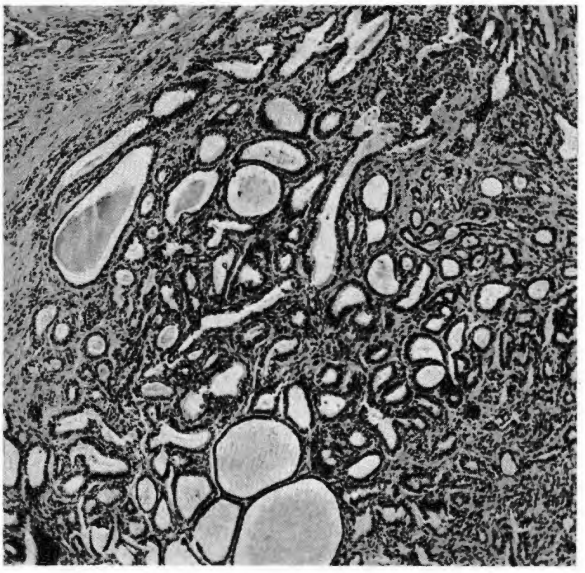


FIG. 226. Cancer occurring in adenosis. Photomicrograph showing lobular hyperplasia and irregularity.

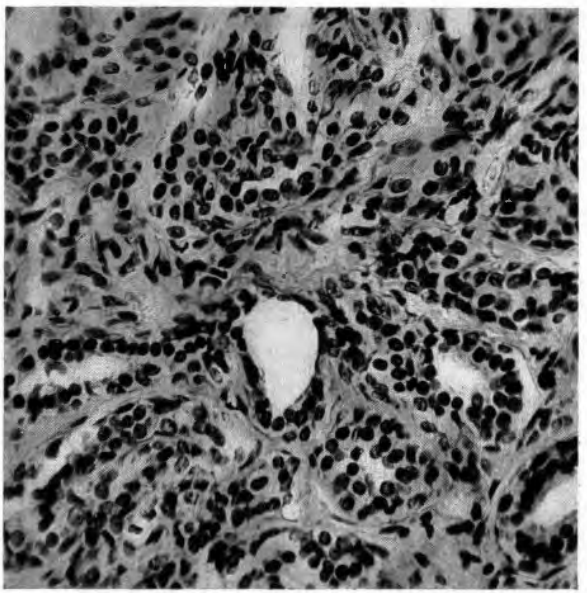


FIG. 227. Cancer occurring in adenosis. High-power photomicrograph of infiltrating cancer taken from the upper margin of the lobule shown in Figure 226.

The following observations have been cited in support of the doctrine that there is a causal relation between mammary dysplasia and cancer:

1. In many cases breasts removed for cancer show the changes of some form of chronic cystic mastitis either grossly or microscopically.
2. Transitional stages between the two conditions have been traced by histologic investigation.
3. In the experimental production of mammary cancer in mice, using estrogenic hormones, mammary changes resembling those found in cystic disease and adenosis precede the cancerous changes.
4. Among patients treated conservatively for mammary dysplasia, a number develop mammary cancer subsequently.

COINCIDENCE OF MAMMARY DYSPLASIA AND CANCER

Clinical Data

Both mammary dysplasia and cancer in the same patient should occur coincidentally in a certain percentage of the population, even if the diseases are etiologically unrelated, since both have their maximum incidence in women between the ages of 35 and 50 years. (Figs. 224-227.)

Dr. Dublin of the Metropolitan Life Insurance Company has calculated for the author the probable incidence of cancer of the breast in white women between the ages of 35 and 50 years as 1.14 per 1000 (see: Incidence of Mammary Cancer in the Normal Population, end of chapter). The percentage of mammary dysplasia in the clinic patient is twice as high as that of cancer, based upon the author's experience and that of Bloodgood and upon observation in other hospitals (de Chòlnoky). This would bring the incidence of mammary dysplasia in women for the same age group to 2.3 per 1000. A series of 2500 mammary cancers and 1200 cases of mammary dysplasia, on the basis of these calculations, should include seven patients (7.05 cases) in which the two diseases co-existed in the same patient. Actually there were 19 cases in which mammary dysplasia and cancer were found at the time of examination (Table XXIX). Although allowance must be made for increased accuracy of diagnosis in the 19 observed cases, the frequency with which the two diseases co-exist at the time of clinical examination suggests an etiologic relationship.

The expected number of cases in which the two diseases co-exist,

however, is increased if the age period covered is extended to include those patients with a previous history of treatment for mammary dysplasia or cancer and further increased if there are included (on the basis of follow-up reports over a like period) those patients who subsequently developed either one of the two conditions. Combining a series of 2500 mammary cancers and 1200 cases of chronic cystic mastitis, a group of 64 patients was found who were affected by both conditions (although not always simultaneously), whereas the calculated number of cases was placed between 25 and 30 (Table XXIX).

TABLE XXIX

THE CO-EXISTENCE OF MAMMARY DYSPLASIA AND CANCER BASED ON CLINICAL FINDINGS

History of mammary dysplasia among 2500 mammary cancers	26 Cases
Previous operations for cancer among 1200 cases of mammary dysplasia	9 Cases
Mammary dysplasia and cancer at time of examination	19 Cases
Cases of mammary dysplasia subsequently developing cancer	10 Cases
(Total Number of Cases Studied—3700)	64 Cases
(Total Expected Cases)	25 to 30 Cases

The number of observed cases is twice as great as the expected figure and is of etiologic significance, although the figure is not high. The basis on which these calculations were made was as follows:

In considering the incidence of mammary cancer among 1200 cases of chronic cystic mastitis, the probability of the development of malignancy is 2.8 per 1000 in the ten-year age period between 35 and 45, and 5.5 between the ages of 45 and 55 (Table XXX). Among 1,000 women of age 45, there may be expected 8 cases of cancer within the two decades from ages 35 to 55. (10 years covered by the history taken at the time of examination and 10 years by the follow-up period after examination.) Since only 67 per cent of the cases had both adequate histories and adequate follow-ups, the calculated number of cancers is between 5 and 6.

In calculating the likelihood of chronic cystic mastitis among 2500 cancers in a similar 20-year period, these figures were doubled because of the increased incidence of chronic cystic mastitis and again doubled because of the greater number of cases (2500). On this basis four times as many cases of mammary dysplasia should occur among the cancer group or from 20 to 24. A total of 25 to 30 cases is thus obtained in which both cancer and mammary dysplasia should occur at some time during the course of observation.

The small number of cases in which the two diseases are found in the same patient has been reported by Campbell. In a series of 88 mammary cancers, he found four with an antecedent history of

TABLE XXX

CHANCES PER 1,000 THAT A WHITE FEMALE OF A STATED AGE WILL DEVELOP MAMMARY CANCER WITHIN THE NEXT 10 YEARS [1]

AGE	SURVIVORS PER 100,000	NEW CASES WITHIN NEXT 10 YEARS	CHANCES PER 1,000 OF MAMMARY CANCER WITHIN NEXT 10 YEARS
35	88,608	244.5	2.8
40	86,785	360.5	4.2
45	84,538	461.8	5.5
50	81,527	550.8	6.8
55	77,545	581.9	7.5
60	71,871	563.1	7.8
65	63,755	513.2	8.1

(1) Based on Table XXXVI, Page 286.

cystic disease. In 444 cases of cancer, Johnson found but two with a similar history.

Microscopic Data

Microscopic changes resembling those seen in mammary dysplasia are relatively common in breasts removed for cancer. This has been stressed by Ewing, MacCarthy, Cheatle, Konjetzny, Semb, and others. The incidence of such changes in cancerous breasts has been estimated as 50 per cent by Ewing and by Konjetzny; as 24 per cent by Semb, and 20 per cent by Cheatle. Such findings have been put forward as an indication that cancer may arise from such abnormalities in the mammary gland. However, mammary tissue removed at autopsy from women in the cancer-age group but who have had clinical evidence of neither mammary dysplasia nor cancer shows similar microscopic changes in even a larger percentage of cases.

Borchardt and Jaffe studied histologically autopsy material from the mammary gland in 100 women over 40 years of age who had been free from specific breast symptoms. Four to five sections were made from each breast. Atypical involution microscopically similar to mammary dysplasia was found in 93 per cent of the cases, and in 70 per cent of the cases the condition was bilateral. The great frequency of these pathologic changes makes it impossible to consider them precancerous lesions.

Franzas, in 1935, investigated histologically the breasts of 100 women coming to autopsy between the ages of 18 and 98 years. Careful clinical records in these cases disclosed that none had evidence of chronic cystic mastitis or cancer. Nevertheless, he found microscopic changes similar to those in chronic cystic mastitis in 55 per cent and in 25 per cent the condition was bilateral. Similar

findings were reported by Walchshofer who studied the breasts in 65 women coming to autopsy between the ages of 19 and 24 years. More recently a similar series was reported by Lindgren.

The author has studied 100 cases in which mammary tissue was removed at autopsy from women with clinically normal breasts and between 30 and 50 years of age. In women between 30 and 40 years of age, lobular irregularities and cystic dilatation of the tubules occurred in 33 per cent of the cases. In women between 40 and 50 years of age similar findings with cystic changes predominating occurred in 55 per cent of the cases (see Chap. 1).

When one considers the frequency of microscopic changes resembling chronic cystic mastitis in the so-called normal adult breast (25 to 93 per cent of all cases) and the relatively low incidence of mammary carcinoma (0.05 per cent of all cases), such atypical involutional changes must be considered relatively innocent and without special significance in the etiology of mammary carcinoma. If mammary tissue were routinely taken at autopsy, the proper pathologic interpretation of these changes would have been well established before the onset of the present century.

TRANSITIONS BETWEEN MAMMARY DYSPLASIA AND CANCER

Alleged Microscopic Proofs

Those observers who have considered the microscopic changes of mammary dysplasia significant in the etiology of mammary cancer have sought to trace the histologic beginnings of the disease to such a starting point. Aschoff believes that cancer can have its beginnings on the soil of such "preblastomatous proliferations." Ewing, however, states that, although he considers mammary dysplasia as precancerous, in no case can one trace the evolution of suspected areas into fully developed cancer. Cheatle and Cutler believe that carcinoma may have its beginning in a gradual series of changes occurring in "cystophorous desquamative epithelial hyperplasia." A cyst may be present toward the end of the second and in the early years of the third decade of life (according to Cheatle and Cutler); during the next decade it may gradually pass into a state of benign epithelial neoplasia; and the same lesion may then develop into a carcinoma (usually during the late forties or early fifties).

Campbell in discussing this view states "if such a theory were indeed a fact, the maximum incidence of adenocystic forms (epithelial neoplasia) would be found in a higher age group than that of simple cystic disease. Such is not the case, however, for the maxi-

mum incidence of adenocystic disease is between the ages of 30 and 40, cystic disease between the ages of 40 and 45." This corresponds with the findings in the author's cases presented in the preceding chapters. The peak of age incidence for adenosis or adenocystic disease was from 35 to 40 years, and for cystic disease from 40 to 45 years.

The deductions drawn from histopathologic studies of fixed tissues leave much to be desired. If whole sections are cut through the entire breast removed for mammary carcinoma, the findings of adenomatous hyperplasia or cystic changes in one or more portions do not necessarily indicate the condition preceding malignancy at the tumor site. This is because the various ducts, tubules and lobules within the same breast differ widely in their physiologic state at any given time. Thus, even in such intense physiologic periods as pregnancy and lactation, lobules and tubules may be found in the same microscopic field some of which show maximum physiologic activity while others remain in a quiescent virginal state. Hence, the microscopic findings of epithelial hyperplasia in breasts removed for cancer do not furnish proof that the epithelial structure affected by the carcinoma was in the same condition immediately preceding the onset of the malignancy.

Histologic study made on human breast tissue cannot be cited as convincing evidence of the transition of hyperplasia or involutional dysplasia into malignancy so long as morphologic criteria are lacking to distinguish between benign neoplasia and early malignancy. Pathologists differ in the criteria on which they rely to make a diagnosis of early malignancy and none of the criteria is infallible. Many of the early and slowly growing adenocarcinomas of older pathologists are classified at the present time as benign adenosis. Bloodgood emphasized this in his discussion of "Borderline Lesions," stating that follow-up studies have shown that a definite group of these alleged adenocarcinomas of the earlier authors did not terminate fatally. Thus, in the Surgical Pathological Laboratory of the Johns Hopkins Hospital, 15 per cent of the cases of carcinoma reported by Halsted as cured by his radical operation and classified by Welch as adenocarcinoma, were reclassified by Bloodgood as benign cyst-adenomatous changes in chronic cystic mastitis.

In cancers of the breast which are of large size, it is not possible to judge whether the mammary dysplasia in the surrounding tissue was present at the original site of tumor formation when the malignancy began. In cancers of small size (1.5 cm. or less) the presence of such changes at the tumor site is highly suggestive. The author has studied the sections on 90 cases of such small mammary cancers. The majority of these cases had their origin within areas of atrophy and

fibrosis, in a region where small fibro-adenomatous nodules were present, or within lobules which were undergoing atrophic and secre-

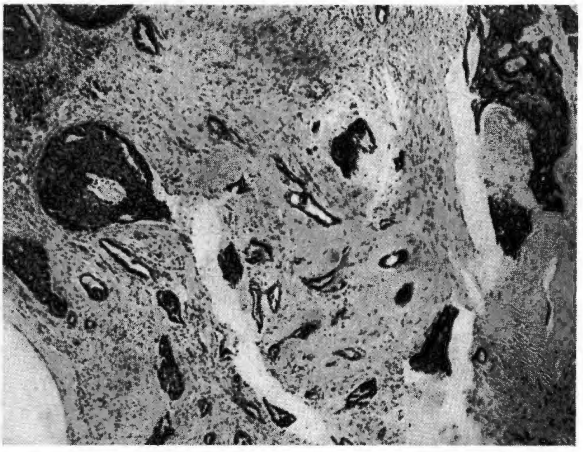


FIG. 228. A small mammary cancer beginning in a fibro-adenomatous area. The photomicrograph shows the section from a cancer which measured 8 mm. at the time of its removal.

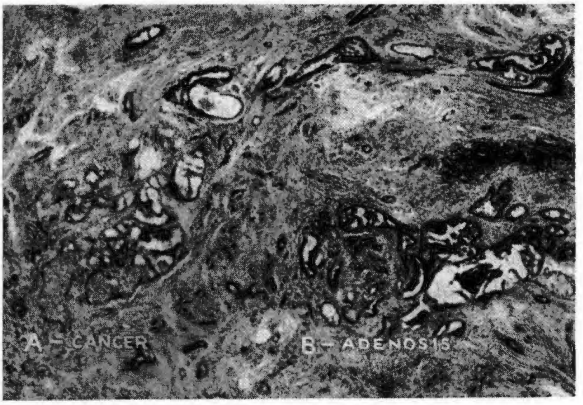


FIG. 229. Photomicrograph of a cancer (less than 1 cm. in diameter) developing at the margin of a zone of adenosis.

tory changes (Fig. 228). However, in six cases (6.6 per cent), the histologic appearance suggested origin in an area of mammary dysplasia (Figs. 229-232).

Animal Experiments

In recent years it has been possible to produce mammary cancer in mice and rats by large and prolonged doses of estrogen. If large doses, in oil, are injected at repeated intervals, cystic changes ac-

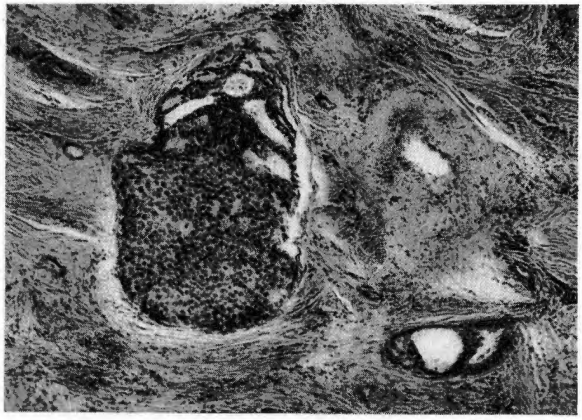


FIG. 230. Photomicrograph showing higher magnification of the cancerous area (A) shown in Figure 229.

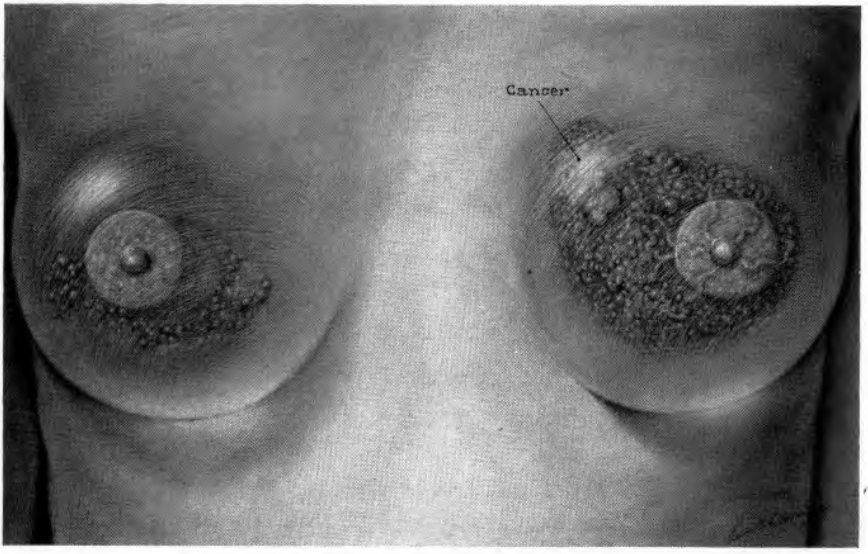


FIG. 231. A case of adenosis with early duct cancer. Drawing showing the condition of both breasts at the time of examination.

companied by various degrees of epithelial hyperplasia precede the formation of cancer by several weeks or months. Cheatle has reviewed Lacassagne's experiments and believes that they indicate that the changes of mammary dysplasia are an essential precursor of mammary carcinoma produced in response to the estrogenic hormone.

In producing cancer in the rat's breast by a variety of methods of overdosage with estrogen, the author has shown that various initial changes such as cyst formation and the formation of benign fibro-

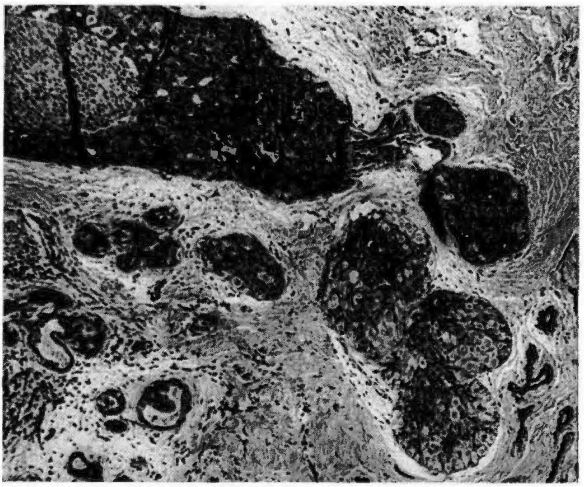


FIG. 232. Photomicrograph showing the cancer and the surrounding breast tissue at the time of operation.

adenomas may occur. Such changes do not necessarily predispose to cancer formation unless they are pushed to the point where normal regeneration of the tissue is exhausted.

Two essential features of these experiments bear upon the problem of the relationship of mammary dysplasia to cancer. First, mammary cancer is not necessarily preceded by the cystic and hyperplastic changes characteristic of mammary dysplasia. Second, when these changes do precede the development of mammary cancer a definite period of continued estrogenic stimulation must intervene. In other words, the changes seen in mammary dysplasia are not essential to the appearance of mammary cancer, and when they do occur they are not usually the immediate precursors of the malignant state.

The earlier conclusions regarding the relation of cystic changes to cancer, drawn from results obtained in animals receiving estrogen,

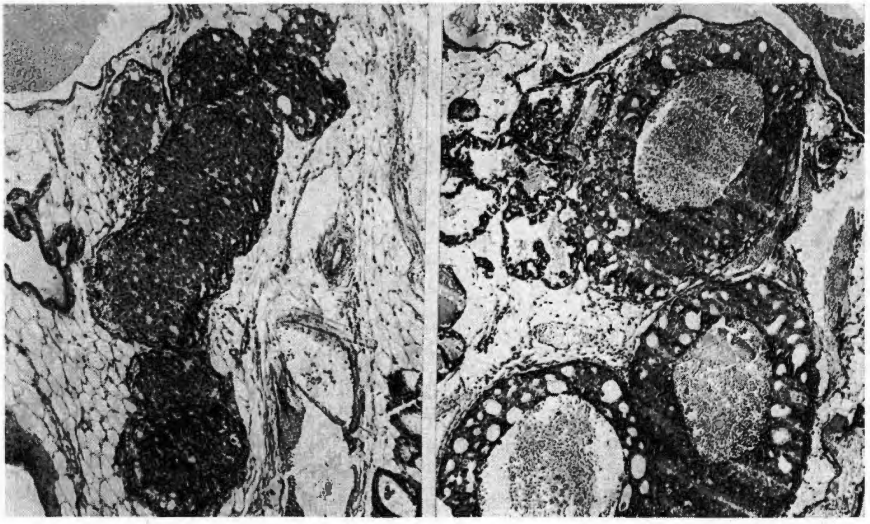
were based upon a single method of dosage in mice: inordinately high doses injected once or twice weekly. When various methods of estrogen dosage are employed either in the absence or presence of luteal hormones, it is possible to analyze in more detail the relationship of the benign mammary changes to subsequent cancer formation.

Mastodynia-Like Changes. The changes in the rat's breasts resembling mastodynia bear no direct relationship to cancer. In the absence of luteal hormones, doses of estrogen within the range of physiologic limits, injected for a few months, will produce mastodynia whether or not normal lobule formation has previously occurred. The most typical changes occur relatively early and disappear in a few months to be followed by atrophy if treatment is maintained (see Chap. 33). With high estrogen dosage in the presence of luteal hormones, mastodynia is more readily produced and persists for longer periods before the changes of adenosis appear. A period of relatively normal lobule formation separates the two conditions. It is apparent, therefore, that mastodynia is an early phase of an endocrine imbalance which is often transient and brief in character. It is either self-limited and followed by atrophy or lobule formation, and when persistent, gives rise to adenosis (or, more rarely, to cysts), so that there is no direct transition between this disease and cancer. This corresponds with clinical experience.

Adenosis-Like Changes. The changes in the rat's breast, duplicating adenosis, may result from a prolonged moderate stimulation with estrogen in doses at the upper physiologic limits either in the absence or the presence of diminished luteal stimulation. Cancer has not been found to arise in the rat under these conditions even when the experiment is started at the age of one month and continued until the rat has reached senility (two to three years of age). To determine if the rat's breast under these conditions is more susceptible to cancer: After one and two years rats with such advanced adenosis were given extremely high doses of estrogen for a period of one to two months, thus simulating that which may occur at the menopause in women with long-standing adenosis (see Chap. 34). Under these conditions cancer occurred rapidly in all of the animals (Figs. 233-236). Hence, long-standing adenosis in the human breast may predispose to cancer, if this is followed by adequate estrogenic stimulation near the menopause, or, more rarely, at other times in cyclic women.

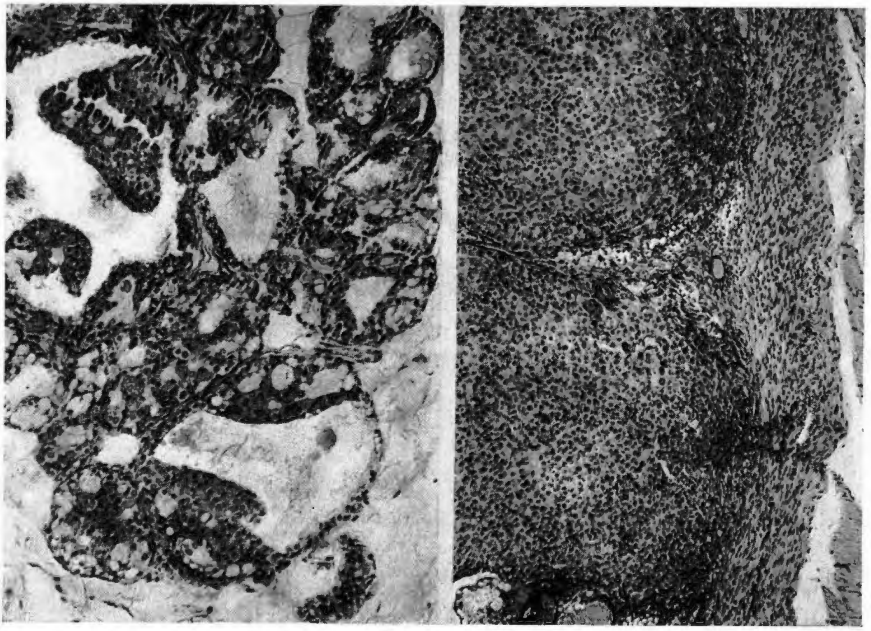
It is significant that in these rats the changes which occurred under the final estrogen stimulation (that which produced the cancer) were not always a more advanced degree of adenosis. In most

FIG. 233 FIG. 234



The Experimental Production of Cancer in the Rat's Breast Following Adenosis.
FIG. 233. Adenosis with solid duct adenoma following prolonged high doses of estrogen.
FIG. 234. Comedo carcinoma occurring in the same animal six weeks later under continuous treatment.

FIG. 235 FIG. 236



FIGS. 235, 236. Cancer of the rat's breast occurring in pre-existing adenosis. The photomicrographs show persisting adenosis and cancer in an animal treated in the same way as the one shown in Fig. 233.

of the animals, fibro-adenomatous nodules and areas of epithelial degeneration in dilated secreting acini preceded the malignancy. Only rarely does the cancer occur in areas of hyperplasia characteristic of adenosis.

To verify this on human material, a group of cases with the clinical picture of adenosis complicated by mammary cancer was studied microscopically. The cancer and the surrounding breast tissue

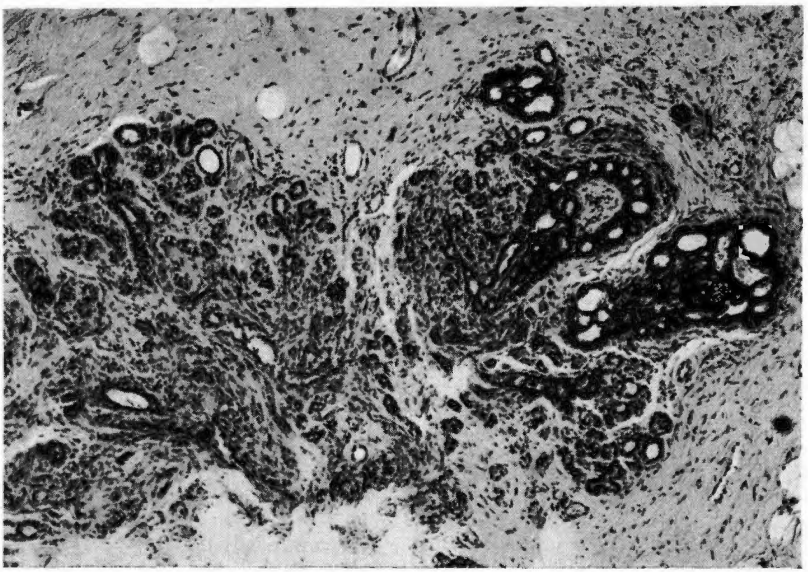


FIG. 237. A case of mastodynia with adenosis and precancerous changes resulting from overtreatment with estrogen. The patient received over one million I. U. of Estradiol Benzoate over a period of 20 months. The photomicrograph shows adenosis and epithelial proliferation bordering on malignancy.

usually showed no evidence of adenosis although this was marked in the remainder of the breast. In other words, although women with adenosis have an increased susceptibility to mammary cancer, the truly precancerous tissue only rarely shows persisting changes characteristic of adenosis.

Cystic-Disease–Like Changes. Cystic disease may be produced in the rat's breast in the absence of luteal stimulation either with extremely high doses of estrogen over a period of a few weeks, or with more moderate dosage over a period of months. Under the conditions last mentioned, the cysts are smaller and more numerous. In either case, cancer does not develop unless estrogen stimulation is maintained for months beyond the time of cyst formation, to the time when degeneration, accompanied by concretions of inspissated

secretion and disruption of the cyst wall has occurred in the cysts (see Chap. 33).

In patients, the majority of cysts occur abruptly in response to intense, unopposed estrogen stimulation near the menopause followed by estrogen withdrawal. Since such stimulation is not maintained beyond the menopause in most cases, cancer does not develop. In younger patients multiple cysts may occur under a more prolonged and more moderate stimulation. Since there is greater opportunity for further estrogen stimulation in these younger patients, the probabilities for cancer are somewhat greater. Multiple cysts are rare in young individuals, however, and the possibilities of regression are greater in patients during the childbearing period.

Thus, in terms of estrogenic stimulation there are two factors, intensity and duration, which must be considered in analyzing the interrelationships of the several forms of mammary dysplasia and cancer.

1—Mammary cancer results from both. It is produced by abnormally INTENSE AND PROLONGED estrogenic stimulation.

2—Mastodynia is the EARLIEST SIGN OF EITHER, BUT NOT BOTH. With intense estrogenic stimulation mastodynia is an early, transient phase which may precede cyst formation. With moderate but prolonged estrogen it is a transient but more lasting effect preceding adenosis.

3—True cystic disease is produced by INTENSE ESTROGENIC STIMULATION of brief duration complicated by secretory effects following estrogen withdrawal.

4—Adenosis is produced by moderate but PROLONGED ESTROGENIC STIMULATION and if this is increasingly intense polycystic disease or cancer supervenes.

Relation of Mammary Dysplasia to Cancer as Determined by Follow-up Reports

At present the most reliable method to determine the tendency of cancer to supervene in the various forms of mammary dysplasia is to follow a large group of cases for a sufficient number of years. In the present series, 793 patients have been followed for periods of from five to 30 years. These comprised 231 cases of mastodynia, 184 cases of adenosis and 378 cases of cystic disease. The length of time (average 10.2 years) during which these cases have been followed is deemed adequate, for most of them, when last heard from, had passed into or beyond the peak of the cancer age. Since mammary dysplasia is a diffuse process, cases treated by local excision may be justifiably included along with those cases in which no

operative procedure was performed. Since the disease is bilateral in a large percentage of the cases, the ultimate results in patients with unilateral amputations are also of interest. *Those with bilateral amputations were excluded, of course.*

On the basis of Dr. L. I. Dublin's figures, the expected number of cases of mammary cancer in the general female population for this age group (av. 40 years) during the period of 10 years through which these cases have been followed is 4.2 per thousand or 0.42 per cent (Table XXX). In the group of 793 patients with mammary dysplasia followed, mammary cancer should develop in 3 or 4 cases.

Among 378 cases of cystic disease adequately followed, four developed cancer of the breast. Among 231 cases of mastodynia none got the disease,[1] and among 184 cases of adenosis six ultimately developed mammary cancer. The incidence of cancer in the 793 cases of mammary dysplasia followed for an average of 10.2 years is 1.26 instead of 0.42 per cent. The percentage of cancers which occurred was significantly high in adenosis, where it was seven times as great as calculated or approximately 3 per cent. In cystic disease the number of mammary cancers observed was three times the calculated number, and in mastodynia it was less.

In evaluating the significance of these figures, it is proper (in the author's opinion) to consider, among the 10 patients developing mammary carcinoma, only those seven who are known to have died of metastases. This is justified: first, because of the frequency with which the changes of mammary dysplasia are confused with cancer; and second, because no allowance has been made for the undiagnosed cases of mammary cancer in the general population but the calculations were made on the basis of the number of recorded deaths from the disease. On this basis, the incidence of mammary cancer in the 793 followed cases of chronic cystic mastitis is 0.88 per cent instead of the calculated 0.42 per cent. Among the cases of adenosis, the cancer incidence is 2 per cent or five times the expected figure; in cystic disease, 0.79 per cent or twice the expected figure; and in cases of mastodynia, below the calculated number, or zero per cent.

The histories of the cases of mammary dysplasia in which carcinoma supervened follow:

PATIENTS WITH ADENOSIS WHO ULTIMATELY DEVELOPED CANCER OF THE BREAST

Case 1. A woman, 45 years old, had a fibro-adenoma removed from the outer upper quadrant of the right breast four years ago. In September, 1925, she was examined for tenderness and nodularity near the scar in

[1] A patient of 44 years seen in 1922 for mastodynia was reported dead of mammary cancer in 1923. In 1930, further correspondence with the patient's husband and her physician failed to elicit any accurate information on the cause of death. This case has therefore been excluded.

the right breast. The surrounding breast tissue was shotty and tender to palpation. No operation was advised. In April, 1931, the patient was re-examined. Both breasts were diffusely shotty and there was a slight depression over the small nodule near the scar in the right breast. Again no operation was advised.

In April, 1932, there was retraction and fixation of the nipple and an indefinite mass 3 cm. in diameter, near the right areola. An exploratory operation was done. A carcinoma 8 mm. in diameter was found and a complete operation was done. The patient was well in 1938.

Case 2. A woman, 40 years old, had noticed a discharge from the right nipple for several months. The right breast was painful and nodular. An examination in April, 1928, showed a scar where a lactation mastitis had been incised 10 years previously. Nothing could be expressed from either nipple. No operation was advised. In July, 1930, a definite tumor was palpated in the lower hemisphere of the right breast. It was explored, found to be carcinoma and a radical operation was performed. The patient died in November, 1934, with extensive metastases.

Case 3. A white woman, 37 years old, was examined in 1914 for a discharge of blood from the right nipple which had been present three months. Six and a half months before examination, a benign tumor had been excised from the right breast. Both breasts were shotty with small indefinite tumors, but no discrete mass was made out. Operation was not advised. In 1919, cancer appeared in the region of the scar in the right breast and a radical mastectomy was performed. In 1921, a recurrent mass was excised from the chest wall. In 1932, the patient died with metastasis.

Case 4. A single woman, 35 years old, was examined for painful breasts in March, 1912. There was a lump 2 cm. in size in the lower hemisphere of the left breast. The left breast was slightly enlarged and contained multiple indefinite lumps. There was an indurated area in the right breast. There was no change in the breasts when the patient was seen in 1915 following pelvic irradiation for uterine myomas. In October, 1919, a tumor 6 cm. in diameter was palpated in the upper mid zone. A radical amputation was performed and postoperative irradiation was given. The patient died three months later with metastasis.

Case 5. A single woman, 45 years old, had noted pain and a mass in the left breast for the past six months. A simple mastectomy was done in 1901. The tissue showed adenosis only. In 1920, 19 years later, the patient reported that there was no trouble on the left side, but recently the right breast had been removed for cancer. A pathologic report on the tissue removed could not be obtained, however.

Case 6. A single woman, 35 years old, was seen in 1912 for nodularity of the left breast. Both breasts had been painful and lumpy for a period of three years. Examination showed multiple, bilateral, pea-sized nodules in both breasts. The large tender nodule in the left breast was excised in January, 1912, and proved to be typical adenosis. The patient returned seven years later with carcinoma in the left breast. The radical mastectomy was performed in March, 1919. The patient died with metastasis in 1926.

PATIENTS WITH CYSTIC DISEASE DEVELOPING CANCER

Case 1. A single woman, 30 years old, was seen because of a tumor in her right breast in July, 1907. A cyst, 2 cm. in diameter, was palpated in the lower inner quadrant of the right breast. An operation was scheduled

but the cyst had disappeared. She was again seen in August, 1917, ten years later. She was married, had one child aged eight years and her breasts were negative. She was again examined in 1924 at the age of 47 years, two years after an artificial menopause had been induced by irradiation because of uterine myomas. At this time there was pain and a mass in the right breast, which had been irradiated elsewhere. The lesion was explored in 1925, found malignant and a radical operation performed. The patient who had always suffered from cancer phobia died in an institution for the insane with pneumonia in 1928 at age 51.

Case 2. A married woman, 40 years old, with one child, had a solitary cyst excised in 1921 from the right breast. In 1924, she returned with a tumor about 2 cm. in diameter in the left breast. The lesion was explored and found to be cancer. The patient died with metastasis seven years later.

Case 3. A woman, 50 years old, had a lump in her left breast which was present for six months. The mass was excised in 1911. It proved to be a nest of small cysts surrounded by dense fibrous tissue. In 1913 she returned with pain and tumor formation in the outer quadrant of the same breast. A hard mass, 2 cm. in diameter, was found. This was explored and found to be cancer. The radical operation was performed. In 1922, eleven years after the first admission, the patient returned with a nodule in the right breast which was excised, proved to be cancer and a second radical operation was performed. The patient died with extensive metastases in 1922.

Case 4. A woman, 45 years old, complained that her left breast was larger than her right. A movable cyst 3 cm. in diameter was found in the outer upper quadrant. This was not excised, but she was kept under observation for one year. At the end of that time the mass had doubled in size. The lesion was explored and a small cyst surrounded by cancer was found. The radical operation was performed in December, 1922. She was reported dead with metastasis in April, 1927.

Clagett et al followed 265 cases of different forms of chronic cystic mastitis, 104 cases of fibro-adenoma and 8 miscellaneous benign lesions of the breast for 5 to 6 years and found that 1.8 per cent developed mammary carcinoma. These authors calculated that the incidence of cancer of the breast was five times as great as in the control group of women in the state of Minnesota.

McKinley followed 60 cases of chronic cystic mastitis, diagnosed 1932-42, in 1943. None had developed cancer.

Warren recently reported that the cancer rate for women with pre-existing benign breast lesions is 4.5 times as great as for all women; and this predominance is especially marked in the decades below 50 years of age. He used an entirely different method of calculation[1]

[1] According to Warren, "The most difficult problem is to establish a fair norm for the morbidity rate of female breast cancer. In order to allow for those patients cured, about 20 per cent of all cases seen, and those never diagnosed, we have estimated the annual attack rate at twice the death rate. Doubling the death rate for all females (29.7 per 100,000) and for those over 30 years of age (50.3 per 100,000) gives an annual attack or morbidity rate of 0.06 per 100 for the total Massachusetts 1930 female population, and a rate of 0.12 per 100 for those women over 30 years of age."

TABLE XXXI

COMPARISON OF FEMALE BREAST CANCER RATES, EXPECTED AND OBSERVED PER 100[1]

	MASSACHUSETTS FEMALE CRUDE ATTACK RATE	MASSACHUSETTS AGE-ADJUSTED ATTACK RATE	OBSERVED ATTACK RATE WITH FOLLOW-UP ADJUSTMENT	OBSERVED ATTACK RATE WITHOUT FOLLOW-UP ADJUSTMENT
Chronic Mastitis				
Samples I and II, Incomplete	0.06	0.12	0.56 + 0.21	5.69 + 2.09
Complete	0.06	0.12	0.62 + 0.41	8.00 + 3.83
Total	0.06	0.12	0.64 + 0.19	6.35 + 1.86
Canada total	0.06	0.12	0.23 + 0.14	2.34 + 1.34
All groups total	0.06	0.12	0.47 + 0.12	4.65 + 1.23
Chronic cystic mastitis				
Samples I and II, Incomplete	0.06	0.12	0.45 + 0.17	3.81 + 1.41
Complete	0.06	0.12	0.51 + 0.19	4.49 + 1.66
Total	0.06	0.12	0.48 + 0.13	4.12 + 1.07
Canada total	0.06	0.12	0.20 + 0.08	1.74 + 0.65
All groups total	0.06	0.12	0.33 + 0.07	2.83 + 0.61
Chronic mastitis and chronic cystic mastitis				
Samples I and II, total	0.06	0.12	0.54 + 0.11	4.87 + 0.95
All groups total	0.06	0.12	0.37 + 0.06	3.35 + 0.56
Adenocystoma				
Sample I total	0.06	0.12	1.32 + 0.76	14.3 + 7.65
Canada total	0.06	0.12	0.26 + 0.18	2.82 + 1.97
Adenoma				
Sample I total	0.06	0.12	0.26 + 0.19	2.86 + 2.00
All cases				
Samples I and II total	0.06	0.12	0.53 + 0.10	4.96 + 0.88
Canada total	0.06	0.12	0.22 + 0.06	1.99 + 0.56
All groups total	0.06	0.12	0.38 + 0.06	3.48 + 0.53

[1] S. Warren: The Relation of "Chronic Mastitis" to Carcinoma of the Breast, Surg.. Gynec., and Obst., 71:257, 1940.

than that herein presented: 1,000 risk years for the patients followed were compared with the morbidity rate for mammary cancer in 1,000 women of corresponding ages taken from the general population of Massachusetts (Table XXXI). He found 35 cancers occurring in 1,044 individuals with varying types of benign breast lesions, followed for a period averaging 9.3 years; these represented a total exposure of 9,393 risk years. Warren included cases of fibro-adenoma and intracystic papillomas. According to his figures, women with chronic cystic mastitis have 4.5 times the likelihood to develop cancer (as the normal). In women with fibro-adenoma, the chance is twice as great and in women with intracystic papilloma it is eleven times as great. Warren does not state on what information the diagnosis of cancer was based in his 35 cases, and it must be emphasized that radical amputations are often performed because the changes of mammary dysplasia are mistaken for mammary carcinoma.

SUMMARY

In a series of 2500 mammary cancers and 1200 cases of mammary dysplasia, the two conditions co-existed in the same patient in 19 cases, slightly more than twice the expected number. The incidence of mammary cancer in 793 cases of mammary dysplasia followed for an average of 10.2 years was 1.26 instead of the calculated 0.42 per cent. The percentage was highest in adenosis where it was seven times as great as expected or approximately three per cent. In cystic disease the mammary cancers which developed were between 2 and 3 times the calculated number and in mastodynia it was less. A study of 90 cases of early mammary cancer (1.5 cm. or less in diameter) showed that the majority had their onset in fibro-adenomatous nodules with atrophic changes. However, in 6 cases (6.6 per cent), the histologic appearance suggested an origin in an area of mammary dysplasia. In the rat's breast an attempt was made to determine experimentally whether or not the changes of adenosis predispose to cancer. After two years' stimulation with estrogen in low doses rats with advanced adenosis were given extremely high doses for a period of one to two months, simulating conditions that may occur at the menopause in women with long-standing adenosis. Under these conditions mammary carcinoma developed rapidly in all of the animals. Hence, long-standing adenosis in the human breast may predispose to cancer, if this is followed by adequate estrogenic stimulation near the menopause, or, more rarely, at other times in cyclic women.

Mammary dysplasia, however, is not truly precancerous since an added stimulus is required to produce the malignant change. It may, however, form the focus for subsequent mammary carcinoma in 1 to 2 per cent of women so affected. Since the disease is bilateral, unilateral mastectomy, if practiced in all cases, would protect less than 1 woman in 100, a salvage which would hardly offset the operative mortality.

TREATMENT OF CHRONIC CYSTIC MASTITIS

The methods available for the treatment of mammary dysplasia may be classified into three groups:

I. Surgery: (a) aspiration of cysts; (b) simple excision; (c) mastectomy.
II. Medical Measures: (a) reassurance; (b) removal of focal infection; (c) endocrine therapy.
III. Radiation: (a) radiation of mammary tissue; (b) x-ray castration.

Surgical treatment either in the form of aspiration of a cyst, or the excision of nodular tissue is indicated whenever there is the slightest possibility that mammary cancer may be present. A single aspiration suffices to establish diagnosis in most cases of cystic disease but is insufficient treatment in two-thirds of these cases. For this reason, simple excision is usually the treatment of choice.

Surgery

The incidence of mammary cancer in patients with chronic cystic mastitis is too low to warrant mastectomy. This is the opinion of Warren and also of the author. In cases of fully developed adenosis, where the condition is recurrent or progressive, such a measure may be considered, but the condition is bilateral, and unilateral amputation does not protect the opposite breast. It is the author's practice to use radical mastectomy for those cases of adenosis in which mammary cancer is definitely proved or where the microscopic diagnosis is inconclusive in ruling it out. In all other cases, simple excision of a suspicious nodule is employed. Where a definite nodule develops subsequent to the excision of a former nodule, in adenosis, a simple mastectomy may be advisable.

Medical Measures

In mastodynia the condition is usually transient, a definite nodule is rarely present and in these cases medical measures should be

tried, such as simple reassurance against the fear of cancer and removal of any focus of infection particularly in the pelvic region. In persistent cases, endocrine therapy and an uplift brassiere give adequate relief. (P. 254.) In cystic disease and in adenosis, corpus luteum therapy is usually justified only after excision has been employed to establish diagnosis. It may then be used where the condition is multiple or bilateral or to safeguard against recurrence. The best form of endocrine therapy in all forms of chronic cystic mastitis is normal pregnancy and lactation, and this should be recommended to the patient whenever feasible.

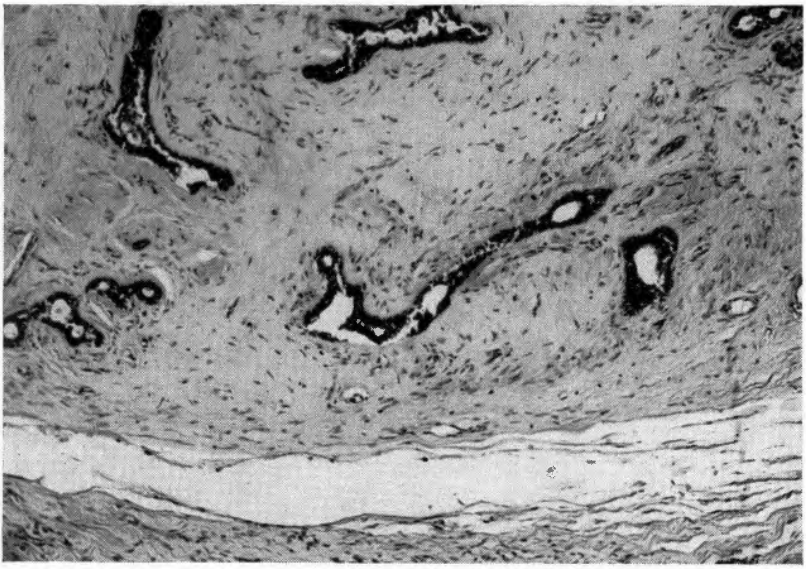


FIG. 238. A fibro-adenomatous nodule apparently resulting from estrogen treatment.

Radiation Therapy

Radiation therapy has a limited usefulness in the treatment of mammary dysplasia. Roentgen-ray castration may be used in patients near the menopause, but may lead to a prolonged estrus rather than castration, and increase the susceptibility to mammary cancer. In two of the 10 cases of mammary dysplasia developing mammary cancer such irradiation was used for uterine myomas. Radiation of the mammary tissue has been recommended by Taylor and others. It is beneficial in about one-half of the cases. It may also be a factor in increasing the susceptibility to mammary carcinoma by prema-

turely aging the radiated tissue. One of the 10 patients developing mammary cancer had radiation applied to both the breast and pelvis.

For explicit directions in administration of these therapies, see the chapters in Part VI, Treatment.

INCIDENCE OF MAMMARY CANCER IN THE NORMAL POPULATION

(Statistical Supplement to Chapter 12)

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Method of Calculation. We have used an average duration of 4.0 years from onset to death for mammary cancer, an assumption which is derived from data in an article by Nathanson and Welch.[1] From a chart on page 46 and a table on page 48 of this article, which show the per cent of *treated* patients dying within specified years after onset, we have found the average duration of the disease to be 4.6 years. From a graph on page 45 of the article, which relates to *untreated* cases, the average duration is estimated to be 3.4 years. Taking treated and untreated cases together, an estimate of 4 years is obtained for the average duration from onset to death. It should be pointed out in this connection that the figure of 3.5 years used by Nathanson and Welch for the average length of life after onset is actually not this quantity, but is the duration after which half of the *treated* cases have died. For this reason, and also because the figure relates only to treated cases, our judgment is that the figure of 4.0 is preferable to Nathanson and Welch's figure of 3.5.

From the nature of the simplifying assumptions made, the results are to be regarded only as approximations which may be subject to considerable modification if the assumptions themselves are modified. It is also to be stressed that the results obtained are no more accurate than the assumptions upon which they are founded. This situation must not be lost sight of either in presenting or in interpreting the current case rates, the onset rates, or the chances of acquiring a mammary cancer.

A second assumption is that none of the cases acquiring a mammary cancer died from any other cause. This tends to understate the onset rate. The error involved is probably small, since the average duration of the disease is short, and since the disease occurs at ages in which the general mortality rate is still moderate.

We have proceeded from the recorded deaths of cancer of the breast among white females in this country in the three-year period 1934-1936, as shown in the official mortality statistics in Table XXXII. The deaths, given in five-year age groups, were interpolated for individual ages with the results shown in the second and fifth columns of Table XXXIII.

In order to find the current case rate corresponding to a given age, the following approximate method was used. The deaths in the given year of age and the three subsequent years of age were added together. The

[1] Nathanson, I. T., and C. E. Welch: Life Expectancy and Incidence of Malignant Disease; I. Carcinoma of the Breast, Amer. Jour. Cancer, 28:40, 1936.

total gave the number of cases that passed through the given year of age while affected with a mammary cancer, during a period of six calendar years, 1931 to 1936 (since the deaths were observed during 1934 to 1936). Thus, in Table XXXIII, the current cases at age 40, namely 2,156, is the sum of the deaths recorded opposite ages 40, 41, 42 and 43.

In order to compute the current case rate at age 40, we must know the size of the population out of which the cases at this age arise. Consider first the deaths at ages 40 to 43 in 1936. On the basis of our hypothesis that the average duration of a case is four years and that the deaths are evenly distributed in time, the deaths at age 40 account for one quarter of the cases current at age 40 in 1936, the deaths at age 41 in 1936 account for one quarter of the cases current at age 40 in 1935, and so forth, with similar reasoning applied to deaths at age 42 and 43. To compute the current case rate at age 40 from these cases alone, we would have to divide them by the sum of one quarter of the population at age 40 in each of the years 1933 to 1936 inclusive. From similar considerations in regard to the deaths at ages 40 to 43 in 1935 we find that we must use the sum of one quarter of the population age 40 in each of the years 1932 to 1935; and corresponding to the deaths at ages 40 to 43 in 1934, the population is the sum of one quarter of the population at age 40 in each of the years 1931 to 1934. Since we have added together the current cases arising from the deaths in the three-year period 1934 to 1936, we must correspondingly add together the populations out of which the current cases may arise. If we denote the size of population at age 40 by P with a subscript to indicate the year to which it relates, we find the total population out of which the current cases may arise to be

$$\tfrac{1}{4} P_{36} + \tfrac{1}{2} P_{35} + \tfrac{3}{4} P_{34} + \tfrac{3}{4} P_{33} + \tfrac{1}{2} P_{32} + \tfrac{1}{4} P_{31}$$

Current case rates were computed for five-year age groups as follows: The current cases for individual ages set forth in Table XXXIII were summed into five-year age groups, as shown in the second column of Table XXXIV. Similarly, the populations obtained for individual ages by the formula of the preceding paragraph were summed for five-year age groups. The last column of Table XXXIV shows the current cases per 100,000 of population.

Our procedure in computing onset rates was as follows: Again, on the assumption that the average duration from onset to death was four years, the age at onset corresponding to the deaths shown in the second and fifth columns of Table XXXIII is four years less than the age shown in the first and fourth columns. Thus, the onset age for the 415 deaths at age 39 was 35 years, and the onset ages for the 2,571 deaths at ages 39 to 43 of Table XXXIII were 35 to 39 years. In this way the figures in Table XXXV were obtained. Since the deaths relate to the period 1934-1936, the onset period was four years earlier, namely 1930-1932. The population for the latter period, subdivided according to the ages at onset, was therefore used in computing the onset rates shown in the last column of Table XXXV.

Table XXXVI shows in detail the method by which we computed the chances that a white female of a stated age will acquire a cancer of the breast within the next 10 years. As the first step, the onset rates shown

TABLE XXXII

DEATHS AND DEATH RATES PER 100,000 FROM CANCER OF THE BREAST

White Females in the United States, 1934–1936

AGE GROUP	DEATHS	DEATH RATES PER 100,000 WHITE FEMALES
30 to 34	646	5.0
35 to 39	1,633	13.5
40 to 44	2,817	24.1
45 to 49	4,046	39.5
50 to 54	4,875	55.6
55 to 59	5,080	69.2
60 to 64	4,925	86.0
65 to 69	4,337	99.0
70 to 74	3,486	114.0
75 to 79	2,655	141.0
80 to 84	1,493	164.4

TABLE XXXIII

DEATHS FROM CANCER OF THE BREAST IN TABLE XXXII INTERPOLATED FOR SINGLE AGES

Together with Estimate of Current Cases Corresponding to Each Age
White Females in the United States, 1934–1936

AGE	DEATHS	CURRENT[1] CASES	AGE	DEATHS	CURRENT[1] CASES
35	241	1,217	60	1,011	3,973
36	282	1,391	61	1,002	3,914
37	325	1,576	62	988	3,835
38	369	1,766	63	972	3,744
39	415	1,960	64	952	3,642
40	467	2,156	65	923	3,530
41	515	2,349	66	897	3,415
42	563	2,558	67	870	3,283
43	611	2,765	68	840	3,144
44	660	2,966	69	808	3,001
45	724	3,158	70	765	2,856
46	770	3,322	71	731	2,721
47	812	3,481	72	697	2,598
48	852	3,626	73	663	2,473
49	888	3,754	74	630	2,344
50	929	3,864	75	608	2,206
51	957	3,946	76	572	2,047
52	980	4,000	77	534	1,854
53	998	4,036	78	492	1,656
54	1,011	4,057	79	449	1,459
55	1,011	4,064	80	379	1,268
56	1,016	4,068	81	336	1,113
57	1,019	4,063	82	295	975
58	1,018	4,046	83	258	849
59	1,015	4,016	84	224	733

[1] Assuming an average duration of four years from onset of a cancer of the breast to death, the current cases at any specified age are equal to the deaths at the specified age plus the deaths at the three subsequent ages.

TABLE XXXIV

CURRENT CASES OF CANCER OF THE BREAST

Per 100,000 White Female Population United States, 1931–1936, in Specified Age Groups

AGE GROUP	CURRENT CASES	ESTIMATED POPULATION[1]	CASES PER 100,000 POPULATION
35 to 39	7,910	12,090,000	65.4
40 to 44	12,794	11,449,000	111.7
45 to 49	17,341	9,890,000	175.2
50 to 54	19,903	8,505,000	234.0
55 to 59	20,257	7,030,000	288.1
60 to 64	19,108	5,513,000	346.6
65 to 69	16,373	4,229,000	387.1

Population in specified age group =

$$\tfrac{1}{4}P_{36}+\tfrac{1}{2}P_{35}+\tfrac{3}{4}P_{34}+\tfrac{3}{4}P_{33}+\tfrac{1}{2}P_{32}+\tfrac{1}{4}P_{31}$$

where the subscript denotes the year to which the population relates.

TABLE XXXV

RATE OF ONSET OF CANCER OF THE BREAST

Per 100,000 White Females in the United States, 1930–1932[1]

AGE GROUP	NEW CASES	ESTIMATED POPULATION	ONSET RATES PER 100,000
30 to 34	1,407	12,435,000	11.3
35 to 39	2,571	12,111,000	21.2
40 to 44	3,818	10,894,000	35.1
45 to 49	4,752	9,396,000	50.6
50 to 54	5,075	8,059,000	63.0
55 to 59	4,988	6,520,000	76.5
60 to 64	4,482	5,207,000	86.1
65 to 69	3,664	3,973,000	92.2

[1] Since it has been assumed that the average duration of a case of cancer of the breast from onset to death is four years, and since the deaths used as the basis for this computation relate to the period 1934–1936, the period of onset is 1930–1932.

for quinquennial ages in Table XXXV were interpolated for individual ages, with the results shown in the third column of Table XXXVI. These onset rates were next multiplied by the entries at each age from 35 to 74 in the survivorship column of a life table for white females based upon mortality in the general population of the United States during 1936. In this way we obtained the new cases arising at each age from 35 to 74 in a life table cohort (fourth column of Table XXXVI). Summing the new cases at the ten successive ages from 35 to 44 and dividing the sum by the number living in the life table cohort at age 35 yields the chance that a white female of age 35 will acquire a cancer of the breast within the next ten years. Similar computations were made for ages 45, 55 and 65 years.

TABLE XXXVI

CHANCES PER 1,000 THAT A WHITE FEMALE OF A STATED AGE WILL ACQUIRE A CANCER OF THE BREAST WITHIN THE NEXT TEN YEARS

AGE	LIFE TABLE SURVIVORSHIP COLUMN*	ONSET RATE PER 100,000	NEW CASES AT SPECIFIED AGE	NEW CASES WITHIN NEXT TEN YEARS	CHANCES PER 1,000 OF ACQUIRING A CANCER OF THE BREAST WITHIN NEXT TEN YEARS
35	88,608	16.6	14.7	244.5	2.8
36	88,272	18.8	16.5		
37	87,922	21.2	18.6		
38	87,557	23.8	20.8		
39	87,178	26.4	23.0		
40	86,785	29.2	25.3		
41	86,377	32.1	27.7		
42	85,951	35.1	30.2		
43	85,505	38.1	32.6		
44	85,035	41.3	35.1		
45	84,538	44.5	37.6	461.8	5.5
46	84,010	47.6	39.9		
47	83,447	50.6	42.2		
48	82,847	53.2	44.1		
49	82,208	55.7	45.8		
50	81,527	58.1	47.4		
51	80,803	60.2	48.6		
52	80,034	63.2	50.5		
53	79,219	65.7	52.0		
54	78,357	68.5	53.7		
55	77,445	71.3	55.2	581.9	7.5
56	76,478	74.0	56.5		
57	75,447	76.3	57.5		
58	74,343	78.6	58.4		
59	73,154	80.7	59.0		
60	71,871	82.6	59.4		
61	70,483	84.4	59.5		
62	68,983	86.1	59.4		
63	67,365	87.5	58.9		
64	65,623	88.6	58.1		
65	63,755	89.7	57.2	513.2	8.1
66	61,763	90.8	56.1		
67	59,649	92.7	55.3		
68	57,421	94.0	54.0		
69	55,085	96.1	52.9		
70	52,644	98.3	51.7		
71	50,098	100.2	50.2		
72	47,444	101.1	48.0		
73	44,678	101.4	45.3		
74	41,800	101.7	42.5		

* Number of survivors to specified age out of 100,000 born alive, according to life table for white females in the United States, 1936.

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PART IV

BENIGN MAMMARY TUMORS

ORIENTATION

The chapters of Part IV are devoted to a consideration of benign tumors of the mammary gland. Only two groups of these benign tumors are found with any degree of frequency in the breast; fibro-adenomas with a structure of fibrous tissue and ducts, and papillomas composed of epithelial tufts growing within a dilated duct or cystic cavity. Fibro-adenomas occur with three times the frequency of papillomas. While fibro-adenomas are compound growths composed of ducts and fibrous tissue, the fibrous component predominates and represents the neoplastic element. Like other common benign tumors occurring elsewhere in the body these growths arise in relatively unspecialized mesenchymal tissue during the period of maximum normal development of the organ, may reach tremendous size in some instances, forming giant intracanalicular myxomas, and in occasional cases may undergo sarcomatous change. These firm, nodular, encapsulated growths in many of their features resemble uterine fibromyomas, which is the most common benign tumor of the other major female accessory sex organ. The growth of both benign mammary and uterine tumors is dependent upon ovarian function. The most rapid growth of fibro-adenomas is observed during pregnancy or the menopause when estrogenic stimulation is intense and prolonged.

Various forms of other benign mesenchymal tumors occur in the breast, including lipomas, angiomas, myomas, chondromas, and osteomas, but these are rare and of little clinical significance. As previously stated, the other important benign neoplasm is the papillary adenoma or intra-cystic papilloma. This is a soft epithelial growth projecting into a duct or cystic cavity, and is associated in approximately 50 per cent of the cases with a sanguineous discharge from the nipple. While the majority of fibro-adenomas occur before the age of 30, most papillomas occur after this age. The size of fibro-adenomas, which is dependent upon their fibrous component, may exceed 5 or 10 cm. in diameter and maintain their benign character. Papillomas, however, of corresponding size, unless within a cavity distended by encapsulated fluid, are prone to malignant change.

Because of their firm, nodular character excision is indicated for fibro-adenomas in order to confirm the diagnosis by microscopic study, even though the encapsulated, mobile character of the mass and the youthful age of the patient is against the probabilities of carcinoma. Excision is also indicated for benign papillomas. Here, the occurrence of a bloody discharge and a shadow on transillumination present diagnostic features which may also be found in cases of mammary carcinoma. A detailed discussion of treatment is found in Chapter 28, Part VI.

13

Benign Fibro-Adenoma

Fibro-adenoma is the most common benign tumor of the breast in young women in the childbearing period. The firmness of the lesion, its encapsulation and mobility make the clinical diagnosis relatively certain. Gradual enlargement over a period of months or years is the rule. In early adolescence, in pregnancy or toward the menopause, however, more rapid growth may occur. These are times when high concentrations of the ovarian hormone, estrogen, are found. The breast containing the fibro-adenoma is usually well developed, firm and of the virginal type (Fig. 241). These tumors are composed of a growth of ducts and periductal connective tissue. Connective tissue predominates and in tumors that have grown slowly this tissue is adult and fibrous in character; whereas, with rapid growth, the stroma is composed of a loose myxomatous substance which compresses the epithelial elements. This latter group is often referred to as "intracanalicular myxoma." Benign cystic degeneration is not uncommon but malignant change is rare in fibro-adenomas. However, fibrosarcomas may develop in tumors of large size (giant intracanalicular myxoma) occurring at or near the menopause.

FIG. 239. Drawing to illustrate the characteristics of fibro-adenoma on palpation. The nodule is firm, circumscribed, lobulated and freely movable.

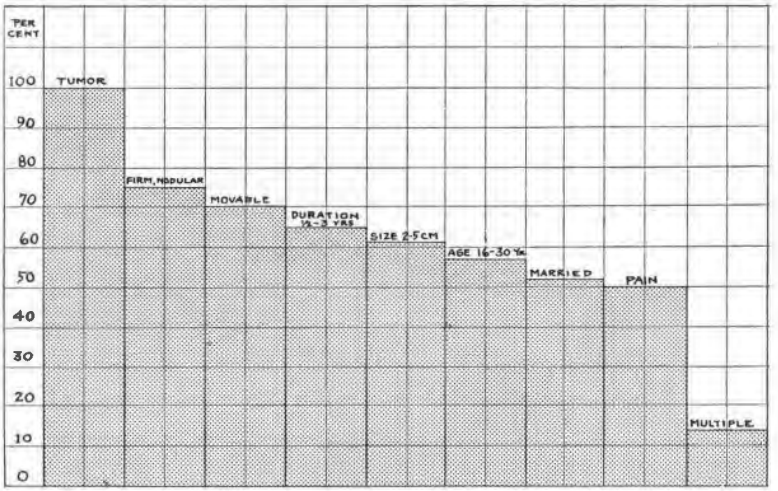


FIG. 240. Chart showing the relative frequency of various symptoms and findings in fibro-adenomas.

The benign nature of these new growths was recognized by Sir Astley Cooper over a century ago, and in the past few decades their clinical and pathologic features have been thoroughly studied. There remains a difference of opinion among pathologists, however.

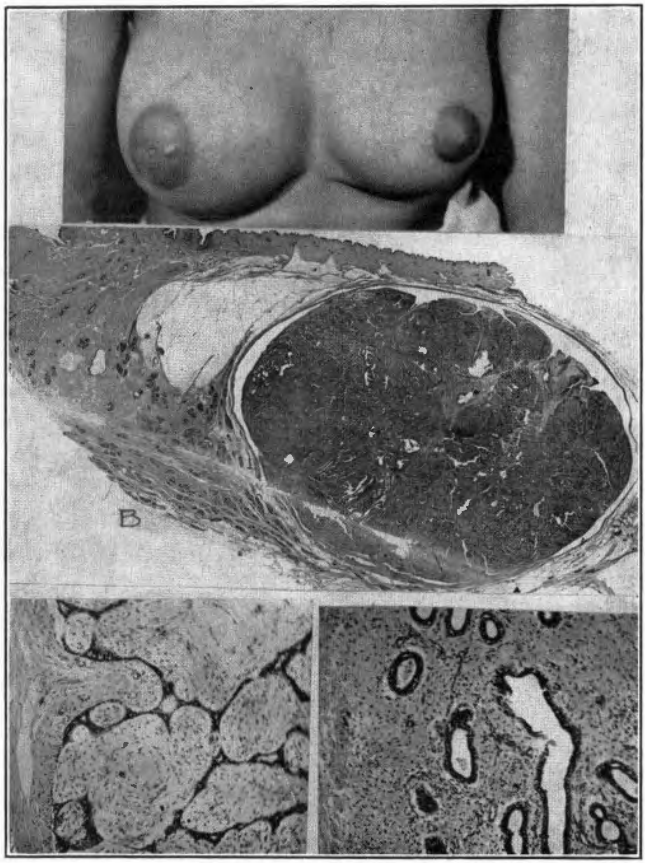


FIG. 241

FIG. 242

FIG. 243

FIG. 244

FIGS. 241-244. Photograph of the patient, and cross section of the breast, and photo micrograph of benign fibroadenoma. The cross section shows the encapsulated character of the tumor and the photomicrographs compare the myxomatous (left) and fibroadenomatous (right) structure common in these growths.

concerning the epithelial, fibrous or compound nature of the neoplasm. In the past 20 years, a series of 100 or more cases has been reported by McFarland, Semb, Oliver and Major, and de Cholnoky. Virchow considered the lesions fibromas and more recently Cheatle and Cutler have similarly classified them. Paget stressed the glandular elements of the tumors and Ribbert regarded them as fibro-

epithelial in nature. Oliver and Major, in 1934, recommended a shift in emphasis from morphologic to physiologic aspects believing that both the fibrous and epithelial elements were responding to the same endocrine stimulus. The author has been able, in part, to confirm this viewpoint by producing experimental fibro-adenomas in rats in which the breasts were stimulated with estrogenic hormone (Geschickter).

However, the histologic structure of fibro-adenoma in which connective tissue predominates, the fact that malignant change gives rise most frequently to sarcoma, rather than to carcinoma, and the growth of these neoplasms under experimental conditions, indicate that connective tissue, rather than epithelium, is the neoplastic component. The large size of many of these growths and their frequent occurrence also supports this interpretation. The benign epithelial tumors of the mammary gland are less common, and those of solid structure rarely grow to large dimensions.

As long as the mammary epithelium follows its specialized function and forms milk-secreting glandular structures, its power of regeneration is relatively limited. For this reason benign epithelial tumors are limited in size and are not excessively common. This limited power of regeneration is demonstrated if the growth of the duct epithelium is stimulated by estrogen. With such stimulation the maximum size of the duct tree is reached in a matter of a few weeks. On the other hand, the less highly differentiated fibrous stroma of the breast is capable of more pronounced and extended regeneration. This is demonstrated by its prolonged and progressive growth over a period of months in response to estrogenic stimulation. Because of this power of regeneration, benign tumors of the mammary connective tissues are relatively common and may progress to large size. Apparently the more primitive and less differentiated tissues of the body, particularly those of mesenchymal origin, are more susceptible to benign tumor formation and to growths which reach appreciable size.[1]

CLINICAL FEATURES

Onset. In the 600 cases studied, the age incidence in benign fibro-adenomas was highest between 21 and 25 years (Fig. 245). Eight per cent of the cases occurred in women past the menopause, and in about 10 per cent girls (between the ages of 9 and 17 years) were affected before the first menstruation. Oliver and Major who previously reported 400 of these tumors noted that the peak of age inci-

[1] Fibro-adenomas, like other common benign tumors, occur in relatively unspecialized tissue with pronounced regenerative capacity and during the period of maximum normal growth.

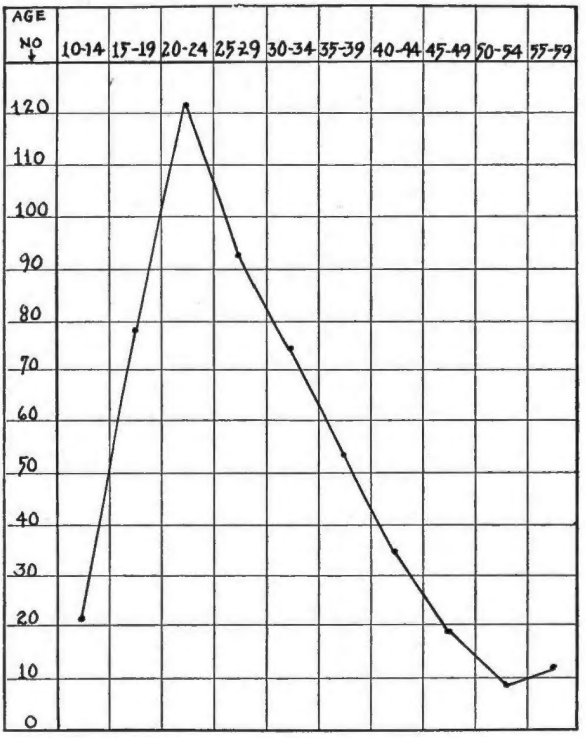


FIG. 245. Chart showing the age incidence of 515 cases of fibro-adenoma.

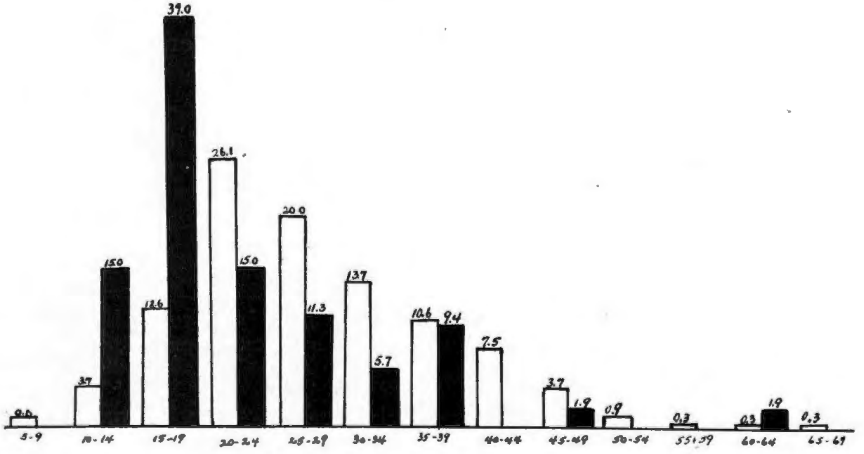


FIG. 246. Chart showing the age incidence of fibro-adenoma in white and colored patients (from Oliver and Major).

dence in colored women was reached five years earlier than in white women. They also showed that although the age incidence of fibro-adenoma is usually supposed to be earlier than that of intracanalicular myxoma, there was little difference between the two groups (Figs. 246, 247). In the present series, married and unmarried women were affected in approximately equal numbers. Among the married women, those with children predominated in a ratio of two to one.

In nearly all cases, the discovery of a lump was the symptom of onset, and in approximately one-half of these patients pain or tender-

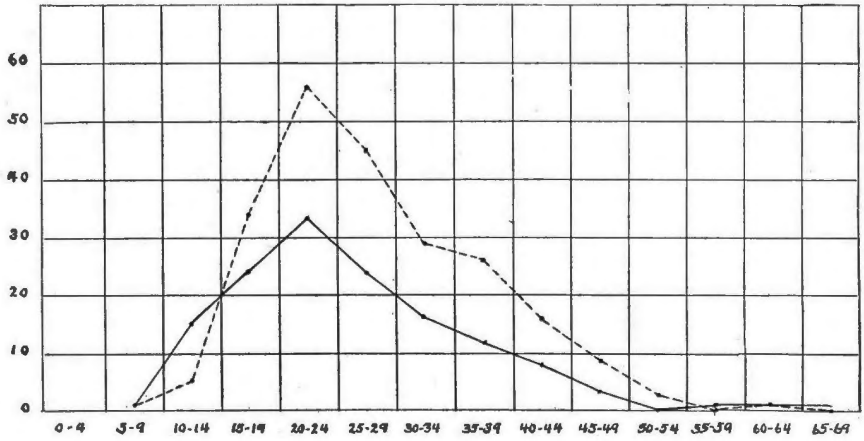


FIG. 247. Chart comparing the age incidence in fibro-adenoma (solid line) and intracanalicular myxoma (broken line) (from Oliver and Major).

ness was noted also. Gradual or progressive growth of the mass is the rule, although one-sixth of these patients stated that the size of the growth had remained stationary for months or years, and in six instances regression or disappearance of the nodule was thought to have occurred. A slight amount of serous or cloudy fluid could be expressed from the nipple in 12 cases. In two instances a bloody discharge occurred.

Number and Size. The fibro-adenoma is usually a solitary lesion, but in 79 cases multiple growths (bilateral in 27 cases) were present. In 15 of these an interval of two to 25 years had occurred between the excision of a previous tumor and the second mass. The tumor occurred most often in the outer and upper quadrant. The upper half of the breast was more frequently affected than the lower, and the outer more often than the inner portion (Fig. 248). At the time of examination the greatest number of fibro-

adenomas were between 2 and 5 cm. in diameter (61 per cent). In about one-fifth of the cases, the size of the growth was compared to a hen's egg (5 to 7 cm.), and in 11 cases the mass was 8 cm. or more in diameter. Most of Semb's cases were between 2 and 6 cm. in diameter and in de Cholnoky's series, 60 per cent were between 1.5 and 3 cm.

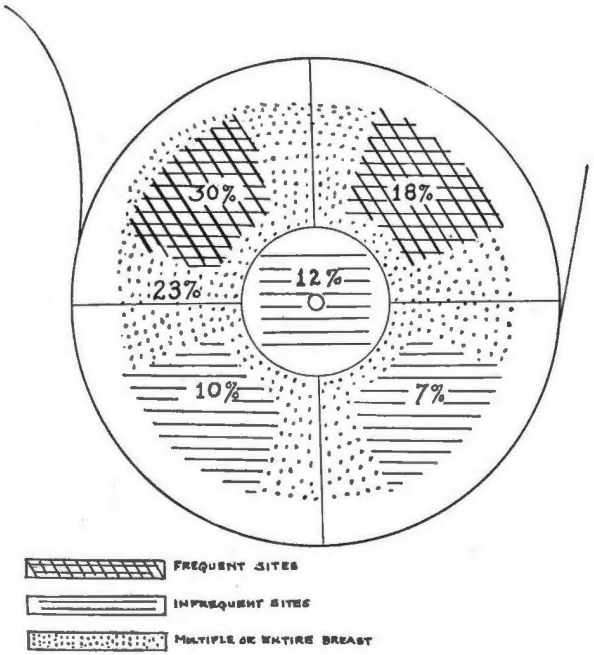


FIG. 248. Chart showing the distribution of benign fibro-adenoma.

Duration. While the average duration of the lump is about three years in cases of fibro-adenoma, one-third of the cases had noted its presence a year or less. An approximately equal number had been aware of the tumor from one to five years, and in 15 per cent the duration was more than 5 or 10 years (a similar duration of symptoms was noted by de Cholnoky: 40 per cent, 3 months to one year; 36 per cent, one to three years).

Characteristics of the Tumor. On examination, the leading characteristics of the tumor are its mobility, its encapsulation, the absence of skin changes and its firmness to palpation. The nipple moves freely and no enlarged nodes are felt in the axilla. The mass is solid or elastic, its contour smooth or lobular. In only 15 cases was the mass described as cystic. Tumors more than 2 cm. in diameter

TABLE XXXVII

DATA ON 600 CASES OF FIBRO-ADENOMA

I. AGE

10–15	21
16–20	79
21–25	121
26–30	93
31–35	74
36–40	53
41–45	36
46–50	18
51–55	7
56 or over	13
	515

II. MARITAL

Single	228
Married	219
Parous	142
Married, childless	77

III. DURATION OF SYMPTOMS

Less than 1 month	32
1 month to 1 year	222
1 year to 3 years	148
3 years to 5 years	84
Over 5 years	58
Over 10 years	33
	577

IV. SYMPTOMS

Tumor	541
Pain or soreness	267
Discharge from nipple (2 bloody)	14
Trauma	47
Rapid or progressive growth	133
No growth	94
Regression	6

V. FINDINGS

Movable	337
Encapsulated	128
Nodular or irregular	173
Hard or firm	178
Fluctuant or cystic	15
Retracted nipple	9
Dimpling skin	11
Ulceration	4
Enlarged axillary nodes	9

VI. LOCATION

Multiple	79
(Bilateral—27)	
(Previous nodules—15)	
O.U.Q.	134
I.U.Q.	82
L.O.Q.	46
L.I.Q.	29
Central	40
Nipple zone	16
Entire breast	28

VII. SIZE

Under 1 cm.	14
1–2 cm.	36
2–3 cm.	116
3–5 cm.	118
5–7 cm.	86
8 cms. or more	11
	381

VIII. TREATMENT

No operation	7
No data	86
Excision	476
Amputation (simple)	11
Radical Amputation	13
Enucleation	7
	600

IX. END-RESULTS

Well over 3 years	67
Well over 5 years	101
Well over 10 years	89
Recurrent fibro-adenoma	27
Cancer of Breast	2
	286

usually cast a shadow on transillumination. Retraction of the nipple, dimpling of the skin, ulceration or enlarged axillary nodes were exceptional findings noted only in cases where the tumor had reached considerable size (Table XXXVII). The surrounding breast was usually normal to palpation and was sometimes lumpy or diffusely nodular. The breast affected may be larger than the unaffected side and in rare instances true virginal hypertrophy may be found (Fig. 249).

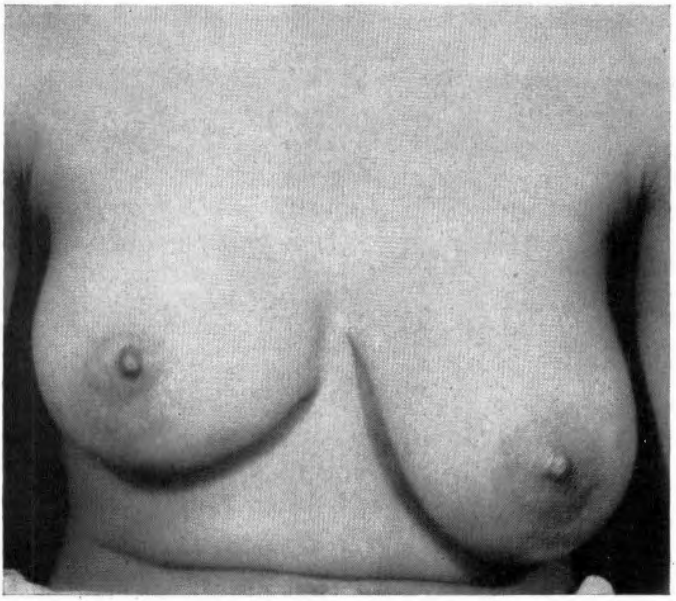


FIG. 249. Fibro-adenoma occurring in a case of unilateral virginal hypertrophy. The enlarged breast contains two fibro-adenomas 4 and 5 cms. in diameter.

While the rate of enlargement varies, it is only in exceptional cases of giant intracanalicular myxoma that the tumor appears to have unlimited power for continuous growth. The maximum size of most fibro-adenomas is 5 to 6 cm. and many of the tumors remain stationary after reaching a diameter of 2 to 3 cm. In some patients, however, the masses not only grow rapidly but successive tumors of identical character appear repeatedly following excision. This is most apt to occur during adolescence or near the menopause. The tumor tissue in fibro-adenoma apparently responds to physiologic stimuli more intensely but in the same manner as the normal breast. Ingleby found that the tumor responded to menstruation and Kilgore, Moran, and Geschickter and Lewis have described the changes occurring in pregnancy and lactation.

DIAGNOSIS

Fibro-adenoma must be differentiated from cancer, cystic disease and the rare lipoma or dermoid cyst of the breast. Fibro-adenoma usually occurs at an earlier age than cancer, the tumor is more sharply circumscribed, more freely movable and is felt beneath the subcutaneous fat; whereas in cancer the atrophy of overlying fat gives the mass an apparently superficial location. The contour of the fibro-adenoma is more smoothly lobulated than the irregular surface of carcinoma and its consistency is more elastic. Retraction of the nipple, dimpling of the skin and enlargement of axillary lymph nodes are rare in fibro-adenomas even when the tumor is 3 cm. or more in diameter. This is generally not true of cancers of corresponding size.

The blue-dome cyst is easily differentiated from fibro-adenoma by its smooth circular outline, its fluctuant character and its fluid content which is readily withdrawn with the aspirating needle. Cysts of 3 cm. or more in diameter transilluminate clearly whereas fibro-adenomas of this size frequently cast a shadow. Lipoma of the breast is an unusual, superficial tumor occurring in elderly patients and has a soft, lobulated character on palpation. The lesion transilluminates. The dermoid cyst is an even rarer tumor. It usually affects elderly patients and is, as a rule, symptomless. (See Chap. 15.)

PATHOLOGY

Fibro-adenomas are sharply delimited growths, easily separated from the surrounding mammary tissue. They are firm, grayish-white or pinkish tumors, usually circular or oval in outline. On cross-section, the bulging surface of the ordinary fibro-adenoma is homogeneous and granular. In the variety known as intracanalicular myxoma, the cut surface is divided into lobules and may show papillary excrescences. (Figs. 250, 251.) Cysts from 1 to several mm. in diameter may be found in tumors of long duration. Some of these older growths contain hard, hyalinized fibrous tissue with occasional areas of calcification.

In benign fibro-adenoma and its subvariety, intracanalicular myxoma, both connective tissues and mammary epithelium take part in the new growth. Four forms of fibrous tissue make up the stroma and supporting tissue of the breast (Chap. 1), but only the forms adjacent to the epithelial structures take part in the tumor. Two of these forms of fibrous tissue, the interlobar and interlobular, are

fascial in type and are unimportant in fibro-adenoma. The third and fourth forms of fibrous tissue make up the true stroma of the breast.

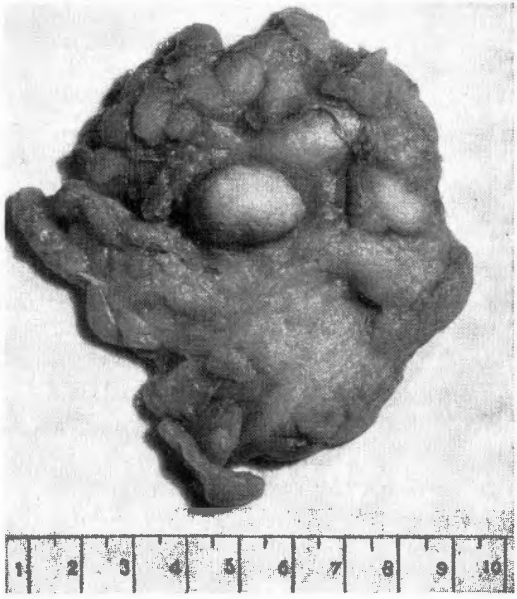


FIG. 250. A small fibro-adenoma: gross specimen.

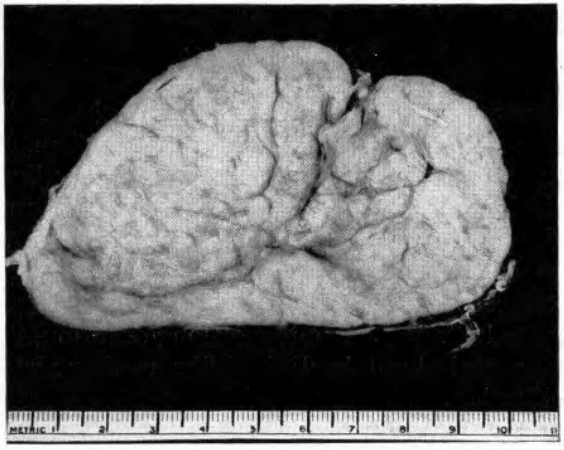


FIG. 251. A lobulated tumor composed largely of myxomatous tissue.

One of these, the perilobular connective tissue, surrounds the ducts and acini in concentric fashion and the other, the periductal or periacinar is found immediately adjacent to the epithelial elements.

In most fibro-adenomas there is a marked increase in the periductal and perilobular connective tissue. During periods of maximum growth and when under pressure the connective tissue has a pale staining and myxomatous appearance (so-called intracanalicular myxoma). In tumors with a more gradual growth, adult eosin staining connective tissue predominates (Figs. 252-255).

In the majority of fibro-adenomas, the number and the size of the ducts are increased. There is a reduplication of the epithelial layers lining these channels. Numerous small cells with occasional mitotic figures at the basement membrane indicate rapid growth. In three-fourths of the cases in the present series there was evidence that such epithelial growth as well as a growth of perilobular and periductal connective tissue had occurred. In the remaining cases the more marked growth in fibrous tissue compressed the duct epithelium or the tumor had reached a quiescent state in which the adult, hyalinized connective tissue predominated. The ratio of fibro-adenomas to intracanalicular myxoma, on the basis of histologic diagnosis, was 2 to 3 in favor of the myxomatous growths. In some cases, deposits of calcareous substance were prominent. (Fig. 256.)

Microscopically, fibro-adenomas often resemble the normal mammary tissue of adolescence. The hypertrophy of duct epithelium, scarcity of mammary lobules and the increase in pale-staining periductal connective tissue found in adolescence are characteristic of these new growths also. More marked pathologic changes may be found toward the center of the growth, however. Here the prolonged and exaggerated growth of connective tissue leads to the formation of dense fibrous tissue, and to an overripening in the duct epithelium with secretory and cystic changes. Papillary masses of adult duct epithelium referred to as "sweat gland" in type may be found (Fig. 254).

The ordinary fibro-adenoma may be looked upon as an exaggerated form of puberty hypertrophy affecting an isolated portion of the breast. The accuracy of this interpretation can be proved experimentally. Typical benign fibro-adenomas occur in the breast of rats and rabbits that have been continuously stimulated with increased amounts of estrogenic hormone (Fig. 257).

Differentiation Between Intracanalicular Myxoma and Fibro-Adenoma

Various pathologic interpretations have been advanced to explain the features which distinguish intracanalicular myxoma from ordinary fibro-adenoma.

MacCallum states that the myxomatous growths are produced by a

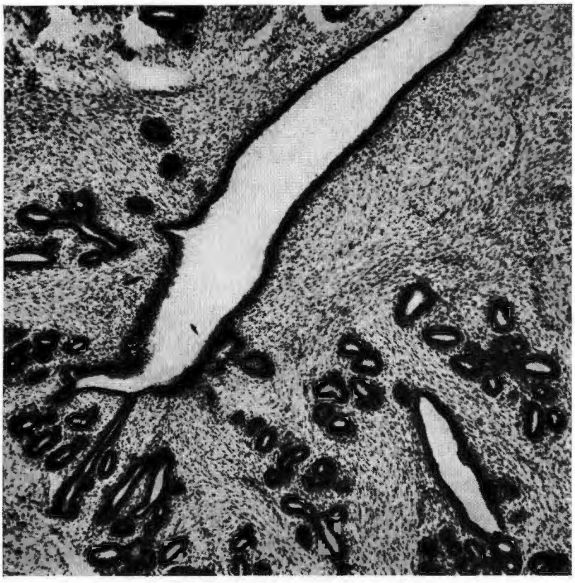


FIG. 252. Typical fibro-adenoma.
FIGS. 252-255 show the varying histologic structure of fibro-adenomas.

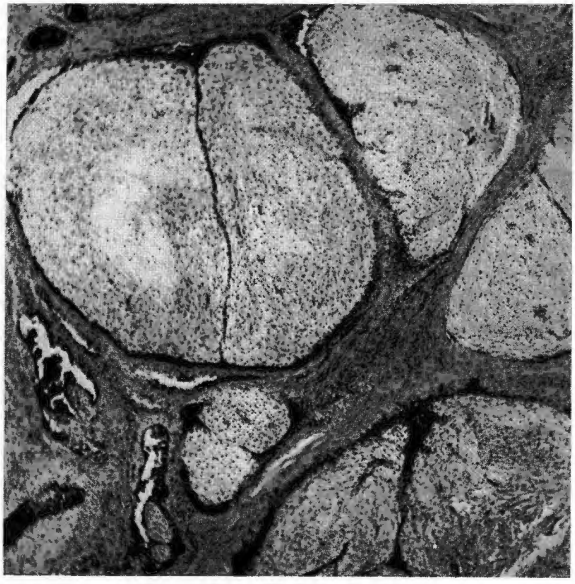


FIG. 253. Typical myxoma.

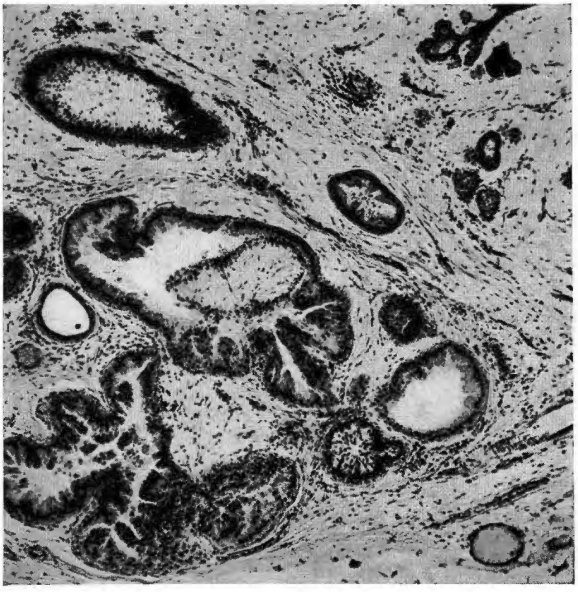


FIG. 254. Fibro-adenoma with epithelium of the sweat-gland type.

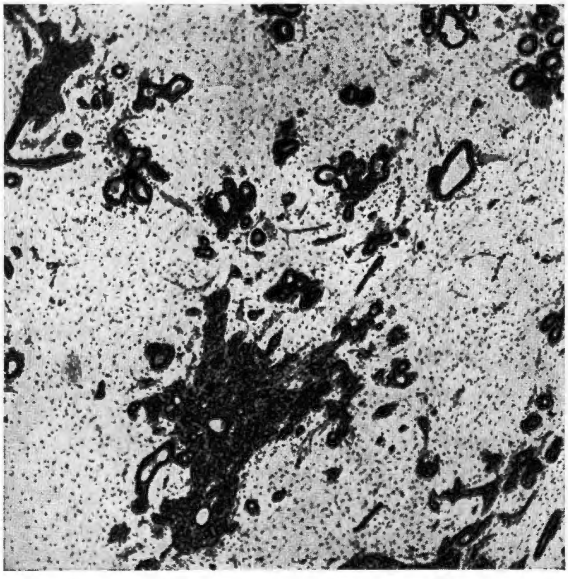


FIG. 255. Adenomyxoma with epithelial proliferation.

series of polypoid masses of proliferating connective tissues which protrude into the mammary ducts compressing the mammary-duct

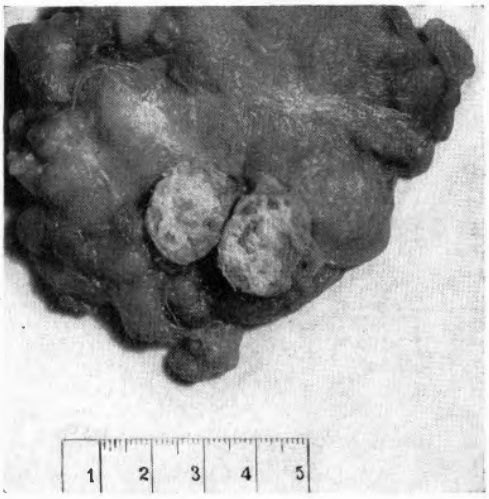


FIG. 256. Fibro-adenoma with calcareous deposits.

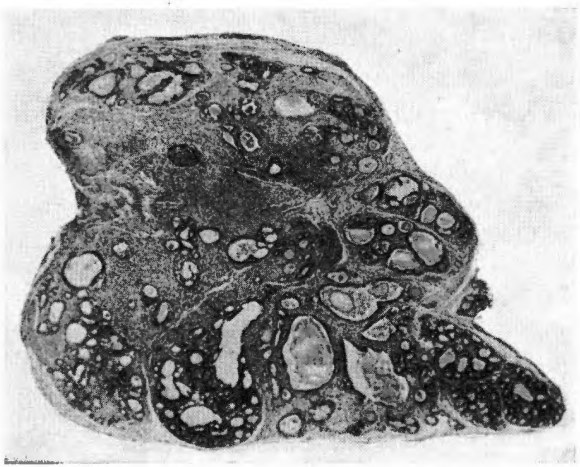


FIG. 257. Fibro-adenoma in the rat's breast. This typical and encapsulated tumor developed in response to prolonged estrogenic stimulation.

epithelium between the expanding tufts. Cheatle and Cutler believe that ordinary fibro-adenomas are formed from periductal or perilobular fibrous tissue, while a proliferation of sub-epithelial fibrous tissue from the basement membrane beneath the epithelial lining of

the milk ducts gives rise to intracanalicular myxoma. Oliver and Major believe that there is no important difference, and that in the

FIG. 258 FIG. 259

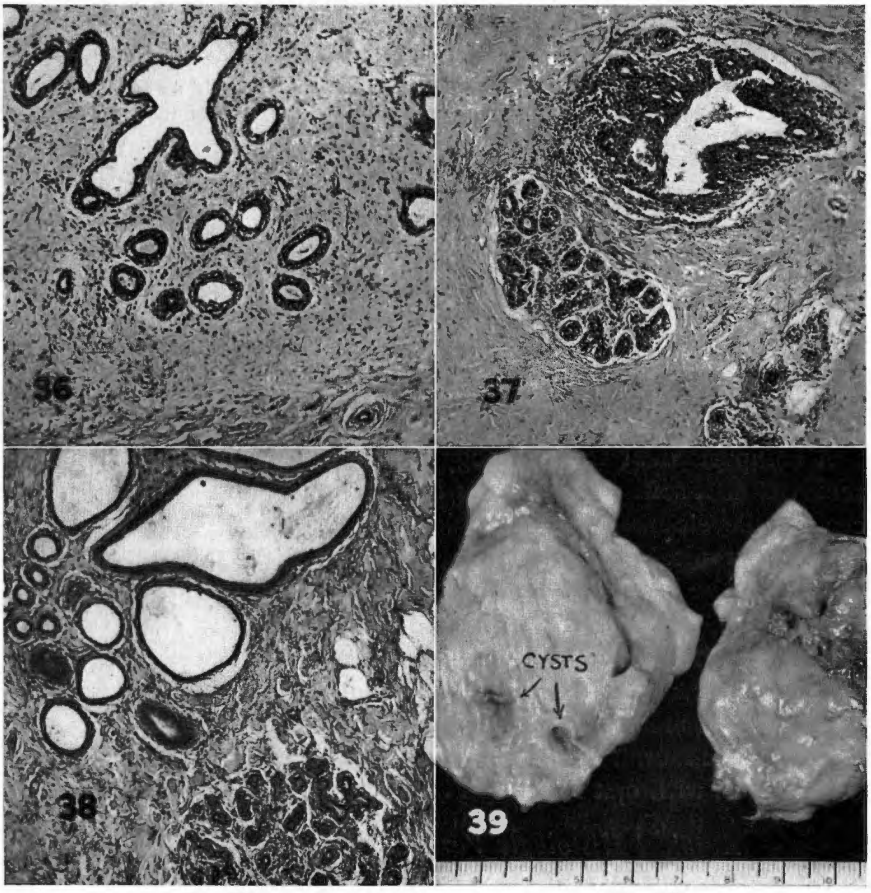


FIG. 260 FIG. 261

FIG. 258. Fibro-adenoma with multiple recurrences. Photomicrograph showing absence of lobule formation in a fibro-adenoma excised at the age of 26.
FIG. 259. Photomicrograph showing lobule formation in a second tumor excised in the same patient at the age of 33.
FIG. 260. Cyst formation in a third tumor excised at the age of 38.
FIG. 261. Gross specimen removed at the last operation.

myxomatous growths there is merely a more rapid and excessive proliferation of connective tissue.

Cysts of varying sizes are common in fibro-adenoma. Macroscopic cysts occurred in 30 of the cases of the present series. Bloodgood, impressed by the number of cysts in some of these tumors, classified

them as cystic fibro-adenoma. These cysts are found most frequently in fibro-adenomas of long standing, indicating that they are the result of involutional changes superimposed upon the pre-existing tumor. These patients are usually older and the tumor is of longer than average duration. This is illustrated in the following case:

A single woman, 38 years old, stated that at the age of 26 years she discovered a small lump in the right breast. In 1924, when the tumor had been present two months and had grown to the size of a walnut, it was excised and proved to be a typical fibro-adenoma. No lobules were present, and the microscopic appearance of the tumor was that of a simple adolescent hypertrophy. In 1931, a similar tumor appeared just above the scar. This was excised and the microscopic structure was similar to that of the earlier tumor, but lobules were superimposed upon the changes seen in the ducts and fibrous tissue. In 1934, there was a second recurrence, with similar tumors in both right and left breasts. These tumors when excised contained numerous cysts the size of a pea, and of a characteristic blue color, embedded in fibro-adenomatous tissue. On microscopic examination the breast showed typical cystic fibro-adenoma. (Figs. 258-261.) The patient was well in 1941.

A comparison of the histology of the tumors in the above case removed at successive operations in 1924, 1931, and 1934 shows the cycle of development in fibro-adenoma. At the first operation the tissue was typical of adolescent hypertrophy with embryonic fibrous tissue, of the intracanalicular myxoma type, surrounding hypertrophic duct epithelium. At the second operation the fibrous stroma was adult, the duct epithelium more markedly hypertrophic, and acinar elements had been added in response to repeated corpora lutea at successive menstruations. At the third operation involutional changes were found. The fibrous tissue was edematous and dilatation of the ducts with cyst formation had occurred.

Atypical Histologic Varieties of Fibro-Adenoma

In the discussion of fibro-adenoma, no mention has been made of the pathologic subvarieties: pure adenoma, cystadenoma, fibroma and fibrosing adenoma. These terms do not apply to separate types of fibro-adenoma but to microscopic peculiarities found upon histologic study.

Pure Adenoma. In nearly every case pure adenomas of the breast are intracystic or intraductal papillary growths which are described in the next chapter under the heading of Intracystic Papilloma. Although the epithelial elements may occasionally predominate in fibro-adenomas in young girls, the fibrous component is always a relatively prominent feature of such solid, encapsulated growths.

This is so because the human breast is unusually rich in fibrous tissue as compared to the glands of other mammals.

Cystadenoma. Cystic change has been described above as an involutional feature of fibro-adenoma. The so-called cystadenoma is a minute, multilocular, cystic dilatation of the mammary lobule. (Fig. 181.) Isolated cystadenomatous areas may be found under the microscope in involuting fibro-adenomas. More commonly the lesion is found in adenosis. (See Chap. 9.)

Fibromas of the breast are forms of fibro-adenoma in which the epithelial elements are all but crowded out by a proliferation of young myxomatous connective tissue. These have been included among the myxomatous forms of fibro-adenoma in the above discussion. If a careful study of the sections is made, compressed epithelial elements will always be found in such fibromas. (Fig. 253.)

The term "fibrosing adenoma" refers to a form of epithelial hyperplasia found in the region of the terminal tubules in cases of adenosis. These are microscopic nodules in which compressed cords of benign lobular epithelium are found embedded in the perilobular connective tissue apparently without a basement membrane. (Fig. 180.)

Pleomorphic Fibro-Adenomas. In rare instances, fibro-adenomas removed from the breasts of young women will cut with unusual firmness, suggesting cancer. Under the microscope, these encapsulated tumors have all the atypical microscopic features described above, including areas of cystadenoma, fibrosing adenoma and solid epithelial lobules which might be termed "pure adenoma." In addition, one or more margins of the tumor show the characteristics of ordinary fibro-adenoma, and other portions contain cuboidal epithelium of the sweat-gland type. The entire microscopic picture is confusing; the distinction between benign atypical fibro-adenoma and mammary carcinoma is made with great difficulty. These cases have been termed "pleomorphic fibro-adenoma" (Geschickter) and are discussed in Chap. 26.

ETIOLOGIC FACTORS

Experimental Production of Fibro-Adenomas

The estrogenic stimulation during adolescence and pregnancy is an important factor in the development of fibro-adenomas. The higher concentration of estrogen, which may occur toward the menopause, may also stimulate their development. Approximately 20 per cent of the patients in this series came under observation during adolescence, or in their twenties or early thirties after the

tumor had been present for a period of over five years (suggesting that the growth had persisted since adolescence). Among the women who had borne children, 49 related the onset of the growth to some phase of pregnancy and in 23 additional cases the tumor had been removed during pregnancy or during lactation. Fifty-four women were at or near the menopause when the lump was discovered. The following tabulation emphasizes the frequency with which fibro-adenoma develops in relation to adolescence, pregnancy and the menopause.

TABLE XXXVIII

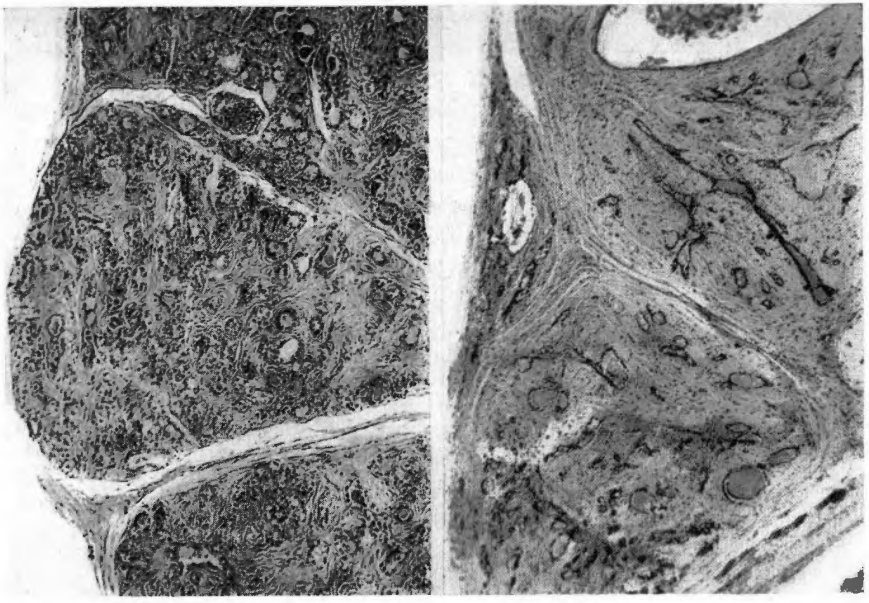
THE NUMBER OF CASES OF FIBRO-ADENOMA RELATED TO PERIODS OF INTENSE ESTROGENIC STIMULATION

Total number of cases in which both age and duration of symptoms were stated	*474*
Tumor diagnosed during adolescence	68
Onset of symptoms during adolescence (patients 18 to 30 but symptoms over 5 years)	77
Tumor diagnosed during pregnancy or lactation	23
Onset of symptoms related to pregnancy	49
At or near the menopause	54
Total number of cases with onset related to period of intense estrogenic stimulation	271 (57%)

In addition to this relation of the onset of the tumor to periods of estrogen stimulation, the rapid growth of a pre-existing fibro-adenoma during pregnancy indicates a special responsiveness to estrogen. Such rapid growth during pregnancy has been reported frequently (McFarland, Kilgore, Geschickter and Lewis, and Moran). The increase in the number of ducts, in their lining cells and in the amount of periductal fibrous tissue found in growing fibro-adenomas duplicates the histologic pattern of rapid mammary growth in normal adolescence and in early pregnancy. This pattern is repeated when the mammary gland of the rat or monkey or human is stimulated with high doses of estrogen (Geschickter, Lewis and Hartman). Heiman and Krehbiel noted that estrogen in combination with gonadotropic hormone increased the number of successfully transplanted fibro-adenomas in rats and stimulated hyperplasia in these growths. Emge and Murphy, although they failed to find that transplanted fibro-adenomas in adult rats were stimulated by estrogen, observed the occurrence of unusual hyperplasia in a fibro-adenoma in a younger animal. Wolfe and Wright compared changes in the hypophysis and ovaries with advancing age in the Albany strain of rats with frequent fibro-adenomas, and in the Vanderbilt strain with infrequent mammary neoplasms. Loss of eosinophils in

the adenohypophysis with colloid degeneration, vacuolization of cells and failure of ovulation with increase in follicular atresia in the ovaries were evidence of advancing age, and all of these changes appeared prematurely in the Albany strain with frequent fibro-adenomas. Failure of ovulation and luteinization of the ovaries, with predominance of estrogenic influence, is the probable underlying cause of increased tumor susceptibility in these animals.

FIG. 262 FIG. 263



Fibro-adenoma in the Rat's Breast Resulting from Estrogenic Stimulation.
FIG. 262. Typical fibro-adenoma with proliferation of both epithelial and fibrous elements.
FIG. 263. Fibro-adenoma of the myxomatous type.

Fibro-adenomas have been produced in the mammary glands of rats by implanting pellets of crystalline estrone under the skin to provide a constant, intense estrogenic stimulation (Geschickter). A constant absorption of moderately excessive amounts of estrogen leads to the formation of these tumors. Thus, if daily injections of large amounts of estrone are given with fluctuations of the concentration large cysts but no fibro-adenomas are found. If, instead, a more constant level of the hormone is maintained by absorption from pellets or if daily doses at the upper physiologic limits are given over many months, fibro-adenomas occur. This corroborates the clinical observation that fibro-adenomas have a tendency to form

during adolescence, pregnancy and the menopause when a relatively constant estrogenic stimulation is maintained, rather than in cyclic women where there is a repeated rise and fall in the level of the hormone.

Fibro-adenomas are produced most rapidly in the rat by injecting derivatives of estradiol have a prolonged action and produce a constant and increasingly intense stimulation. Under such conditions small fibro-adenomas may be found within 3 months. If 5 gamma estrone (which does not have a prolonged action) are injected daily, a fairly constant level of stimulation at the upper limits of normal is supplied. In such experiments approximately 600 days are required for the appearance of the fibro-adenomas. Even then the fibro-adenomas fail to grow to large size unless the daily dose of estrone for 2 months is increased to 100 gamma after 600 days have elapsed. With the implantation of 3 successive estrone pellets weighing 2.5 mg., microscopic fibro-adenomas appear within 4 to 6 months. A large percentage of animals are affected and the tumors grow to large size within 8 to 13 months. (See Chap. 33.)

In rats, as in human beings, fibro-adenomas, once formed, are subject to a variety of changes including (1) pseudolactation, (2) cystic degeneration, (3) fibrosis and hyalinization, and (4) carcinomatous or sarcomatous change. These changes followed progressively long periods of intense estrogenic stimulation. (Figs. 262-265.)

Fibro-Adenoma in Pregnancy and Lactation

The rapid growth of fibro-adenoma during pregnancy and the variety of microscopic changes which this tumor may undergo in response to the hormonal influences of gestation and lactation may lead to difficulties in diagnosis, and as a result needlessly mutilating operations may be performed.

Thirty-three cases of fibro-adenoma have been studied; 13 were removed during pregnancy; 10 others excised during lactation; and another 10, at various intervals after the cessation of lactation. In the 13 cases excised during pregnancy, all but one gave a history of rapid enlargement. In the exceptional case removed in the fourth month of pregnancy, there was microscopic evidence of recent growth, although the patient had been unaware of any change in size.

Nine of the 13 tumors were removed before the end of the first half of pregnancy, the period during which the breast is undergoing its most rapid development. In the remaining cases, the tumor was removed in the fifth, sixth, seventh and eighth months. In spite of enlargement, the tumors retained their mobility and encapsulated

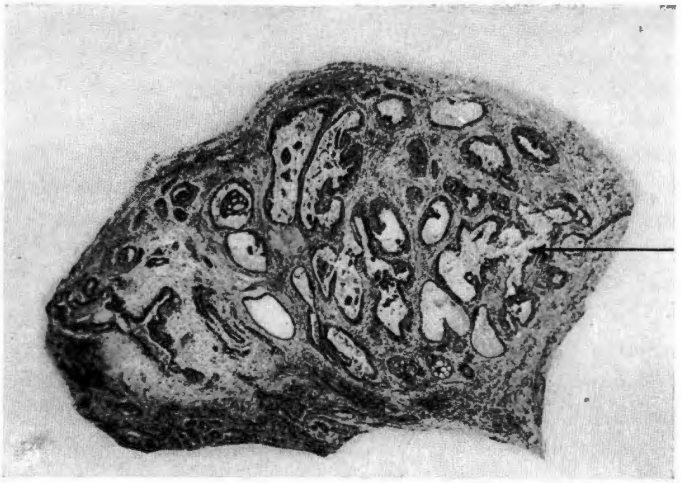


FIG. 264. Fibro-adenoma in the rat's breasts with involutional changes. The tumor has undergone cystic involution after prolonged estrogenic stimulation.

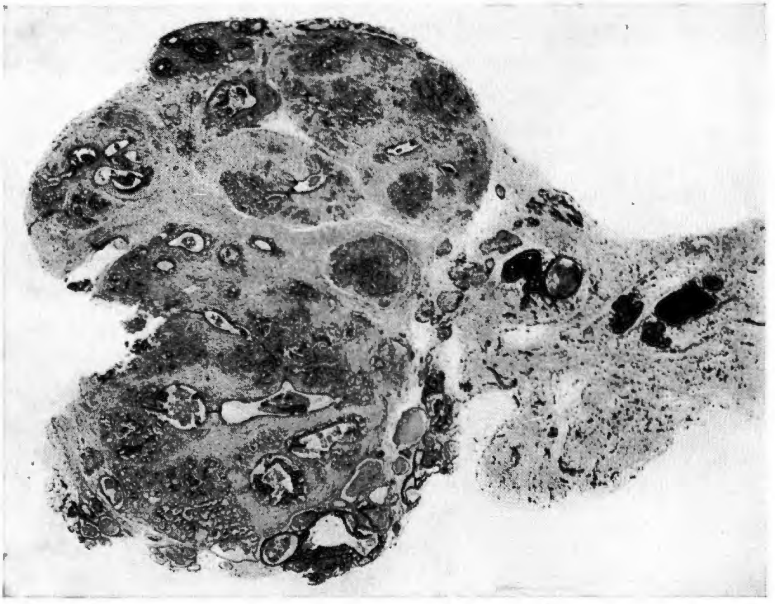
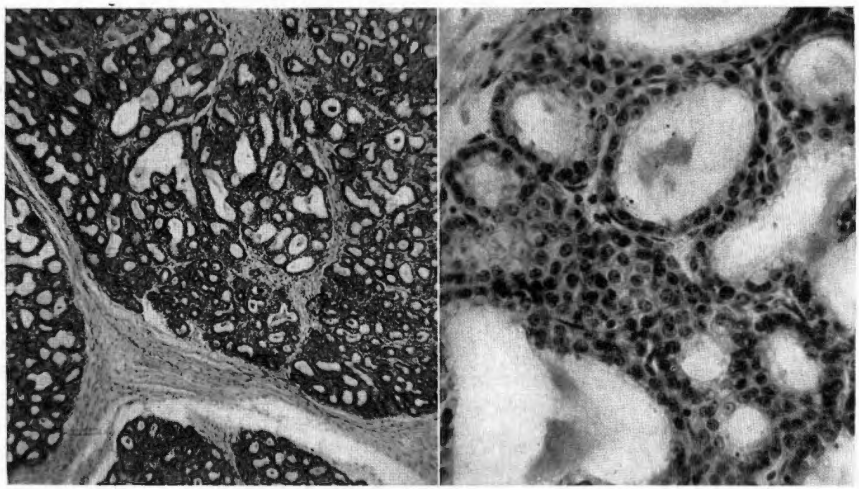


FIG. 265. This benign fibro-adenoma arose following implantation of estrone pellets Later the epithelium within the fibro-adenoma underwent cancerous change. There is also cancer in the mammary tissue outside the fibro-adenoma.

character. Neither the nipple nor the axillary lymph nodes showed changes. Nevertheless, malignancy was frequently suspected because of the rapid growth of the tumor and its firm, nodular character. In the gross, tumors excised during pregnancy may have a fleshy, reddish appearance. Microscopically, epithelial proliferation with many mitotic figures and penetration of the fat may be observed. (Figs. 266-269.)

In general, the microscopic changes occurring in fibro-adenoma during pregnancy correspond to those occurring in the surrounding

FIG. 266 FIG. 267



FIGS. 266-267. Pregnancy changes in fibro-adenoma. Low, and high-power photomicrographs showing the marked lobular development in a fibro-adenoma excised in the sixth month of pregnancy.

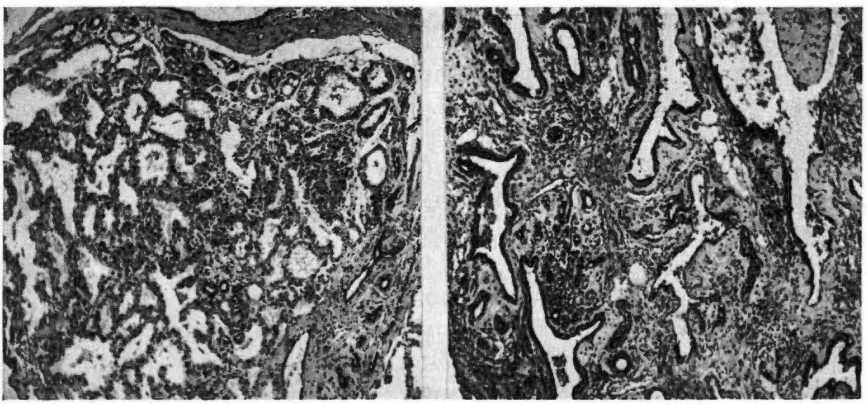
normal mammary tissue. The changes in the tumor, however, are more irregular and most pronounced at the margins. There is a tendency for the tumor at first to exceed and then to lag behind the physiologic development of the normal mammary tissue. Tumors of long standing with hyalinized connective tissue may remain refractory to pregnancy changes. Those which have responded to a previous pregnancy may remain unchanged during subsequent gestation. McFarland has reported a case in which the patient had three fibro-adenomas in the same breast removed during pregnancy. The largest tumor showed marked response, the medium-sized tumor some change, but practically no hypertrophy was seen in the smallest nodule.

The most rapid growth of fibrous and glandular tissue is seen in fibro-adenomas excised during the first third of pregnancy. In the

mid-third, the proliferating tubules tend to be grouped together to form lobules, but the growth of connective tissue may continue. In the last third of pregnancy, lobules with dilated acini predominate and the connective tissue is inconspicuous. There are, however, exceptional cases in which the growth of connective tissue continues into lactation.

During lactation, physiologic changes resembling those in the surrounding breast are seen in the periphery of the tumor. Secretion and dilatation of the acini are prominent so that the fibro-adenoma

FIG. 268 FIG. 269



Lactation Changes in Fibro-adenoma.
FIG. 268. Lobular changes during lactation.
FIG. 269. Stromal changes during lactation.

may undergo cystic changes. In general, the lactating lobules are coarser in structure than in the normal tissue and the lactation effects are more prominent in early than in late lactation. The stroma of the tumor is usually hyalinized. In two of the 10 fibro-adenomas removed in the third and ninth month of lactation, respectively, the cellular growth of the connective tissue (Fig. 155) resembled sarcoma, and mastectomy was performed. Both of these patients have remained well, eight and 25 years later. In one unusual case, cancer developed in the fibro-adenoma during mid-pregnancy. Excision only was performed and postoperative radiation given. The tumor recurred during a subsequent pregnancy and the patient died three years later with mestastasis to the liver.

TREATMENT AND PROGNOSIS

There are three reasons for the prompt excision of benign fibro-adenomas at the time of their clinical recognition:

1. To establish diagnosis.
2. To avoid mutilating operations for large tumors that result from rapid growth during pregnancy or at the menopause.
3. To prevent malignant change in the form of sarcoma or carcinoma at such periods of rapid growth.

Surgery

Because of the discrete and nodular character of the tumor, excision and microscopic study to rule out the presence of cancer is indicated in nearly all cases. Cancer is extremely rare earlier than the age of 25 years, at the time when many of the benign growths occur, but malignancy has been reported in the breast at all ages after the onset of puberty and in several cases in childhood (see Chap. 17). Moreover, the growth potentialities of benign fibro-adenoma cannot be satisfactorily predicted. In young women contemplating marriage and a family, small circumscribed fibro-adenomas which have remained stationary in size over a period of years should be removed. Pregnancy may result in rapid growth of the tumor and, rarely, in malignant change, as in the case cited above. Toward the menopause, giant myxoma or fibrosarcoma may develop in fibro-adenoma, and during this age period no definite nodule in the breast can be safely judged nonmalignant without microscopic study.

The tumor should be excised with a margin of normal tissue. In young patients, when the growth is not located in the upper or inner periphery of the gland, it is often possible to approach the tumor from the under surface of the breast through a lateral or inferior curved incision, to avoid a visible scar. In the strict sense of the word, fibro-adenomas do not recur after excision, but a second or third tumor may appear following removal of the earlier ones.

Excision, as recommended above, was practiced in all but 38 cases in the present series. Seven small fibro-adenomas of stationary size were not excised, seven were enucleated and 24 cases had simple or radical mastectomies. Amputations of the breast were performed for growths of extreme size, for multiple tumors, and for recurrence. Mastectomies were seldom performed because of an incorrect diagnosis of malignancy, if cases of giant myxoma are excluded.

Prognosis

There were 284 cases of fibro-adenoma followed beyond the three-year period; 201 of these for more than five years. Nearly 10 per cent of the cases followed (27) were seen for a second fibro-adenoma in the same or opposite breast. Recurrence was three times more common in the same breast than in the opposite or in both breasts. In one of

these cases the recurrent tumor occurred in the scar of a mastectomy. There is no adequate way to guard against the appearance of additional fibro-adenomas in those rare instances where several tumors make their appearance successively after excision. The author has tried various forms of endocrine therapy (testosterone, progesterone and pituitary lactogenic substance) in such cases without benefit. In young patients in whom one or more fibro-adenomas have ap-

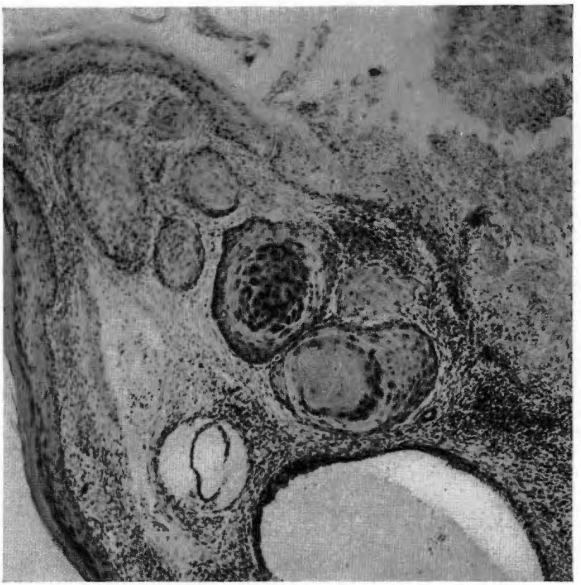


FIG. 270. Squamous cell metaplasia in a fibro-adenoma. The photomicrograph shows islands of keratinizing squamous cells which occasionally may undergo malignant change.

peared after the excision of a similar tumor, it may be wise to postpone excision for a matter of several months provided growth is not rapid. It may then be possible to remove all of the recurrent tumors at a single operation.

The relation of mammary cancer and mammary sarcoma to benign fibro-adenoma has been the subject of divergent opinions. Warren has recently calculated that women who have had a fibro-adenoma excised from the breast are twice as susceptible to mammary cancer as those in the normal population of corresponding ages. Semb expressed a similar opinion. Oliver and Major followed 198 cases for one to 25 years and found mammary cancer in a single case. These authors also studied 37 cases of giant or cellular myxomas and found one patient who died with pleural metastasis from a complicating

fibrosarcoma and two additional patients who were dead of malignancy which may or may not have been related to a similar mammary growth.

In the follow-up of 201 cases in the present series (over a period which averaged just under 10 years) there were two patients who developed mammary cancer (1 per cent). This is twice the expected rate (see Chap. 12), and corresponds to the findings of Warren. The incidence of sarcomatous change which occurs within the tumor itself, and epidermoid carcinomas which may arise within fibro-

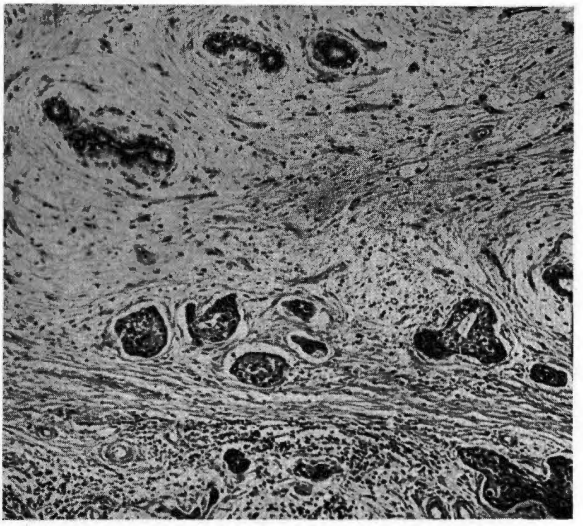


FIG. 271. Cancer occurring in fibro-adenoma.

adenomas undergoing epithelial metaplasia of the squamous cell type (Fig. 270), cannot be calculated from the follow-ups, since, in over 95 per cent of the cases, the entire tumor as well as any recurrent growth, was successfully removed. Unlike mammary dysplasia, fibro-adenoma is not a diffuse process. Our studies, however, show that there is a definite relation between fibro-adenomas occurring toward the menopause (particularly giant myxomas) and mammary fibro-sarcoma (Chap. 16). If mammary carcinoma and mammary fibro-sarcoma occurring within pre-existing fibro-adenomas are added to the patients developing cancer of the breast subsequent to the removal of the growth, the incidence of malignancy in these cases is approximately 3 per cent.

The occurrence of carcinoma and sarcoma within pre-existing fibro-adenoma has been experimentally demonstrated. Heiman and Krehbiel report 14 per cent of sarcoma occurring in benign adeno-

fibroma repeatedly transplanted and grown in 1531 white rats over a period of 10 years. In spontaneous fibro-adenomas produced in the rat in response to estrogen stimulation, cancer developed within the fibro-adenoma in 45 per cent of the animals in which estrogen stimulation was maintained by pellets for more than a year (work done in author's colony). (Figs. 264, 265.)

GIANT MAMMARY MYXOMA

A variety of fibro-adenoma growing to immense size and usually found near the menopause was first described by Johannes Müller

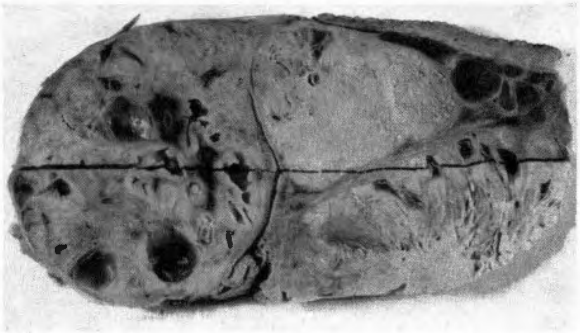


FIG. 272. Sarcoma occurring in a giant myxoma of the breast. The gross specimen showing the large and cystic character of the tumor.

more than a century ago as "cystosarcoma phyllodes." More recently (1931) Lee and Pack reviewed 105 of such cases collected from the literature adding six new cases of their own. Owens and Adams have recently brought the literature up-to-date. These authors recommend the term "giant intracanalicular myxoma of the breast" for these growths. The average age of the patients of the series of Lee and Pack was 44.6 years. Three of these cases occurred in males and 16 per cent in unmarried women.

Clinical Features

The duration of growth usually extends over six to seven years with rapid growth toward the end of this period. The size of the tumor, its long duration, and the absence of nipple involvement or of extensive skin infiltration are diagnostic features. The tumors are large and have numerous cystic spaces into which fibrous polypoid masses project. Under the microscope, myxomatous connective tissue predominates; polypoid fibrous structures are covered by layers of cylindrical or cuboidal epithelium.

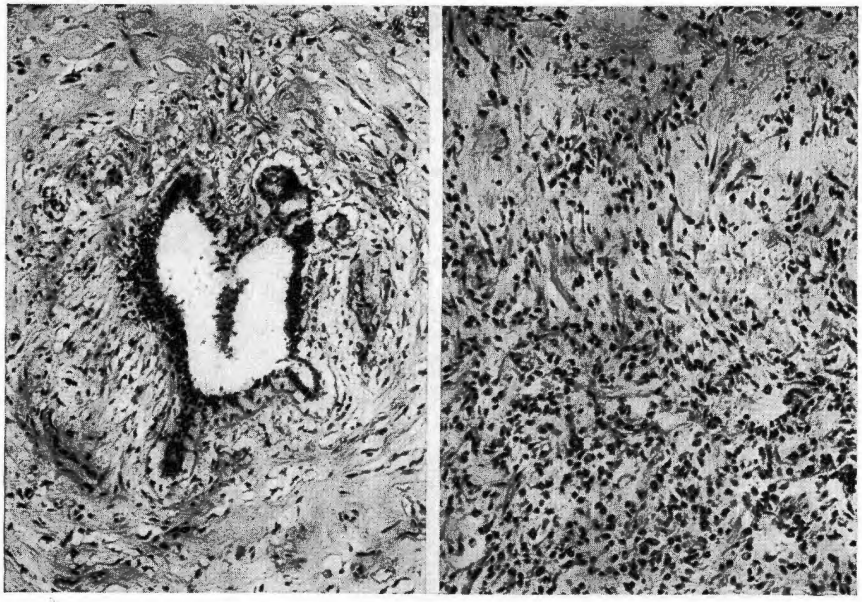


FIG. 273. Photomicrographs showing spindle-cell sarcoma (from the specimen shown in Fig. 272). This patient had recurrence in the scar and supraclavicular region following mastectomy.

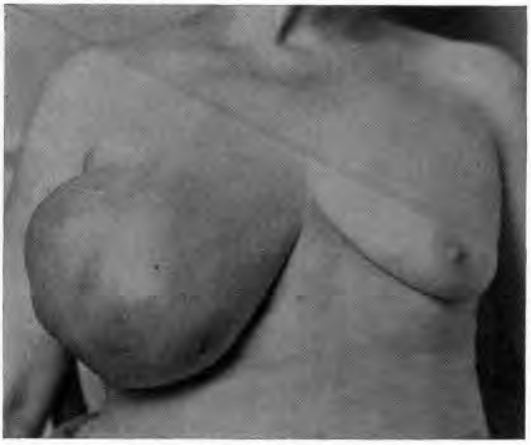


FIG. 274. Photograph of patient with giant mammary myxoma.

The characteristic features of this tumor have been summarized by Lee and Pack as follows:

1. Greatness in size, averaging 7.6 pounds. Frequently the tumor is as large as an adult head.
2. Lobulation and delimitation of the tumor with variable regions of fluctuation and resistance.
3. Encapsulation of the tumor and noninvasion of the breast.
4. Mobility and usual nonadherence to skin and fascia.
5. No retraction of the nipple and no involvement of axillary lymph nodes.
6. Possible occurrence in males (3 per cent).
7. Development from pre-existent fibro-adenomas, probably intracanalicular fibro-adenomas. The transition occurs at the time when a gelatinous metamorphosis of the stroma takes place.
8. Long initial period of quiescence or slow growth, followed by sudden rapid acceleration.
9. Long duration—averaging seven years in 111 cases.
10. Important role of lactation and nursing difficulties in the metamorphosis of simple fibro-adenoma to giant intracanalicular myxoma.
11. Intracystic polypoid excrescences moulded by apposition with each other.
12. Narrow, sinuous, distorted clefts between polyps. These epithelial-lined spaces contain variable quantities of clear yellow fluid.
13. Myxomatous stroma with cellular pseudosarcomatous regions.
14. Benignity; good prognosis with freedom from recurrence.
15. Successful treatment by wide local excision or simple mastectomy.

The classification of these growths is not always easy and while the tendency to regard many of them as sarcoma is unjustifiable, nevertheless sarcoma as well as carcinoma may occur in these larger growths. The differences of opinion in regard to the classification of these neoplasms is demonstrated in the 49 cases reported in this series. Oliver and Major, studying these tumors in 1934, found one carcinoma and one sarcoma and two tumors of questionable malignancy among 37 giant intracanalicular myxomas microscopically studied. In 17 of these tumors which they classed as histologically cellular but benign, one patient died within a few months of pleural metastases and another had metastases to the back. On the other hand, Fox, reporting the same series of cases in 1937, considered

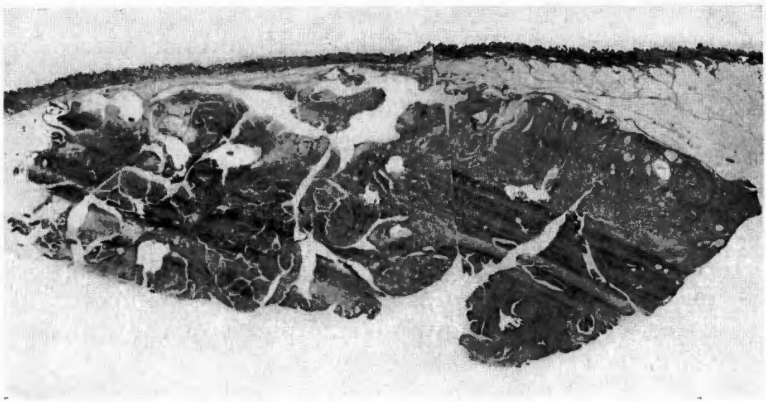


FIG. 275. Cross section of the tumor in a case of giant mammary myxoma.

FIG. 276. Gross specimen of a giant mammary myxoma showing the cystic character of the tumor.

24 of them to be sarcomas, and was able to report six patients who died with recurrence or metastasis. Cooper and Ackerman reported three cases, one of which had metastasis to the axillary lymph nodes.

In our series of 49 cases there are nine fibrosarcomas arising in giant myxomas. The age of the patients corresponds to that reported

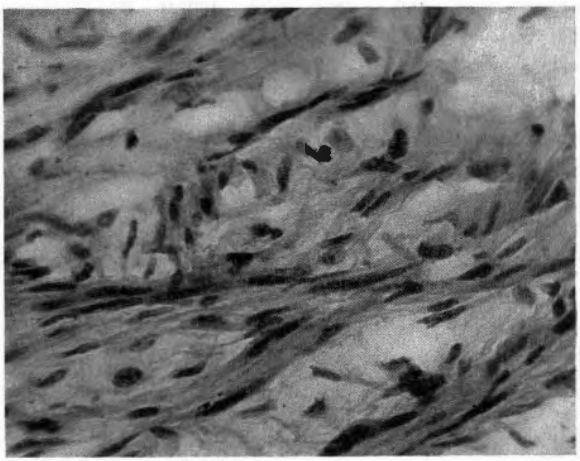


FIG. 277. Photomicrograph showing myxomatous tissue from the case shown in Figure 276.

by Lee and Pack. The majority were between 45 and 55 years of age. About one-sixth of the cases were between 25 and 40 and an equal number 60 years or over. The duration of symptoms ranged from one to 15 years. Most of the cases were treated by excision of the breast together with the pectoral muscle, but in the earlier cases radical mastectomy with axillary dissection was performed.

Treatment

Since intracanalicular myxomas of giant size do not, as a rule, metastasize to the regional lymph nodes, whether or not the stroma shows the histologic features of sarcoma, amputation of the breast including the pectoral fascia and without axillary dissection is the treatment of choice. (See Part VI: Treatment.) In 91 cases in which results were mentioned, in the cases followed by Lee and Pack, there were only six recurrences.

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14

Bleeding from the Nipple and Benign Intracystic Papilloma

INTRODUCTION

Lesions of the breast which show a papillary epithelial structure are fairly common. This group includes (a) papillary hyperplasia which occurs in adenosis, (b) papillary invaginations in the larger ducts which are too small to be palpated but which produce bleeding at the nipple, (c) benign intracystic papillomas of appreciable size, and (d) papillary forms of adenocarcinoma which are usually circumscribed and slowly growing cancers of large size. Many of the fibroadenomas of the breasts (intracanalicular myxomas) are papillary in structure, but their clinical and pathologic features do not warrant their inclusion in this group.

The table on page 326 gives the classification and incidence of these papillary lesions.

A sanguineous discharge from the nipple may occur in any of the papillary lesions. The benign lesions outnumber the malignant in the ratio of two to one.

The problems of diagnosis and treatment present difficulties in

TABLE XXXIX

680 PAPILLARY LESIONS OF THE BREAST

CLASS OF LESION	NUMBER	AGE PERIOD	ZONE OF BREAST INVOLVED	PERCENTAGE WITH BLEEDING NIPPLE
A—Papillary hyperplasia in adenosis	212	30–45	Periphery	4%
B—Bleeding nipple without palpable tumor	68	40–60	Central	100%
C—Benign intracystic papilloma	203	35–55	Central	48%
D—Papillary cancer	197	45–70	Central	10%

this group of lesions. The symptoms of bleeding of the nipple, while found more commonly in the benign growths may be associated with cancer. Simple excision for pathologic examination may prove inadequate since the papillary growths may be multiple or bilateral. Papillary hyperplasia is usually widely distributed in both breasts in cases of adenosis. In cases of bleeding nipple without a palpable tumor in the underlying breast, the site for the exploratory excision is chosen with great difficulty at times. Cancer of the breast may supervene in any of the benign papillary growths: it occurs in 3 per cent of the cases of adenosis, approximately 9 per cent of the cases of bleeding nipple without palpable tumor, and in 6 per cent of cases of benign intracystic papilloma.

Simple mastectomy (either unilateral or bilateral) is practiced by many surgeons for benign lesions of the papillary type, because of the difficulties enumerated above. This is often a needlessly mutilating and radical procedure, however, if the benign nature of the lesion can be definitely established. Refinements in methods of diagnosis and conservative methods of treatment are particularly desirable when women in the childbearing period and younger age-groups are affected.

In a previous chapter, diagnosis and treatment in cases of papillary hyperplasia in adenosis with or without bleeding nipple have been discussed (see Chap. 9). In the present chapter, bleeding from the nipple and benign intracystic papilloma are discussed. Papillary carcinoma is dealt with in Chap. 22.

BLEEDING FROM THE NIPPLE

A discharge of blood from the nipple is usually alarming to both the patient and the physician. There are two schools of thought in

regard to its significance. One stresses the frequency with which cancer of the breast may be associated with such a discharge and hence its diagnostic importance. The other school stresses the frequency with which benign conditions, such as intraductal papilloma, produce bleeding and emphasizes that the findings in the underlying breast rather than the discharge deserve emphasis.

Pathologic Significance

A discharge of blood from the nipple may occur with carcinoma of the breast but is more commonly associated with benign intra-

TABLE XL

FREQUENCY OF BLOODY DISCHARGE FROM THE NIPPLE IN VARIOUS MAMMARY LESIONS

	CASES	SANGUINEOUS DISCHARGE
MALIGNANT LESIONS[1]		
Scirrhous or infiltrating cancer	1482	28
Recurrent and fulminant cancers	350	8
Papillary cancer	197	19
Comedo cancer	106	27
Duct cancer	35	7
Gelatinous cancer	83	8
Medullary cancer	135	3
Total mammary cancer	2393	100
Mammary sarcoma	72	2
Total	2460	102
BENIGN LESIONS		
Mammary complaints without palpable tumor including 375 cases of mastodynia	1102	68
Dilated ducts (inspissated secretion)	72	5[2]
Fibro-adenoma	600	2
Cystic disease	589	0
Adenosis	212	9
Papillomas	203	96
Mastitis	139	5
Acute	(60)	(2)
Chronic	(64)	(1)
Plasma-cell	(15)	(2)
Total	2917	185

[1] Excluded from above are 62 cases of Paget's cancer with discharge in 24.

[2] Dilated ducts beneath the nipple occurring toward the menopause are associated with secretion from nipple in about one-third of the cases. Because of stagnation, the secretions are frequently discolored greenish brown but may be described as bloody (as has been done in the 5 cases listed) although blood is not present.

cystic papilloma. Diagnosis and treatment therefore depend not upon the presence of the discharge but upon what can be learned by careful palpation of the breast, transillumination, a detailed history, and microscopic examination of the discharge.

In cases in which bleeding from the nipple is not associated with a lesion which can be palpated or demonstrated by transillumination, experience teaches that the discharge is caused by minute papillary invaginations in one or several of the mammary ducts. This represents either a transient hyperplasia or a minute papilloma. Here treatment offers a difficult problem since the lesion cannot always be localized by clinical methods.

There were 68 such cases in the present series. Approximately one-half of these patients were between the ages of 40 and 50 years (Fig. 280); parous women were more frequently affected than nonparous women and the discharge was bilateral in 10 per cent of the cases. Usually the symptoms had been present for less than six months at the time of examination although in 12 cases they had existed a year or more. The discharge varies from time to time being serous or amber in color, truly bloody, or a dark brown. The breasts affected are often of the senile fatty type, and the symptom may have its onset at the menopause.

The method of treatment in cases of bleeding nipple must be influenced by the number of cases of cancer of the breast in which such a discharge occurs and upon the incidence of malignancy which ultimately follows such a symptom.

As a Sign of Mammary Lesions

In Malignancy. The incidence of bleeding from the nipple in mammary cancer has been variously assessed. In a review of 617 cancers of the breast treated in the University Clinic at Königsberg, Prass found only a single case with the symptom of bloody discharge. Wolpers found bleeding from the nipple in five of 414 cases of carcinoma of the breast (about 1 per cent). He stated that bleeding is more probable in adenocarcinomas which are highly differentiated or in cases of medullary cancer with a tendency toward necrosis. Adair studied 108 cases with sanguineous discharge from the nipple and found 57 associated with benign and 51 with malignant neoplasms. His findings are similar to those previously reported by Miller and Lewis and by Judd. Adair, however, does not state the total number of carcinomas or benign lesions which he reviewed in order to select his cases with discharge. Since the report is from a cancer hospital it is probable the cases selected were from a series in which cancers predominated. The significance of a sanguineous dis-

charge in the diagnosis of papillary tumors has been emphasized by Gray and Wood who found a discharge in 81 per cent of 227 cases. However, the ratio of benign to malignant tumors in the cases reported by these authors cannot be compared to the other series mentioned, because of the number of intracystic papillomas classified as Grade-I cancer.

The present study is based upon 5377 benign and malignant lesions of the breast. In 2393 cases of mammary cancer, a bloody discharge from the nipple occurred in 100, or 4 per cent. In 72 cases of mammary sarcoma, two showed a similar discharge.

The incidence of bleeding from the nipple was low in infiltrating scirrhous cancer. Among 1482 cases there were only 28 with such a discharge (1.9 per cent). In the more highly differentiated, circumscribed forms including papillary adenocarcinoma and gelatinous and comedo cancers, there were 54 cases of discharge among 386 (14 per cent). Among 35 duct cancers, 7 had this symptom. Paget's cancer of the nipple was excluded because of the association of discharge or weeping with ulceration of the nipple. Among 62 cases of Paget's cancer there were 24 cases of discharge (38 per cent). In the two cases of sarcoma with bleeding nipples, the discharge was a late symptom.

In Benign Lesions. On the other hand, in 2917 benign lesions, 185 cases (6.3 per cent) had a sanguineous or serosanguineous discharge. The incidence of bloody discharge was highest in benign intracystic papilloma. There were 203 cases of palpable intracystic papillomas verified by operation of which 96 were associated with a bleeding nipple (48 per cent). In 212 cases of Schimmelbusch's disease or adenosis characterized microscopically by papillary cystadenoma, there were 9 cases of sanguineous discharge (4 per cent). The 68 cases of sanguineous discharge without a palpable tumor occurred among 1102 women with mammary complaints (excluding infectious mastitis) such as pain, hypertrophy, keratosis of the nipple, etc.

In Mastitis. A discharge of blood from the nipple is rare in both acute and chronic mastitis. In acute puerperal mastitis the milk may be blood-tinged when the mastitis is preceded by cracked and bleeding nipples. This occurred in two of 60 cases. In chronic mastitis, discharge from the nipple is rare. In 64 such cases one had a watery discharge of two-days' duration and one a history of bloody discharge which had been noted intermittently for a period of 20 years. In plasma-cell mastitis there is frequently a history of secretion, but this is rarely bloody and is usually of the kind observed with dilated ducts (p. 146).

Dilated ducts beneath the nipple occurring toward the menopause

are associated with a secretion from the nipple in about one-third of the cases. Because of stagnation and infection with *B. pyocyaneus* the secretion is discolored, usually a greenish brown, but it may be described as bloody although blood is not present. In five of 72 cases the discharge was described as bloody, but there was no way to verify this from the history. This emphasizes the importance of microscopic examination of the discharge.

This study indicates that a sanguineous discharge from the nipple is more frequent in benign than malignant lesions and is rarely a symptom of onset in infiltrating or scirrhous mammary cancer. It is, however, of some diagnostic importance in adenosis, in benign intracystic papillomas, and in circumscribed forms of adenocarcinoma where it may be the first symptom to attract the attention of the patient. Moreover, in the benign conditions of adenosis and intracystic papilloma, malignancy may subsequently develop; hence, proper investigation of the symptom is of the utmost importance.

Bleeding from the nipple occurred in 4 per cent of the mammary cancers studied, but this symptom preceded the discovery of a mass by the patient in only 22 of the 100 cases with such a discharge. Moreover, these patients (with six exceptions) did not consult a physician until tumor formation as well as discharge was present. In 94 of 100 cases, therefore, diagnosis and treatment were governed not by the character of the discharge but by the nature of the lump in the breast.

Prognosis

Fifty-seven of the 68 cases of bleeding nipple (without a palpable tumor) were followed for three or more years (17 beyond the 10-year period) and of these, seven died of unrelated causes, eight had intermittent discharge when last heard from, five developed mammary cancer, and the remainder were well. Of the five patients with a sanguineous discharge from the nipple who were ultimately operated upon for mammary cancer, none had a palpable tumor of the breast, and it was Dr. Bloodgood's rule not to operate on such a case when a mass could not be felt.

The incidence of mammary cancer is therefore about 9 per cent in patients having a sanguineous discharge from the nipple but without a palpable mass. In four of the five patients who developed mammary cancer there were findings in addition to the sanguineous discharge. Two of the patients had a definite shadow in the breast on transillumination although no tumor could be felt; and in two the scar of an old lactation mastitis was present, and the surrounding breast tissue was indefinitely lumpy. In these cases, there was a

two-fold error in clinical judgment, if we overlook for the time being the failure to ascertain the cause of the discharge. An area which transilluminates darkly and palpates like the surrounding breast tissue may be a papillary tumor (either benign or malignant) or a comedo cancer and it is imperative to explore the lesion for diagnosis. On the other hand, a palpable zone of residual lactation mastitis which is even dubiously concerned in the production of symptoms should be explored because of the established tendency of cancer to develop in such a lesion. (See Chap. 20.) The histories of the five cases under discussion are:

Case 1. A woman, 56 years old, with four children, had noted intermittent retraction of the nipple since the birth of her last child, 14 years ago. At the time of her examination in 1933, she complained of a sanguineous discharge from the left nipple which she had noted for the past ten months. Examination disclosed a slight crust on the left nipple and a sanguineous discharge. Above the nipple there was an indefinite cystic mass about 1 cm. in diameter. Pressure here produced an amber secretion from the nipple. Transillumination revealed a dark area about 5 cm. in diameter. The examining physicians disagreed on the presence of a tumor; operation was postponed and the patient advised to return a year later. On re-examination in 1934, the findings were the same, and operation was again postponed.

In 1937, the patient returned because the left nipple had been discharging continuously for the past six months. At this examination a firm mass was felt in the area which transilluminated darkly. The lesion was explored and found to be comedo carcinoma. Radical amputation was performed June 15, 1937. The patient was reported well in October, 1939.

Case 2. A woman, 50 years old, was seen in 1932 for an amber discharge from the nipple of three weeks' duration. No lump could be felt and no shadow brought out on transillumination. The patient reported yearly for re-examination and, in 1934, a soft mass 1 cm. in diameter which transilluminated darkly was found just beneath the nipple. At operation in October, 1934, the excised mass was diagnosed papillary carcinoma. A radical mastectomy was performed. The patient was reported well in 1939.

Case 3. A woman, 42 years old, with three children had an abscess lanced when she nursed her last child eight years ago. Two years ago a swelling appeared at the site of the old abscess and subsided. Five months ago there was bleeding from the nipple on this side. Seven roentgen-ray treatments were given elsewhere without benefit. When examined in 1928 both breasts were indefinitely lumpy and blood could be expressed from both nipples. Operation was postponed. In 1932, the patient was found to have a mass 4 cm. in diameter which was adherent to the scar at the site of the former abscess. Pressure on this mass produced a bloody discharge from the nipple. The mass was explored in December, 1932, elsewhere, and a papillary tumor was excised. This was interpreted as benign by the surgeon but malignant by the pathologist. In May, 1934, the patient returned with an enlarged node in the left axilla. A radical operation was performed in December, 1935, following preoperative radiation. The

axillary lymph node showed metastasis. The patient was reported well in July, 1938.

Case 4. A woman, 40 years old, had mastitis with her last child, 10 years ago. She was examined in 1927 for a bloody discharge from the right nipple which had been present for three weeks. Indefinite nodular tissue was found on either side of the scar of an old abscess and bloody fluid was expressed by pressure on this site. Operation was not advised. In 1930, the patient returned with a mass adherent to the scar and radical mastectomy was performed in July, 1930. The patient died with metastasis in 1934.

Case 5. A single woman, 72 years old, was seen in May, 1933, for a sanguineous discharge from the left nipple which was associated with a dark shadow on transillumination about 4 cm. in diameter just above the areola. No definite mass could be felt in this region. Operation was not advised. The patient returned a year later and a definite tumor could be felt in this region. The lesion was explored in July, 1934; the frozen sections interpreted as comedo adenocarcinoma, and a simple mastectomy was performed.

Bleeding from the nipple is a more common symptom in circumscribed and low-grade mammary cancer than in scirrhous cancer and more commonly precedes the discovery of the lump in such low-grade malignant neoplasms. In the 18 cases with sanguineous discharge among 189 patients with papillary cancer, the discharge was a primary symptom in four cases and preceded the lump by periods ranging from three to 24 months. In 27 cases of sanguineous discharge among 105 cases of comedo carcinoma, the discharge preceded the discovery of the lump in eight. In eight of 85 cases of gelatinous carcinoma with a similar finding, the discharge was the initial symptom only once.

That a discharge of blood from the nipple may precede the discovery of cancer by 10 or more years is illustrated by the following two cases:

Case 1. The patient was a woman who had a sanguineous discharge from the left nipple for eleven years. She had one child 25 years ago which died at birth. Six years ago she noted that the left nipple had become retracted. In the past two years a lump appeared in the left breast and had gradually enlarged. When examined in 1916 a firm mass 6 cm. in diameter was found in the left breast. The left nipple was retracted. A few drops of yellowish discharge could be expressed. A radical mastectomy was done for cancer in July, 1916. The patient died with metastasis in October, 1917.

Case 2. A married woman, 45 years old, had had difficulty with the left breast since the birth of her last child 20 years ago. She had a lactation mastitis, could not nurse the child on this breast and has had a blood-stained discharge from the left nipple off and on for the past 20 years. Eight months ago an indurated mass appeared at the site of the former abscess (the breast at this site she says has never felt normal). Her doctors in 1934 differed as to the significance of the mass. It was

treated with hot compresses for a period of several months at the end of which time a discharging sinus developed. The induration, however, did not subside. In 1936, three years after the re-appearance of the mass and a year after the formation of the sinus, a biopsy was made. Again expert opinion differed as to whether mastitis or cancer was present. However, a radical mastectomy was performed. The patient soon after developed metastasis to the lumbar spine and died in August, 1937.

Diagnosis

Although a number of patients with adenosis complicated by bleeding from the nipple have remained well for five or more years without operation, and although the majority of the patients with microscopic papillary invaginations in the larger ducts and a bleeding nipple have remained well without surgery, a review of the data emphasizes the importance of exploring the breast when a sanguineous discharge is present. The duct in which the discharge arises usually can be located by palpation and transillumination. Otherwise, pressure with the finger should be made successively along the various radii proceeding from the nipple to determine where pressure produces a discharge. In difficult cases the injection of radio-opaque solution into the larger ducts and roentgenographic studies may be indicated. Hicken, Best and Tollman have reported success with this method for the localization of the lesion.

A smear of the discharge expressed from the nipple should be studied microscopically in every case. This is essential to distinguish between the brownish inspissated secretion that occurs in dilated ducts beneath the nipple and true blood. When the likely source of bleeding in the breast is determined, an incision over this region extending radially from the nipple should be made and the underlying ducts thoroughly explored and the affected zone excised. The excised tissue should be subjected to proper pathologic examination. In the past it appears that proper emphasis has not been placed upon the possibility that malignancy and bloody discharge may be associated with an old residual lactation mastitis. No case with the history of chronic lactation mastitis followed by sanguineous discharge from the nipple should be treated without surgical excision and pathologic examination of the affected tissue. The same rule applies also to patients with such a discharge and a zone of breast which fails to transmit light on transillumination.

Treatment

Surgery. Amputation of the breast without dissection of the axilla is a needlessly radical and mutilating operation in cases of bleeding nipple. When a palpable tumor is present, the tumor should be ex-

plored and subsequent treatment based upon the character of the tumor as determined by gross and microscopic examination. When an indurated zone of residual lactation mastitis is palpated, a similar procedure should be followed. When no palpable mass is found, a radial exploratory incision over the most suspicious region indicated by transillumination, compression or roentgenographic examination is indicated. In the author's opinion, such an operation is preferable to excision of the nipple and the underlying ducts.

Excision of the nipple has the following disadvantages: The removal of the nipple is usually considered mutilating by the patient. If papillary excrescences exist in the smaller ducts and are left behind, they may give rise to definite papillomas or papillary cancer, yet the patient remains unaware of the difficulty because the ducts are incapable of discharging. Finally, the operation appears needlessly radical from the patient's viewpoint if a discharge subsequently develops from the opposite breast.

Estrogen Therapy. In 1934, Mazer recommended estrogen therapy for bleeding of the nipple in women at or near the menopause. The author has treated four patients by this method, the earliest in 1934, the most recent one in 1939. The earlier patients received 30,000 to 50,000 international units of estrone; the most recent had 20 mg. estrone in a pellet implanted in the back. All of these patients are well and free from discharge at the present writing. However, the value of this mode of therapy is questionable since good results were obtained without treatment of any sort in 53 of 68 cases of bleeding from the nipple without a palpable tumor. Such endocrine methods of therapy are not sound in the author's opinion since, of 57 patients seen in Dr. Bloodgood's clinic between the period of 1912 and 1935 and in whom no operation was advised, five were ultimately operated upon for cancer of the breast. These mistakes in treatment could have been avoided had exploration been instituted, and the most suspicious zone excised and examined microscopically.

BENIGN INTRACYSTIC PAPILLOMA

The condition described as benign intracystic papilloma refers to a tumor, usually 1 to several cm. in diameter, which occurs in adult women in the central zone of the breast and which is frequently associated with a sanguineous discharge from the nipple (Figs. 278, 279). Local excision usually suffices to cure. A variety of names has been used for this lesion including adenoma, duct papilloma and proliferating cystadenoma. In the older literature this tumor was re-

terred to as a low-grade papillary or duct cancer which metastasized rarely or relatively late. These growths are still regarded as Grade-I cancer by some pathologists, simple or radical mastectomy is recommended (Gray and Wood). Among the first hundred cases in the present series recorded prior to 1925, 73 were treated by simple or radical mastectomy. There were only 20 such operations among the cases recorded between 1925 and 1944.

There are a number of reasons for the radical treatment previously practiced in cases of benign intracystic papilloma. A discharge of

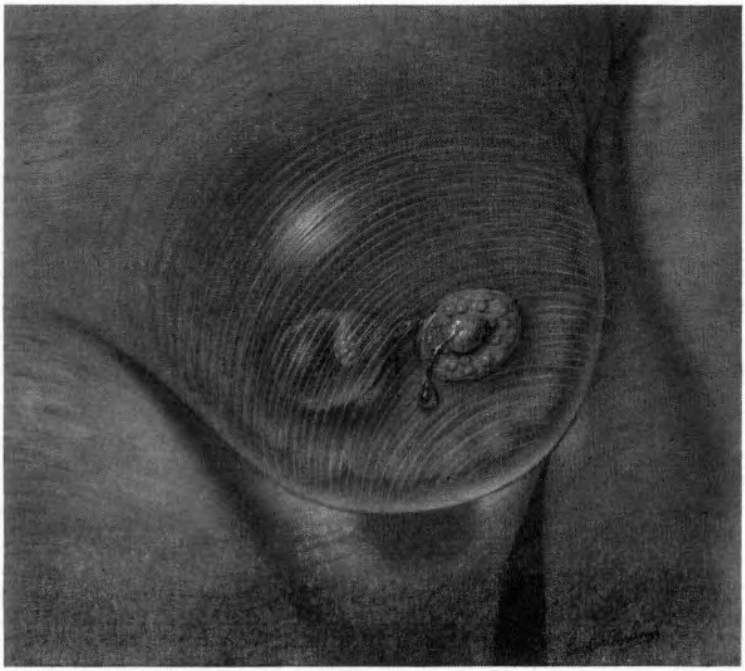


FIG. 278. Drawing to show the characteristics on palpation of benign intracystic papilloma. The tumor is circumscribed, soft and freely movable. Hemorrhagic fluid is often expressed from the nipple during palpation.

blood from the nipple may occur in both benign and malignant papillary tumors of the breast and this finding alone is considered by some to be sufficiently ominous to warrant radical surgery. The presence of bloody contents in these cystic tumors at exploration is another reason for such treatment. The malignant change which occurs in some of these growths and the multiplicity of the lesion in one-fifth of the cases are additional reasons. Finally, difficulty may be experienced in differentiating the benign from the malignant

tumors on microscopic study. A thorough knowledge of the clinical and pathologic features of benign intracystic papilloma is essential to avoid needlessly radical operations or unnecessary radiation.

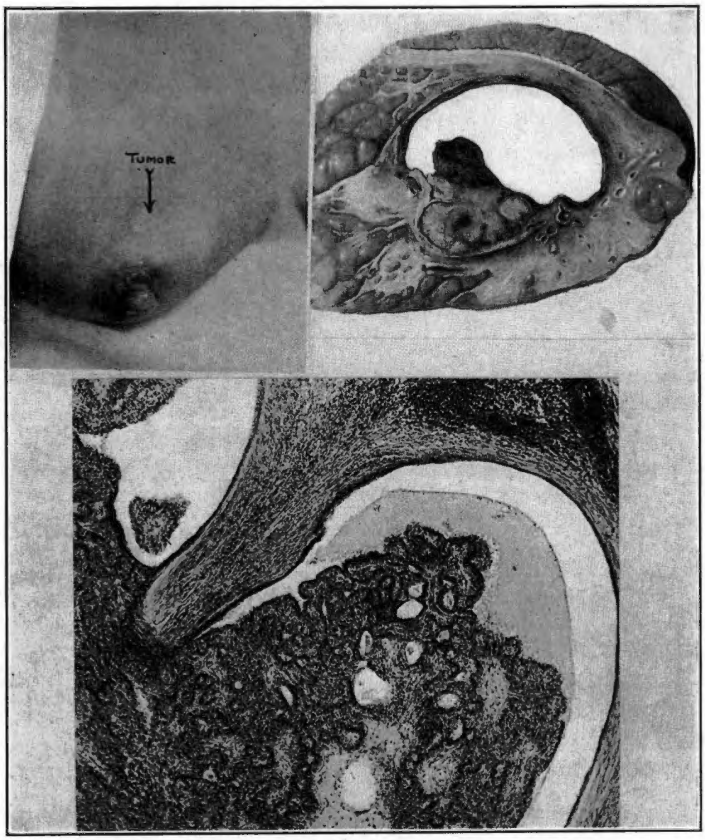


FIG. 279. Benign intracystic papilloma. The patient, gross specimen and the photomicrograph showing the stalk of the papilloma. The tumor is near the nipple and is completely encapsulated.

Clinical Features

The peak of age incidence in benign intracystic papillomas was between 40 and 45 years. (Fig. 280.) The youngest patient was 15 and the eldest 74 years old. These tumors occur with equal frequency in nulliparous and in parous women and may occur either before or after the menopause. The leading symptoms are a sanguineous or serosanguineous discharge from the nipple, the discovery of a lump, usually in the central region of the breast, and pain which is rarely severe and occurs in slightly less than one-half of the cases

(Fig. 281). Variation in the size of the tumor following profuse discharge from the nipple was sometimes noted. Change in the position of the nipple occurred in 10 cases. The nipple was either slightly retracted or protruded abnormally. Fixation occurred in two instances complicated by infection. The nipple may be enlarged when the growth is situated near the exit of the main ducts, and in such cases ulceration of the nipple may occur.

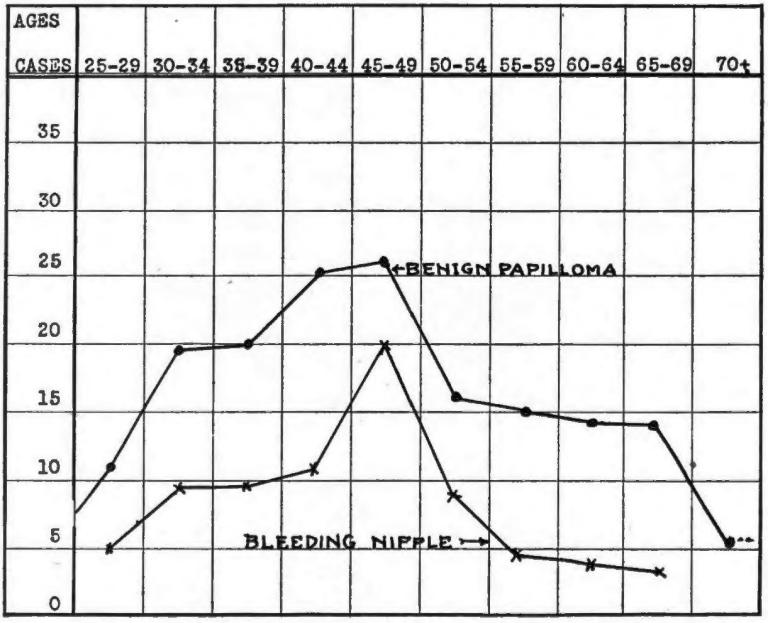


FIG. 280. Chart showing the age incidence of benign intracystic papillomas.

Duration of Symptoms. In approximately one-half of the cases of intracystic papilloma, the duration of symptoms is between six months and five years; about one-fourth of the cases, however, noted trouble for less than six months and an equal number for more than five years. In cases with a prolonged history, the presence of a mass or discharge from the nipple antedates the appearance of pain, which was rarely present for more than two years. One patient, aged 67 years, with a papilloma 3 cm. in diameter toward the inner side of the left nipple, stated that the lump appeared about the time of her menopause, 17 years previously. A discharge from the nipple had been noted for the past seven months, and pain in the region of the tumor for only one month. In another patient, 54 years old, a sanguineous discharge had appeared from the left nipple 10 years previously and had been present only occasionally in the past two years.

At the end of that time, slight induration and retraction of the nipple accompanied by a small mass were noted. In a third case, a lump had been noted for 10 years, bloody discharge and retraction of the nipple for five years, and pain for the past year. In all there were nine cases with a duration of symptoms of 10 or more years. None of these cases showed malignant change when studied microscopically.

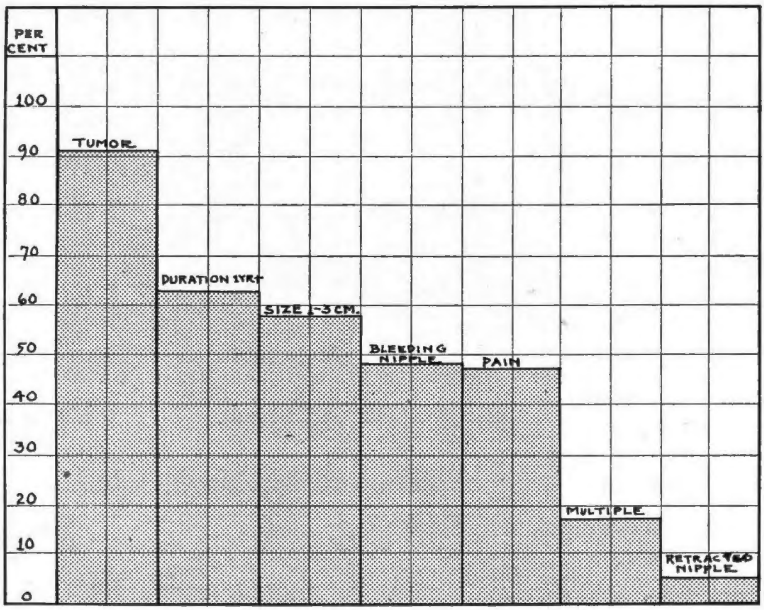


FIG. 281. Chart showing the relative frequency of the leading symptoms and findings in benign papillomas.

Size. Benign intracystic papillomas are rarely of large size. The average diameter in the present series was 2.2 cm.; two-thirds of the cases had a diameter of 0.5 to 3 cm. In 5 per cent of the cases, however, the tumor was between 5 and 10 cm. in size. These larger tumors were nearly all cystic in character, associated with sanguineous discharge, and the patients had noted fluctuation in size from time to time or a recent sudden increase. The large growths contained relatively more intracystic fluid, the papilloma itself rarely exceeding 3 cm. in diameter (Fig. 282).

Location. Intracystic papillomas have a characteristic location near the nipple or in the central zone of the breast. The tumor occupies the larger ducts or may grow within the ampulla of the nipple itself (there were nine such cases in the present series which involved the nipple). In all, 98 per cent of the growths were in the central or

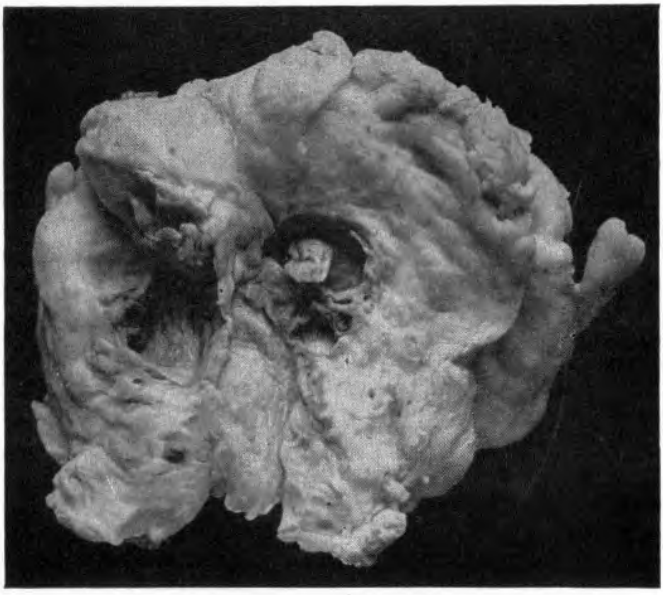


FIG. 282. A small papilloma within a larger cystic cavity. The gross specimen shows the cyst surrounding the papilloma. The hemorrhagic fluid which filled the cavity has been removed.

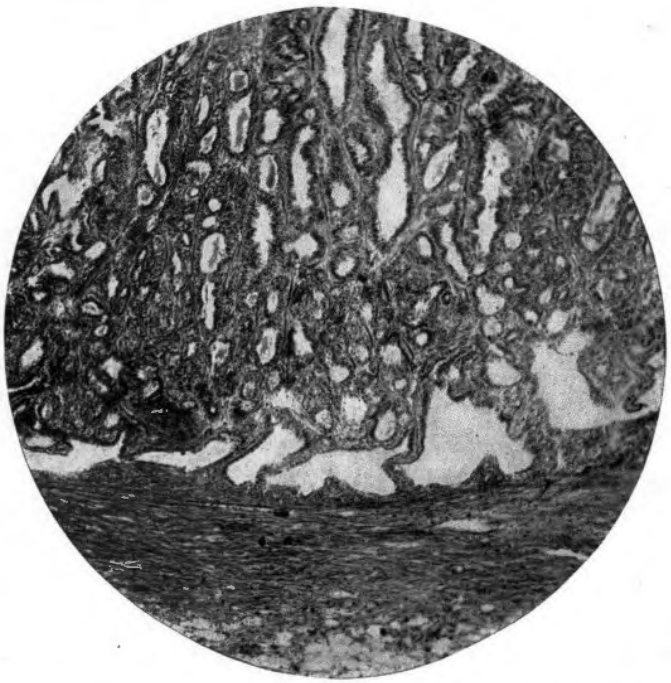


FIG. 283. Photomicrograph showing the structure of the papilloma shown in Figure 282.

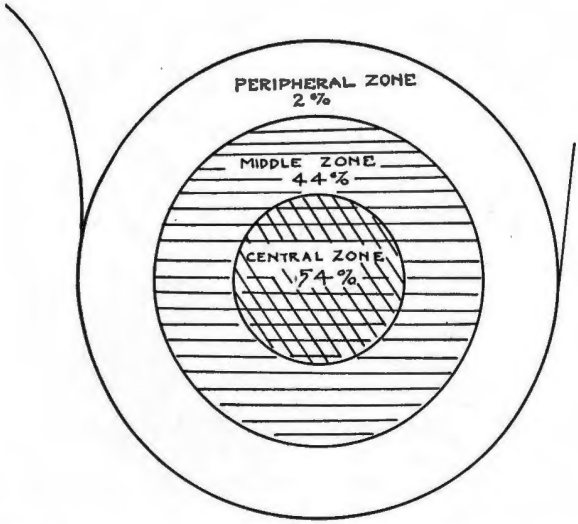


FIG. 284. Chart showing the distribution of papillomas of the breast.

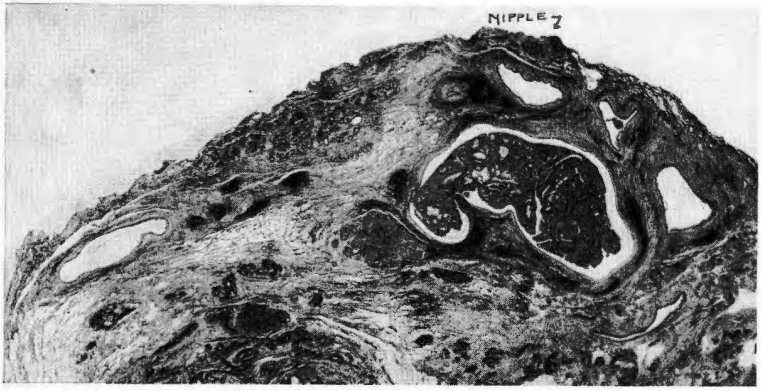


FIG. 285. Cross section of a breast showing a papilloma in a large duct beneath the nipple.

mid-zones (Figs. 284, 285). The majority of the growths are solitary but multiple or bilateral tumors may occur. On pathologic examination, papillomas which palpate as a solitary mass may be found to be composed of multilocular cysts containing several papillomas or a main duct and its branches may be affected (Figs. 286-289).

Multiple papillomas were found in 35 cases (17 per cent). In nine cases both breasts were involved either with bilateral palpable tumors or a bilateral sanguineous discharge. In seven cases, multiple tumors were palpated in the same breast. In the remaining cases, the multi-

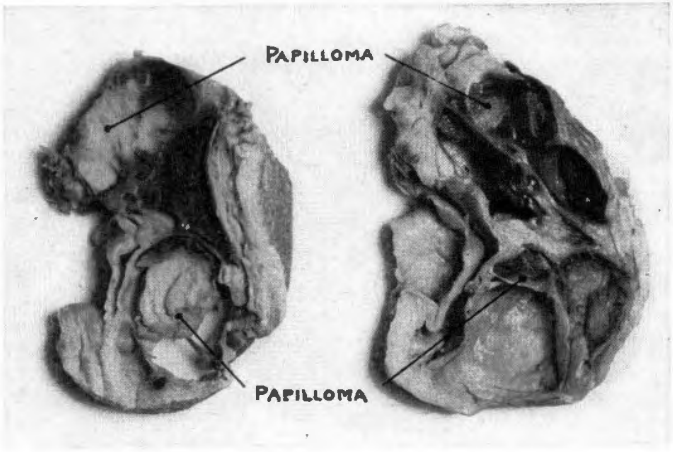


FIG. 286. Multiple papillomas. Gross specimen of multiple intracystic tumors.

plicity of the growths was established by pathologic examination rather than by clinical findings.

Multiple, shot-like nodules and bloody discharge from the nipple may occur in cases of adenosis. At operation small intracystic papillary growths 1 to several mm. in diameter are seen. If such cases are included among the benign intracystic papillomas, the incidence of multiple papillomas in one or both breasts is much increased. These, however, have been excluded (see Chap. 9).

On palpation, the tumor was soft or cystic, freely movable and clinically benign in the majority of cases. The growth felt hard or suspicious of malignancy in only 14 instances. The skin was adherent in 12 cases, altered in color in six (had a red or bluish tint) and was ulcerated in two instances. Even when immediately adjacent to the nipple the mass may be readily displaced by digital pressure.

Diagnosis

In a woman past middle life, the clinical diagnosis of benign intracystic papilloma can be established by the presence of a sanguineous

discharge from the nipple of six or more months' duration, together with a freely movable, soft palpable mass in the region of the nipple, which is 1 to several cm. in diameter, and casts a shadow on transillumination. When the mass feels smooth and cystic it can be distinguished from cystic disease (mammary dysplasia) by its opacity on transillumination, its nearness to the nipple or overlying skin and the appearance of a bloody discharge when pressure is applied.

TABLE XLI

DATA ON 203 CASES OF BENIGN INTRACYSTIC PAPILLOMA

I.—AGE

15–20	6
21–25	7
26–30	12
31–35	21
36–40	17
41–45	26
46–50	26
51–55	16
56–59	28
70+	5

II.—MARITAL

Nulliparous	85
Parous	93

III.—DURATION OF SYMPTOMS

Under 1 month	20
1– 6 months	29
7–12 months	15
1– 2 years	31
2– 5 years	35
Over 5 years	42
	172

IV.—SYMPTOMS

Pain	93 (47%)
Tumor	182 (91%)
Discharge (bloody)	96 (48%)
Retracted nipple	8 (4%)

V.—LOCATION

Bilateral	9
Unilateral	194
Multiple	35
Solitary	168
Nipple zone	110
Mid-zone	86
Periphery	5

VI.—SIZE

0.5–1 cm.	30
1–3 cm.	94
3–5 cm.	26
Over 5 cm.	12
Average size	2.2 cm

VII.—TREATMENT

No operation	0[1]
Excision	110
Simple mastectomy	46
Radical mastectomy (7 bilateral)	47

VIII.—END RESULTS

Not followed	66
Well 3 years+	31
Well 5 years+	49
Well 10 years+	45
Recurred	8
Cancer of breast	3

[1] These were 68 cases of bleeding nipple which were not operated upon but these have been excluded from the above tabulation.

Differential Diagnosis. A discharge from the nipple containing or resembling blood may occur in a variety of conditions which must be distinguished from intracystic papilloma. Bleeding from the nipple occasionally follows a severe blow to the breast. In such cases of mammary hematoma, there is a history of recent injury, acute pain, tenderness with ecchymosis in the affected region. The symptoms

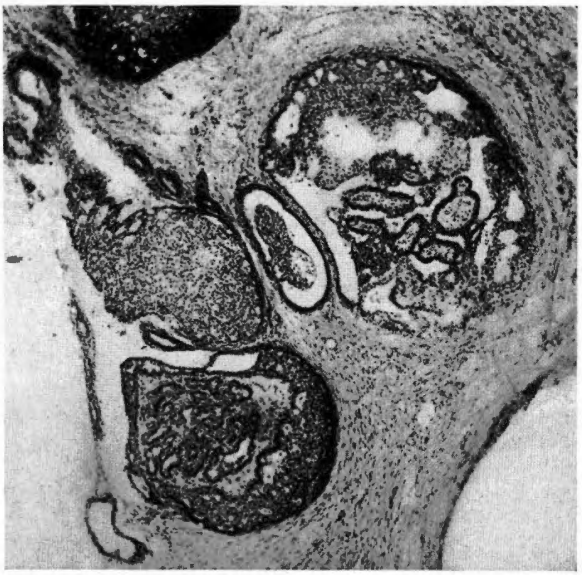


FIG. 287. Photomicrograph of multiple small papillomas occurring in the wall of larger cystic spaces.

rapidly subside after a few days, the bruise going through the characteristic color changes.

Occasionally, in an abscess in lactation mastitis, blood and pus are discharged from the nipple, but in such cases the presence of lactation and the systemic reactions of fever, leukocytosis and malaise permit a ready diagnosis.

In women who are at or near the menopause, a dark brownish discharge may accompany dilated ducts beneath the nipple, and one or more tortuous, distended ducts may be palpated. The microscopic examination of the exuded material reveals the amorphous debris of inspissated secretion, rather than red blood cells.

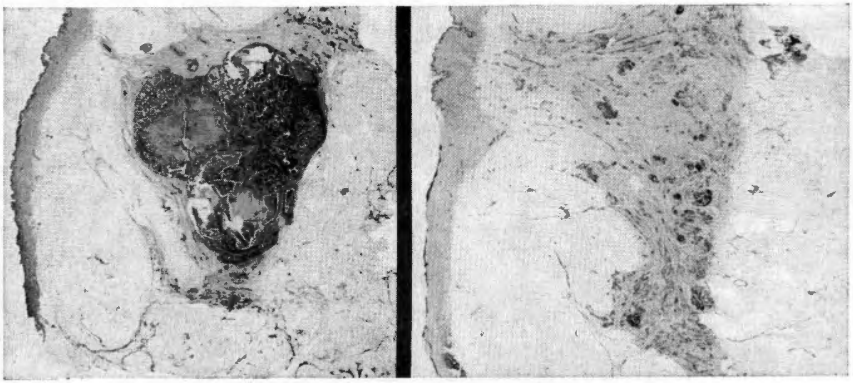
In Paget's disease of the nipple, the source of the bleeding is found on careful inspection to be coming from the ulcerated or cracked surface of the nipple itself, and epidermoid changes produced by thickening and scaling are visible. In cases where the papilloma occurs in

the ampulla of the nipple itself and produces ulceration, biopsy may be necessary for diagnosis.

Papillary growths with sanguineous discharge from the nipple occur in cases of adenosis and papillary cancer as well as in benign cystic papilloma.

In adenosis, the condition of the breasts on palpation is characteristic. The breasts are usually small and unequal in size. There is usually a flat, raised, tender area in one or both breasts which is worse in the premenstruum; the condition is rarely seen after the

FIG. 288 FIG. 289



Whole Section of the Breast Showing Bilateral Multiple Papillomas in the Larger Ducts.
FIG. 288. Right breast showing a large papilloma directly beneath the nipple.
FIG. 289. Left breast showing the papillomas distributed along the course of several ducts.

menopause. Multiple, pea-sized nodules are found in one or both breasts and the breast has a saucer-like edge when grasped between the fingers.

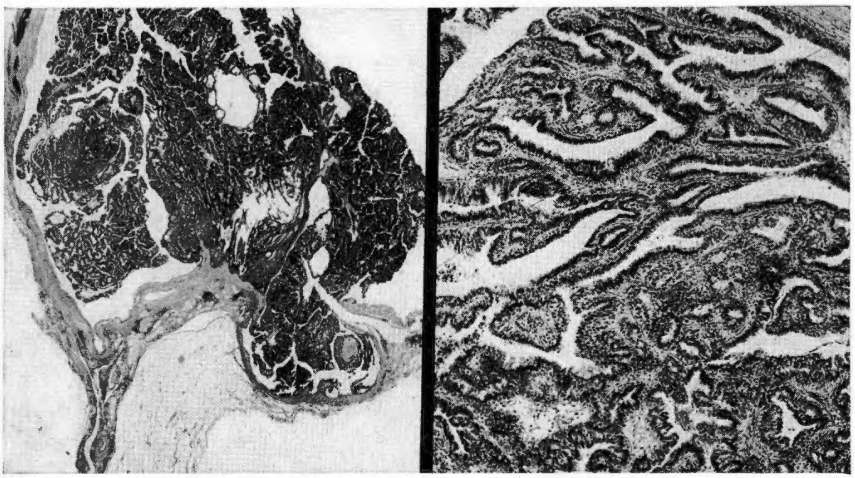
In papillary adenocarcinoma, a sanguineous discharge from the nipple occurred in 10 per cent of 197 cases. Whereas in benign papillomas the discharge often precedes the discovery of the lump by months or years, in cancer, the discovery of the mass rather than the discharge is the initial finding. In papillary adenocarcinoma, the size of the growth is often a distinguishing feature. These cancers average 5.8 cm. in diameter as compared to 2.2 cm. for the benign growths. Changes in the overlying skin in the form of dimpling, discoloration, or ulceration are frequent in these malignant neoplasms.

Pathology

Benign intracystic papillomas are encapsulated growths in which the epithelial tufts are bathed by varying amounts of serous or san-

guineous fluid enclosed within a fibrous wall. Often the tense, bloody, encapsulated fluid gives a bluish or purplish hue to the unopened cyst. A solitary papilloma may partly or completely fill the cavity, or multiple papillomas may be found in the compartments of a multilocular cyst. Smaller papillomas may be found in dilated tortuous ducts, rather than within a cyst, and more rarely multiple outgrowths may occur along the course of a main duct and its

FIG. 290 FIG. 291



Microscopic Structure of a Benign Papilloma.
FIG. 290. Low power showing the encapsulated character of the growth.
FIG. 291. High power showing the intact rows of epithelium covering the branches of the fibrous stalk.

branches. The ducts in such cases may be distended with clotted blood. (Figs. 288, 289.)

The papilloma is composed of branching tufts having a framework of delicate stalks of fibrous tissue transmitting blood vessels to the reduplicated epithelial covering. Usually the cluster of branching stalks is attached to the cyst wall only at its base. Shreds of tissue may be readily separated from the papilloma. This friable epithelial tissue is not found outside the cyst wall in most of the benign cases.

On microscopic examination the arborescent fibrous stalks supporting the neoplastic epithelium are prominent and well formed, and this fibrous portion of the growth often exceeds the epithelial elements in amount. The epithelium surmounting the fibrous core is orderly in arrangement, usually one to two layers in thickness and the outer layer is composed of tall, columnar cells which present a

frayed secretory border. Mitotic figures are scarce and the nuclei are regular in size and staining reaction. (Figs. 290, 291.)

Histogenesis of Papillary Tumors. Lesions of the breast which have a papillary epithelial structure occur at varying ages. In adenosis, papillary hyperplasia is common in adult cyclic women in the thirties and early forties. It usually affects both breasts toward the periphery. Papillary invaginations in the main ducts are found in women during or past the menopause, the majority of whom are between the ages of 35 and 55 years. They occur as minute, nonpalpable growths in cases of bleeding nipple, and as palpable intraductal papillomas in the central region of the breast. The larger malignant growths (papillary adenocarcinomas) are also in the central zone of the breast. They are found in later life, in women between the ages of 46 and 70 years.

Apparently these different forms of papillary growths, occurring at different ages, are associated with varying phases in the histogenesis of the epithelial buds which give rise to the ducts and lobules of the breast.

The mammary ducts originate in the embryo from sprouts of basal cells beneath the nipple (see Fig. 1). These invade the underlying tissue, branch and are canalized to form the milk channels. Branching and extension of the ducts before birth proceed from solid cords of basal cells in the nipple zone. In adolescence and in pregnancy branching of the ducts with lobule formation proceeds from basal cells in the ends of the mammary tubules at the periphery of the breast. Papillomas may originate in the larger ducts (intraductal growths) or in the lobular buds of the terminal tubules, when they have undergone cystadenomatous change (intracystic growths). The intraductal growths are most often seen in a senile fatty breast; the intracystic growths arising in cystadenoma are usually found in younger women with adenosis.

Experimental Production of Intracystic Papillomas. In the rat, papillomas may be produced in the larger ducts or in the region of the terminal tubules. (Figs. 292, 293.) Benign papillomas in the larger ducts are found in the precancerous phase of estrogen stimulation, when potent estrogens with prolonged action (estradiol benzoate) are injected daily in doses of 100 gamma. Such intraductal papillomas are rare and are followed by papillary adenocarcinoma later in the course of estrogen injections (see Chap 33).

Intracystic papillomas in the region of the terminal tubules form from cystadenomas produced in the lobules of the rat's breast in response to prolonged estrogenic stimulation. In lobular structures which have undergone cystic dilatation (cystadenomas), papillary

hyperplasia similar to that occurring in adenosis may be found in the periphery of the breast. (Fig. 293.) Later, large benign papillomas may arise in such lobules. Such benign tumors arise under a con-

FIG. 292

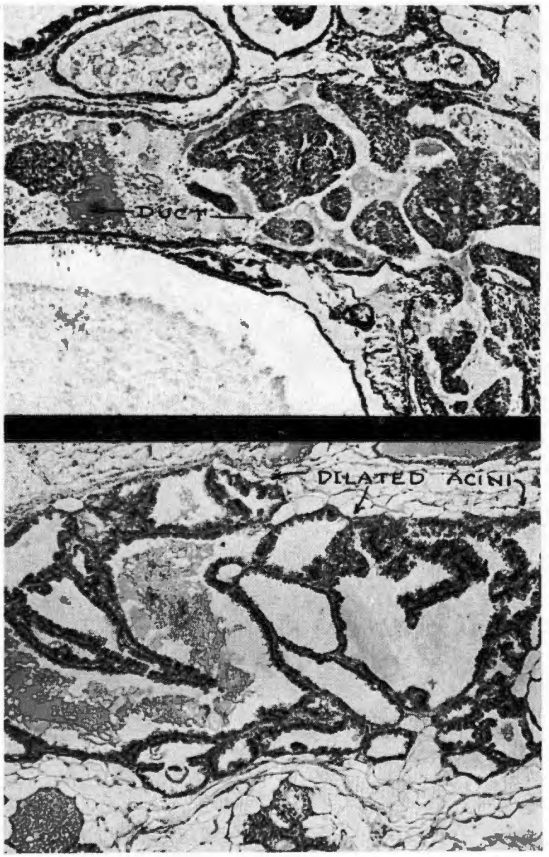


FIG. 293

The Histogenesis of Benign Papillomas in the Rat's Breast.

FIG. 292. Papilloma forming in a main duct (after 100 gamma of estradiol benzoate daily for 120 days).

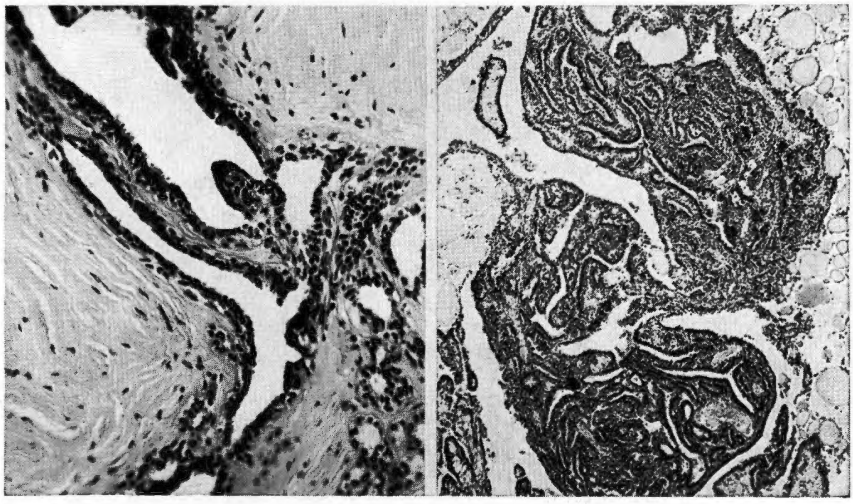
FIG. 293. Beginning papilloma in a cyst-adenoma occurring in a lobule with dilated, involuting acini (after 200 gamma of estrone daily for 216 days).

stant but moderate estrogenic stimulation. These experimental papillomas and also papillary adenocarcinomas were most frequent in animals in which, beginning at birth, the mammary gland was stimulated by the implantation of successive estrone pellets after 70 days of twice daily injections of 25 gamma estrone in oil. The estrogen

stimulation was similar to that used in the experimental production of fibro-adenomas. While the fibro-adenomas occurred in 130 to 190 days, however, the papillomas formed in 350 to 515 days.

These experiments indicate that benign papillomas are the result of epithelial regeneration which projects into the free space of a

FIG. 294 FIG. 295



Histogenesis of Papilloma.

FIG. 294. Photomicrograph showing persisting buds of mammary epithelium at the point of bifurcation in the larger ducts beneath the nipple in the human breast.

FIG. 295. Photomicrograph of benign papilloma occurring in the rat's breast. The tumor was found at autopsy after 415 days of estrogenic stimulation which was begun with injections twice daily at birth until the 70th day of life. Thereafter, successive estrone pellets were implanted on the 70th, 156th, and 260th day.

large duct or cystic cavity. The characteristic papillary structure results because the supporting stroma and vascular supply for the adenomatous tissue is provided only at a single point or zone of contact with the wall of the duct or cystic cavity. Three factors, therefore, enter into the histogenesis of papillomas: (1) epithelial buds which are remnants of normal mammary development, (2) their distribution along the large ducts or at the terminal tubules, (3) prolonged regenerative activity in the epithelial buds. Usually the last occurs at the menopause or after prolonged estrogen stimulation.

Prognosis

Although the first simple excision of benign papilloma in the present series was performed in 1896 and the patient remained well

35 years, this conservative treatment was not frequently practiced until the past two decades. In all, 110 patients were treated by excision, while 46 had simple mastectomy, and 47 had the radical operation for cancer.

Forty-eight of the cases treated by excision were followed from three to 35 years and remained well. Eight additional cases had a second operation for recurrent benign papilloma. With one excep-

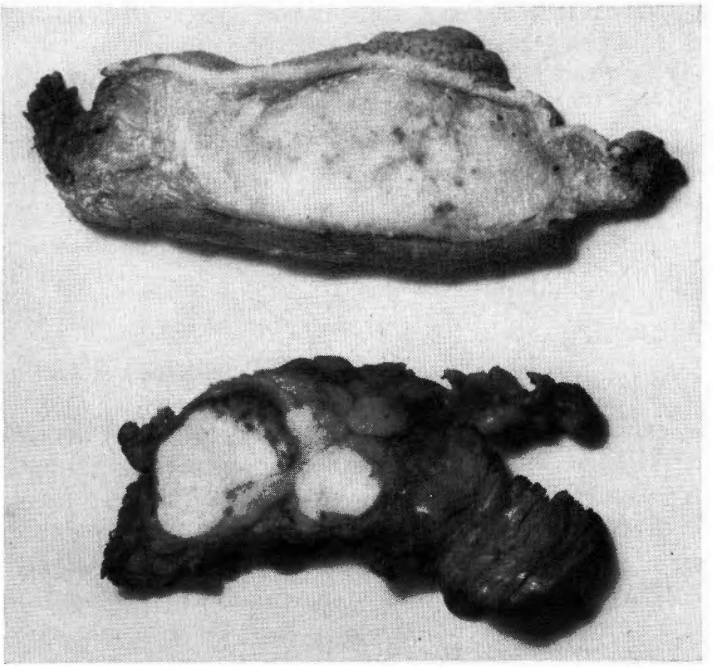


FIG. 296. Recurrent, malignant papilloma. Gross specimen from a mastectomy performed for a recurrent malignant papilloma. The tumor occurred in the scar two years after an excision performed for benign papilloma.

tion, where two operations were performed the second was either simple or radical mastectomy. In three cases, excision of a papillary tumor was followed after several years by a radical mastectomy for papillary carcinoma. In one case, the papilloma was excised at the age of 18 years and a radical operation was performed 23 years later for papillary carcinoma. Six years later a recurrent papillary cancer with mucoid change was excised from the scar. This patient is well six years after the third operation. In the second case, local excisions had been performed 10 years previously in the left, and seven years previously in the right breast. In 1924, a radical mastectomy

was performed on the right breast for papillary carcinoma, the gross specimen showing a papillomatous cyst with cancer in the wall. This patient died in 1934 with ovarian carcinoma. In the third case, a cystic adenoma was excised from the right breast in 1920, and in 1922 radical mastectomy was performed for a papillary cancer which developed in the scar. This patient died of cancer two years later. (Fig. 296.)

Thirty-nine of the 46 patients treated by simple mastectomy have been followed and have remained well from three to 30 years. Thirty-eight cases among the 47 treated by radical mastectomy have been similarly followed with equally good results.

In all, there were 105 cases of benign intracystic papilloma followed more than five years and for a period averaging just under 10 years. Fifty-four of these cases were treated by excision only, and of this group three developed mammary cancer (about 6 per cent). In calculating the incidence of malignant change, it does not seem proper to include the cases treated by simple or radical mastectomy because benign papillomas, unless associated with adenosis, are rarely bilateral.

Treatment

Local excision is the treatment of choice in cases of benign intracystic papilloma. The tumor should be excised with a zone of surrounding breast tissue and the wall of the cyst at the base of the papilloma carefully examined in the gross and by frozen section for evidence of invasion. At operation microscopic examination of the base of the papilloma should be a routine procedure and any thickened point in the wall of the cyst should be similarly studied. If islands of papillary tissue are found extending beyond the fibrous capsule or islands of malignant epithelial cells are found, radical operation for cancer should be performed.

When excising the tumor, any tortuous, dilated, or thickened ducts that can be palpated in the surrounding tissue should be opened and examined for the presence of secondary papillary growths. If extension of the papillary process is found in the neighboring ducts, simple mastectomy should be performed. Where the size of the papillary growths exceeds 5 cm. in diameter, malignant change has probably occurred. There were only 12 cases in the present series where benign growths exceeded this dimension. It is a safe clinical rule to perform radical mastectomy for such large growths unless competent pathologic opinion on the benign nature of the growth can be obtained based on the frozen section.

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15

The Nipple, Areola, and Nonindigenous Tumors of the Breast

INJURIES AND FOREIGN BODIES

Trauma to the breast may result in a bruise or hematoma. The site of the injury is usually tender and indurated and shows the characteristic discoloration of a bruise. Cold applications with mechanical support or binding usually result in prompt relief and the swelling or induration subsides within a few days.

A severe blow, particularly in the lactating breast, may be followed by an abscess which requires incision and drainage. In rare instances an organizing hematoma or fat necrosis may form a residual palpable mass which warrants exploration. It is important to remember that relatively insignificant trauma often attracts the attention of the patient to a pre-existing neoplasm. For this reason, any mass which is present one or more weeks following an injury but which was not observed immediately following the trauma should be explored.

Lacerations and stab wounds of the breast require the same attention given similar injuries elsewhere in the body. The possibility of hemorrhage deep in the breast and of injury to the internal mammary artery should be borne in mind. It is well to close such wounds with a small drain.

Infections and sloughing of the mammary tissue resulting from hypodermoclysis are rarely observed, since this ill-advised procedure has been abandoned in most hospitals.

Operative wounds for the excision of benign mammary tumors may remain indurated and tender for some weeks following the operation and may cause the patient some concern. No special treatment other than reassurance and careful observation to rule out the possibility of infection or the collection of serum into the wound is indicated. In some cases a painful keloid may form in the scar. This may be associated with a costobrachial neuralgia, particularly in breasts operated upon for mastodynia. If the condition does not respond to diathermy and a short course of roentgen-ray therapy over the incision, the hypertrophic scar should be excised and the line of excision irradiated.

Foreign bodies in the breast are rare and if not painful or accompanied by infection require no therapy. The painful objects reported in our series have been spicules of bone from osteomyelitis in a rib, buck shot, and portions of a needle or unresolved catgut remaining from a former operation.

PARAFFINOMA OF THE BREAST

Following the injection of paraffin into the female or male breast, conditions resembling mammary cancer have been described. Such injections were used as an aid to cosmetic surgery early in the present century, when it was thought that pure paraffin was a harmless and indifferent material which was well tolerated by the body. It was soon learned that in many cases it was necessary to remove the paraffin, for it produced chronic inflammation and necrosis in the surrounding tissues. Zorraquin reported the case of a young woman with multiple hard tumors in both breasts with a typical "orange peel" appearance of the skin. Several years previously she had had injections of melted paraffin in both breasts in order to increase her physical attractiveness. De Cholnoky has reported the case of a paraffinoma in the male breast simulating mammary cancer. The breast had been injected for chronic mastitis with unpleasant throbbing sensations in the right nipple. Paraffinomas of the breast lead to indurated tumors, reddening of the overlying skin, pain and tenderness.

Histologically, the tissues infiltrated by paraffin show a foreign body reaction with an accumulation of foreign body giant cells, foam cells and epithelioid cells, and elliptical spaces indicate the site of the paraffin in the fixed sections.

The treatment is excision of the affected tissues.

AFFECTIONS OF THE NIPPLE AND AREOLA

The Nipple

Affections of the nipple include (1) abnormal secretion, (2) changes in size or position, and (3) organic lesions

Abnormal secretion has been discussed elsewhere (see Chap. 5 for nonpuerperal secretion; and Chap. 14 for bleeding nipple).

Changes in Size or Position. Congenital retraction of the nipple has been discussed in Chap. 5 in relation to lactation, and the incidence of acquired retraction is discussed in connection with the various benign and malignant neoplasms of the breast. In most cases congenital retraction of the nipple is associated with abnormal development and denotes the persistence of a feature characteristic of the nipple pouch in the embryo. Sometimes the so-called congenital retraction arises following a neonatal mastitis in infants who have had active mammary secretion during the first few weeks of life. Acquired retraction or change in position of the nipple was observed in 21 per cent of mammary cancer 5 cm. or less in diameter and in over 90 per cent of larger malignant growths. (Chap. 19.) The incidence of such changes in the nipple in benign tumors is between 1 and 3 per cent and may be higher in plasma-cell mastitis. Whenever retraction of the nipple cannot be related to a congenital anomaly or to a true neonatal mastitis, exploration is indicated. Intermittent retraction is a rare clinical finding. It may be a symptom of benign or malignant papillary tumors affecting the larger ducts (see Chap. 14). It also occurs in women who have chronic cystic mastitis and are approaching the menopause. There were only three instances of this condition among our patients with cystic mastitis. In all three, both nipples were ultimately affected. These patients noticed intermittent retraction for several months or years finally resulting in permanent retraction. First one, and then the second nipple was affected. In these cases the underlying tissue was explored and the nipple excised.

Bulging of the nipple may occur with either benign or malignant tumors of the breast. An intraductal papilloma is the most common cause of acquired bulging of the nipple. (Chap. 14.) In nine instances bulging and bleeding were associated with intracystic papilloma in the ampullae. Excision was required to differentiate these cases from Paget's disease. Bulging of the nipple has also been observed in cases of gelatinous carcinoma (Fig. 416, Chap. 23) and an enlarged, red granular nipple may be an early symptom of Paget's disease (Fig. 442, Chap. 24).

Organic Lesions. Ulcerations and tumors of the nipple should always bring to mind the possibility of Paget's cancer. If the Wassermann reaction is negative, a biopsy should be performed in ulceration of the nipple. The most common benign tumor of the nipple is an epidermal or keratotic thickening. Among 97 such cases of warty nipple, there were 45 associated with scabbing or cracking which necessitated biopsy to rule out Paget's cancer (see Chap. 25). Benign intracystic papillomas occurring within the ampulla of the nipple are next in order of frequency. These are associated with enlargement and a bloody discharge. Excision of the nipple suffices for diagnosis and treatment. Pedunculated fibromas (usually neurofibromas) and true neuroma of the nipple have been described (Hertzler, Stewart). Leiomyomas of the nipple have been reported by Lieber and by Deaver and McFarland. Excision of the nipple with a core of underlying tissues should be practiced for the diagnosis and treatment of these rare conditions.

Areola

The areola, the circular pigmented area of skin surrounding the nipple, contains 12 to 15 elevations arranged in circular fashion which mark the site of the glands of Montgomery. There is some difference in opinion as to whether these are sebaceous glands or rudimentary milk glands. The thin epidermis of the areola rests upon a corium devoid of fat but containing a layer of smooth muscle continuous with that of the nipple. In addition to the glands of Montgomery, typical sebaceous and sweat glands are found in the areola peripheral to the glands of Montgomery.

Apparently the areola represents the altered epidermal lining of the nipple pouch which is present in marsupials and which has become everted and superficial along with the nipple, by the process of protrusion which occurs during development. As was noted in Chapter 1 in describing the comparative anatomy of the mammary gland, the mammary bud of marsupials develops epithelial sprouts which separate into three groups (Fig. 1 e_2). One group provides for the milk ducts, another for the sebaceous glands, and a third for the mammary hairs. If the structures of the nipple and areola are carefully examined in parous women it will be found that this same order persists in the human breast. The nipple at the center represents the grouping of the milk ducts, the glands of Montgomery about it represent a concentric arrangement of the modified sebaceous glands and the elongated mammary hairs are found frequently at the periphery of the areola.

The size of the areola, its pigmentation and the glands of Mont-

gomery show changes during pregnancy. Apparently this is in response to the luteal hormones.[1] Because of the widening of their ducts and the increased amount of sebaceous secretion in the gland during pregnancy, an acne-like infection of one or several of them is sometimes observed at such a time. Such a pustule may be satisfactorily treated by opening it with a sterile needle, evacuating the contents, and instructing the patient to apply 50 per cent alcohol to the nipples nightly for a period of a week.

Cancer of the breasts which ulcerate may involve the areola, but primary tumors affecting this region are extremely rare. One case of sebaceous adenoma and one each of Paget's cancer and squamous-cell cancer are recorded in the author's series. Benign keratoses which are relatively common on the nipples are rare on the areola. However, any of the generalized forms of skin diseases such as eczema, psoriasis or the infectious forms of dermatitis may involve the areola along with the surrounding epidermis (Fig. 445, p. 555).

NONINDIGENOUS TUMORS OF THE BREAST

While chief interest centers on benign and malignant neoplasms of the mammary epithelium, a variety of benign and malignant tumors which are important from the standpoint of differential diagnosis may arise from the mesodermal structures in this gland; rarely, epithelial tumors, such as dermoid cysts and adenomas of the sweat glands, may be found. These nonindigenous tumors comprise about 1.5 per cent of mammary lesions. The variety and incidence of this group of neoplasms may be judged from the table on page 357.

Benign Mesodermal Tumors of the Breast

If nevi, keloids and neurofibromas involving the skin over the gland are excluded, the most common benign nonindigenous tumors of the breast are those arising in fatty tissue. The fatty tissue tumors may be neoplasms of fat such as lipoma and liposarcoma or phagocytic reactions in traumatized fat (fat necrosis) or lipoid deposits in characteristic foam cells associated with a metabolic disturbance (xanthoma).

Lipoma. Menville has previously reported 24 of the 30 lipomas in this series and collected the literature on similar cases. Practically all of the lipomas were superficial, that is, anterior to the mammary gland proper. In rare instances the tumor may be retromammary,

[1] The sensitivity of the glands of Montgomery to these hormones can be demonstrated by having the patient rub this region nightly with an ointment containing testosterone propionate. Under such treatment the glands enlarge within a period of several days to several weeks.

TABLE XLII

NONINDIGENOUS TUMORS OF THE BREAST

MESODERMAL TUMORS				
Benign		82	Malignant	23
Source:				
Fat	Lipoma	30	Liposarcoma	3
	Xanthoma and Fat necrosis	37		
Vessels	Angioma and	7	Angiosarcoma	2
	Lymphangioma	1	Lympho- and myelosarcoma	12
	Lymphoma	1		
Muscle	Leiomyoma	0		
	Myoblastoma	2	Myosarcoma	3
Skeletal Mesenchyme	Chondroma	2	Osteogenic Sarcoma	3
	Osteoma	2		
EPITHELIAL TUMORS				
Dermoid cysts		28	Squamous cell cancer	9
Sweat gland tumors		7	Sweat gland cancers	16

arising on the posterior aspect of the gland. Superficial lipomas are lobulated, soft, fatty masses which transilluminate clearly. In 5 per cent of the cases there was attachment to the skin and "dimpling" was elicited. Adults are usually affected, the average age being approximately 45 years. The size of the tumor is variable, usually 1 to several cm. in diameter, although, in some instances, the size may exceed 10 cm. The known duration of the tumor averaged three years.

Pain, together with swelling or tenderness sometimes associated with recent trauma, were the complaints for which these patients sought advice. Although in six cases the true nature of the tumor was arrived at clinically because of the soft, lobulated character and the translucent nature, the usual diagnosis was cyst or fibro-adenoma. In three cases, the lipomas were bilateral, and in three there were multiple lumps in the same breast. These tumors at exploration have a lobulated golden-yellow surface traversed by delicate bands of fibrous tissue. (Fig. 297.) They may be difficult to distinguish from the surrounding tissue, but the lobules are larger and the growth less vascular. In four instances the lipomas were discovered when operations were performed for other growths, such as fibro-adenoma or galactocele. Simple excision was practiced in the treatment of all these lipomas. In 17 cases where the patient was followed for more than five years, there was no recurrence.

Fat Necrosis and Xanthoma. Destruction of fat followed by a regenerative process in which phagocytosis and foreign-body giant cells are prominent may occur in the breast with a variety of conditions, such as abscess, benign and malignant tumors and following trauma. The phagocytic process in which large foam cells predominate has been referred to as xanthomatous degeneration, to distinguish it from the primary type of xanthoma which results when there is a generalized disturbance in lipoid metabolism. Primary xanthomata

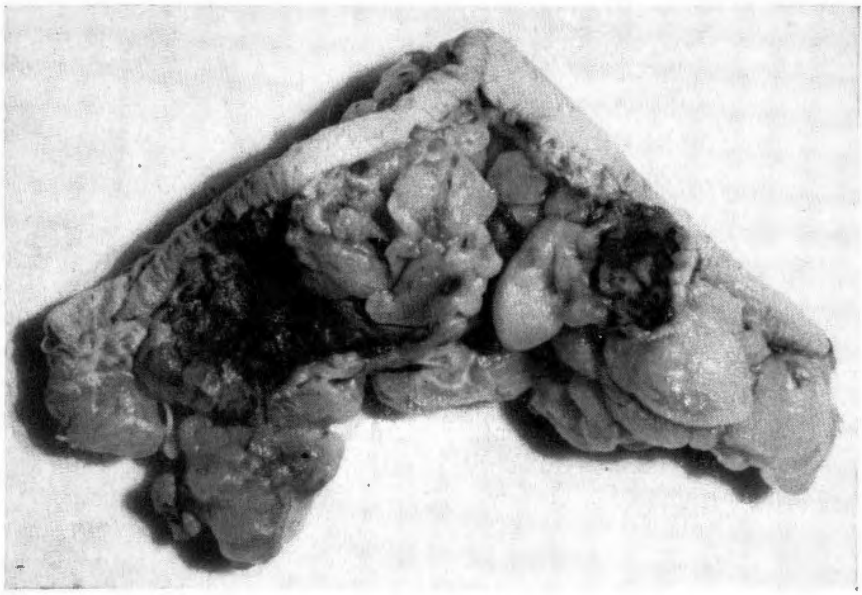
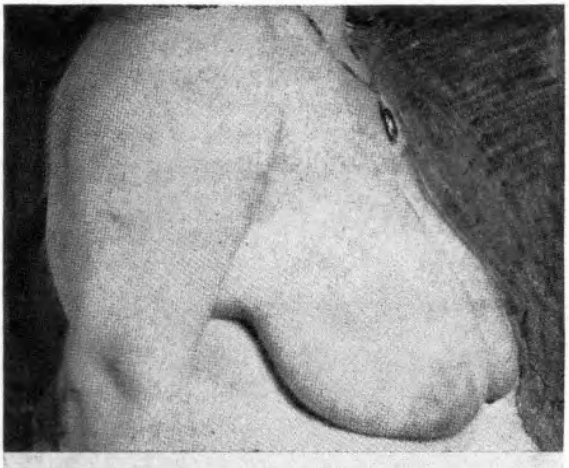


FIG. 297. Lipoma of the breast: gross specimen.

of the breast composed almost exclusively of foam cells have been reported in patients with disturbed cholesterol metabolism and are extremely rare. Haagenson has reported three cases and cited the one previously reported by Cheatle and Cutler.

Fat necrosis and xanthomatous degeneration are among the rare benign lesions of the breast which may be confused clinically with carcinoma. Menville believes that fat necrosis and xanthomatous degeneration are two stages of the same process. Fat necrosis, which may follow a blow to the breast, forms a dense small nodule which may palpate like carcinoma. This is particularly true if cholesterol or calcareous material accumulates in the zone of necrosis. The gross appearance is pale, dull, grayish-white and homogeneous. The degree of change from normal fat depends upon the amount of necrosis and

FIG. 298



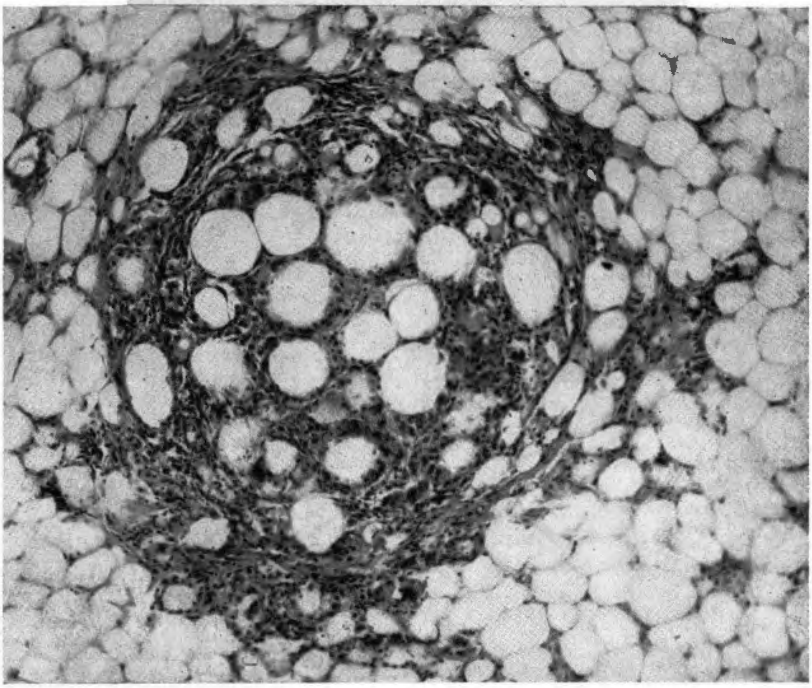


FIG. 299

Fat Necrosis.

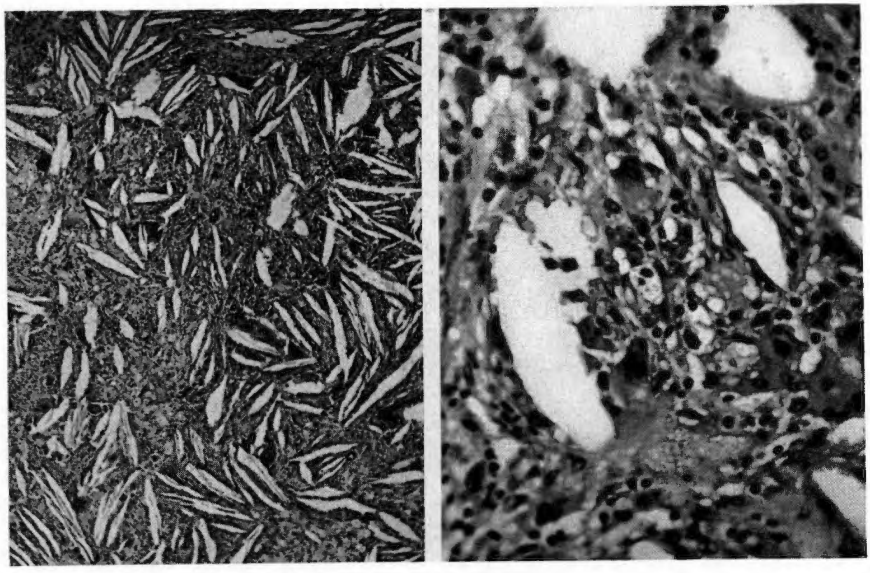
FIG. 298. Obese breast, the seat of fat necrosis.

FIG. 299. Photomicrograph showing the histology of the lesion.

repair present. Dunphy reported two cases in which fat necrosis appeared in the scar of a mastectomy performed for mammary carcinoma; it gave the impression of recurrent cancer.

Large, heavy, pendulous breasts (Fig. 298) are the type usually harboring fat necrosis. These are subject, because of their size, to pressure from their own weight as well as to injury from external causes. In all probability the underlying cause of fat necrosis is an ischemia of the part, produced either by trauma or by pressure.

FIG. 300 FIG. 301



Xanthomatous Changes in the Breast.
FIG. 300. Photomicrograph showing lipoid phagocytes or foam cells surrounding cholesterol crystals.
FIG. 301. High power showing foreign body giant cells and macrophages.

Xanthomatous degeneration may follow or replace fat necrosis. Following a stage of fat destruction there is a granulomatous process in which fibrous tissue, lymphocytes, and giant cells occur together with the characteristic foam cells which are lipoid phagocytes. (Figs. 298, 299.) In such a lesion there may be fixation to the skin and induration suggesting cancer. The gross tumor usually has an orange-yellow or brownish appearance. On section, some of these lesions contain cystic cavities with cholesterol crystals and calcium deposits (Figs. 300, 301). This crystalline material which grits on section and which gives the tumor its hardness to palpation was responsible for

a diagnosis of malignancy in one-third of the cases studied by the author.

The patients with fat necrosis or xanthomatous degeneration in the present series averaged 46 years in age, while the average duration of symptoms was three years. White women were usually affected. Trauma, although a probable exciting cause in the production of fat necrosis, is not an essential factor, and was recalled by only four of the 37 patients.

The size of the tumor, which in some cases is microscopic, varies with the extent of necrosis. The lesion, although sometimes circumscribed, is more frequently stellate; or it may be lobulated, firm and sometimes painful. The tumor is occasionally attached to the skin. The skin retraction is easily explained by the process of fibrous repair. The fibrous tissue acts like a strong cord which is nonelastic and tends to retract.

When the benign nature of the fat necrosis or xanthomatous degeneration is recognized, simple excision suffices to cure.

Malignant Tumors of Fat. Liposarcoma occurs in adults, recurs locally and ultimately metastasizes to the regional lymph nodes and to more distant organs. This form of sarcoma is relatively rare. It is found more commonly in the buttocks and breast than elsewhere. The clinical and pathologic features of the three cases of mammary liposarcoma and a review of the literature are found in Chap. 16 on mammary sarcoma.

Benign Angiomas and Lymphoid Tumors. Angiomas of the breast are extremely rare. Bloodgood stated that he had never explored one, although Menville was able to collect seven benign hemangiomas and one lymphangioma from the records of his laboratory.

Mammary hemangiomas are usually of the cavernous type (Fig. 302). They are nonencapsulated subcutaneous tumors found in the young or middle-aged. On palpation the tumors are semifluctuant and cast a shadow on transillumination. Unless the characteristic blue or red color is discerned through the skin, the lesion is usually confused with intracystic papilloma or papillary cancer. The distinguishing feature is the absence of a sanguineous discharge from the nipple, because the vascular spaces are not connected with the mammary ducts. Exploration and microscopic study is necessary for diagnosis.

In Menville's series only one instance of capillary hemangioma is reported. This was a diffuse growth occurring in an elderly female whose breast was amputated because of the clinical impression of sarcoma. Dahl-Iversen was impressed with the frequency with which intramammary angiomas occurred in the right breast. He believed

that the lesions were congenital, although usually treated between the tenth and thirty-second year. De Cholnoky reported nine cases of mammary angioma, all of them cavernous.

De Cholnoky also reported two lymphangiomas. Menville reports a single case of lymphangioma occurring in a colored infant, aged six weeks. Clinically it was a congenital cystic tumor. Mosettig has also reported a case of lymphangioma of the breast which occurred in a girl, 17 years of age. The nodule was 3 cm. in diameter. Although

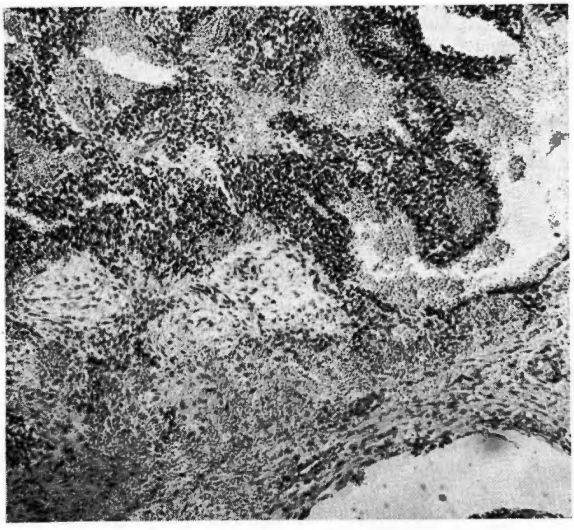


FIG. 302. Hemangioma of the breast. Photomicrograph showing a cavernous hemangioma excised from a young adult.

it had been present since the eleventh year, it had become painful only recently. The tumor was circumscribed and movable, and was diagnosed clinically as fibro-adenoma. This author collected 13 benign angiomatous mammary lesions from the literature.

Benign lymphoma is an ill-defined pathologic entity and is usually described only in connection with benign lymphoid tumors of the gastro-intestinal tract. In our series there is but a single case in which a solitary nodule of the breast was excised and the tumor had the histologic structure of a benign hypertrophied lymph node imbedded in the fatty stroma of the breast. Mammary lymphosarcoma occurred in eight cases. These are discussed in the following chapter under the heading, "Mammary Lymphosarcoma."

Benign Myomatous Tumors. Smooth muscle is found in the mammary gland in the region of the nipple and larger ducts and, according to Cheatle and Cutler, a continuous subepithelial layer sur-

rounds the ducts and acini. Hyperplasia of these myo-epithelial elements occurs when the mammary gland undergoes involution (Kuzma). Beneath the gland are the voluntary fibers of the pectoralis

FIG. 303 FIG. 304

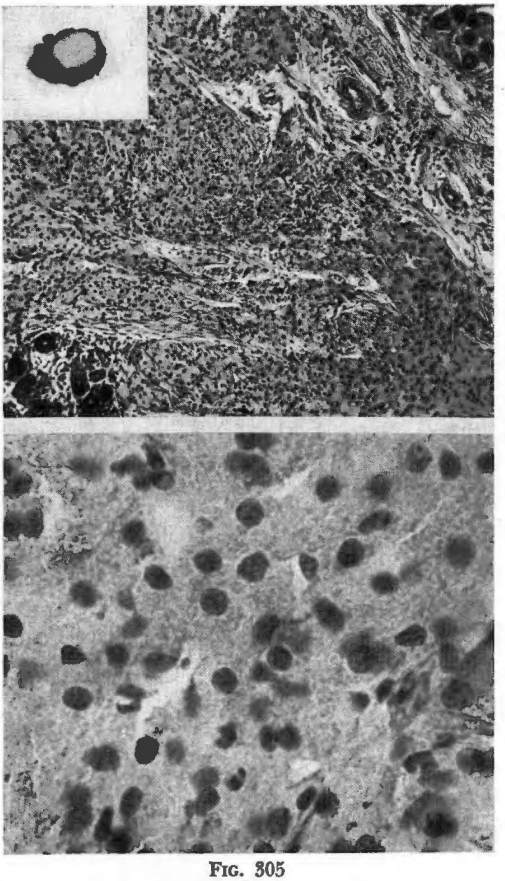


FIG. 305

Benign Myoblastoma of the Breast.
FIG. 303. Gross specimen. FIG. 304. Low power. FIG. 305. High-power photomicrographs. The tumor is small and encapsulated and is made up of cells with a granular cytoplasm with indistinct borders.

major. Tumors of both smooth and voluntary muscle, therefore should be found either in a superficial or retromammary location. As a matter of fact, all forms of muscle tumors have been described in the breast and in a variety of locations, but all of them are exceedingly rare.

Benign tumors of smooth muscle may occur in the region of the nipple or in the breast proper. Lieber described two leiomyomas of

the nipple and a similar tumor in the breast. The tumors in the region of the nipple were painful. Lebowich and Lenz have reported duration. The mass grew slowly, was painless and freely movable; at the time of excision it was firm, encapsulated, 13.8 cm. in diameter and resembled a myoma of the uterus. According to these authors this was the fourth reported case of fibromyoma in the breast proper.

Benign myoblastomas of voluntary muscle were first described by Abrikossoff. Klemperer, who was later able to collect 44 cases, reported two which occurred in the breast. Two additional cases are reported among the nonindigenous tumors of the breast in the present series. (Figs. 303-305.) The myoblastomas are small encapsulated growths rarely exceeding 2 cm. in diameter. The tumors are composed of cells of medium size with granular cytoplasm, small dense nuclei and ribbon-like bands of muscle fibers. The mammary myoblastomas were treated by simple excision and did not recur.

Both leiomyosarcoma and rhabdomyosarcoma have been described in the breast. These are rare and highly malignant growths which recur and metastasize via the blood vessels, rather than by the lymphatics. They are discussed in the chapter on mammary sarcoma.

Benign Chondromas and Osteomas. Benign tumors of cartilage and bone are as rare as myomatous tumors in the mammary gland, and their origin in this organ is more difficult to explain. Deaver and McFarland collected the literature on both of these rare varieties of nonindigenous mammary tumors. Cheatle and Cutler have reported small chondromatous nodules in two cases of fibro-adenoma. In one of these the cartilage was calcified. In the present series a cartilaginous nodule, 2 cm. in diameter, occurred in a case of fibro-adenoma of long standing and in another case cartilage and bone formation were both present in a small nodule occurring beside an intracanalicular myxoma in the breast of a woman, 57 years old. The benign osteomas, like the benign chondromas, are usually seen in elderly women in association with mammary fibro-adenoma. In one case the benign osteomas were multiple. Several small fibro-adenomas were observed in both breasts of a white woman, 73 years old. These had been present for a period of more than 10 years. On excision, one of three of these nodules was ossified. The patient returned one year later with the fourth nodule, 2 cm. in diameter, which, on excision, proved to be an eburnated osteoma. (Fig. 306.)

Bone spicules may occur in the breast as a foreign body in association with lesions of the ribs. A small node in the breast was found in a woman, 50 years old, who had had an injury of the ribs beneath the right breast two years previously. This was hard, freely movable, and about 1 cm. in diameter. Excision revealed two small fragments

of bone surrounded by dense fibrous tissue. In this instance the bone was probably the result of a previous fracture. In another instance, similar spicules of bone were removed from the mammary gland of a patient, 50 years old, who had had an osteomyelitis of the ribs. Pain and tumefaction appeared in the mammary gland following a blow on the breast. The lesion was explored and two small sequestra were removed.

Osteogenic and chondrosarcoma are among the rarer forms of mammary sarcoma. These are discussed in the next chapter.

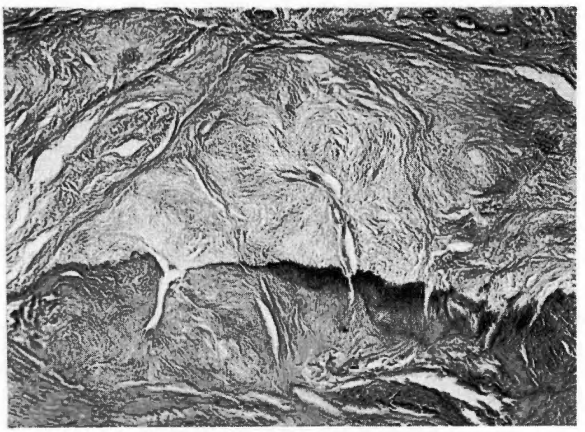


FIG. 306. Structure of an osteoma of the breast occurring in a woman of 73.

Nonindigenous Epithelial Tumors

Mammary Epidermoid Cysts. Epidermoid cysts (also referred to as dermoids, sebaceous cysts, cholesteatoma, and wens) may occur in the breast as well as elsewhere in the body. Either the subcutaneous or the deeper tissues may be affected. Unless they become infected or undergo malignant change these lesions may remain symptomless, and in 10 of the 28 cases in the present series the cysts were discovered incidentally, in operations performed for other benign or malignant conditions of the breast (Figs. 307, 308).

Mammary epidermoids are usually found in women past the age of 45 years. The advanced age of the patient, the solid atheromatous contents, and small size (rarely over 1 to 2 cm.) distinguish these cysts from the more common blue-dome cysts. When occurring subcutaneously the problem of diagnosis is much simplified. The leading symptoms are tumor, mild pain, or redness of the skin accompanying a low-grade infection. An equal number of patients give the duration of their symptoms in terms of months or in terms of years. Rarely,

when a large cyst becomes infected, the clinical picture may resemble mammary abscess or acute cancer. In other cases the atheromatous contents of the cyst, together with the cyst wall, undergo disintegration confusing the microscopic picture so that malignancy is sus-

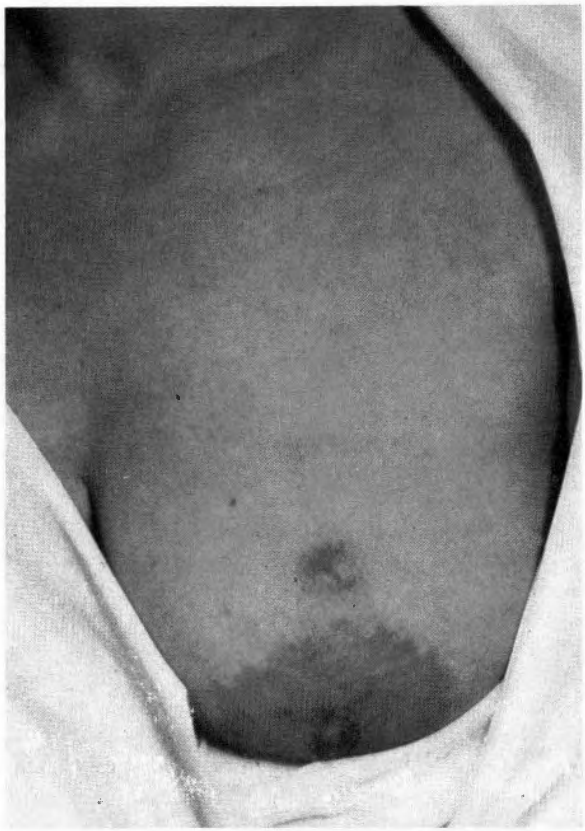


FIG. 307. Photograph of a patient with a dermoid cyst of the breast.

pected. Three such benign cysts in the present series were treated by radical mastectomy.

The pathology of mammary epidermoids resembles that of similar cysts occurring elsewhere in the body. A cheesy atheromatous substance is found within a definite cyst wall. Upon microscopic examination, this wall is formed by a layer of epidermis surmounted by degenerating keratin. When infected, the epithelial lining is disintegrated and granulation tissue with various types of wandering cells and foreign-body giant cells are seen. These cysts have various modes

of origin. The more superficial ones are apparently retention cysts in sebaceous glands. The deeper cysts represent embryonic inclusions. Occasionally, following a previous operation, misplaced epidermis may give rise to such cysts. Cheatle and Cutler have illustrated such a case.

Malignant change resulting in squamous-cell carcinoma is more common in mammary epidermoids than similar cysts found elsewhere in the body. In addition to the 28 benign cysts, there were

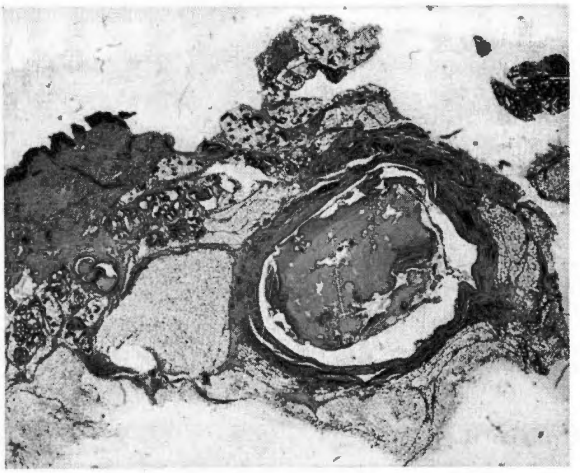


FIG. 308. Cross section of the lesion shown in Figure 307.

9 cases in which squamous-cell carcinoma apparently developed under these conditions. (Figs. 309, 310.) Elsewhere in the body, among 400 cases, only two epidermoid cysts underwent malignant change. The figures given by most authors for the incidence of malignancy in these lesions is 5 per cent (Caylor).

Simple excision suffices for benign epidermoids. Squamous-cell cancer developing in such a cyst is usually of low-grade malignancy, and the majority are cured by radical mastectomy. Only one of the nine patients with this type of malignant growth is known to have died of metastasis. One patient died three years after treatment, of an unstated cause. The other seven cases remained well beyond the five-year period.

Sweat-Gland Tumors

Since the breast, from the standpoint of phylogeny, is a modified sweat gland, it is difficult to distinguish between true sweat-gland tumors derived from the appendages of the skin and mammary

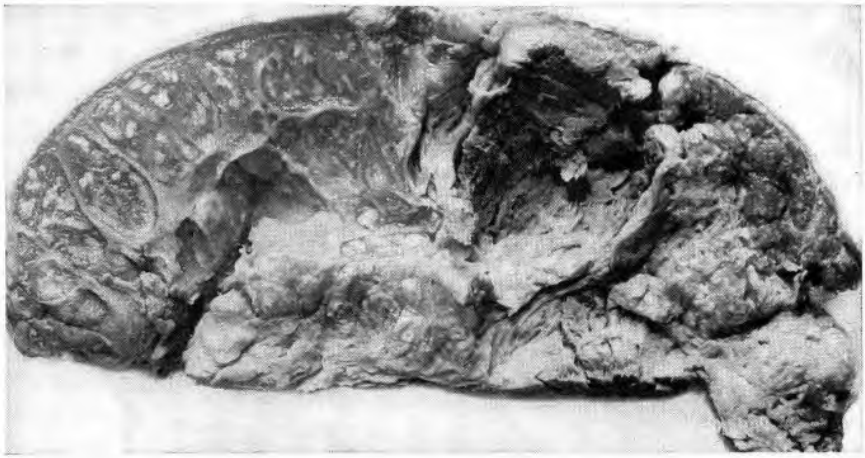


FIG. 309. Gross specimen of squamous cell cancer occurring in a dermoid cyst.

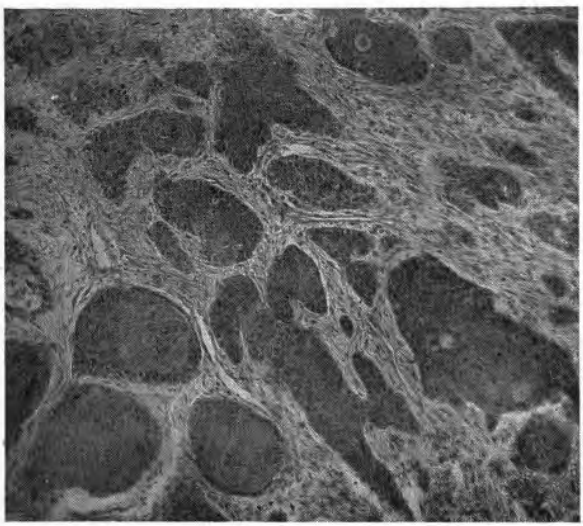
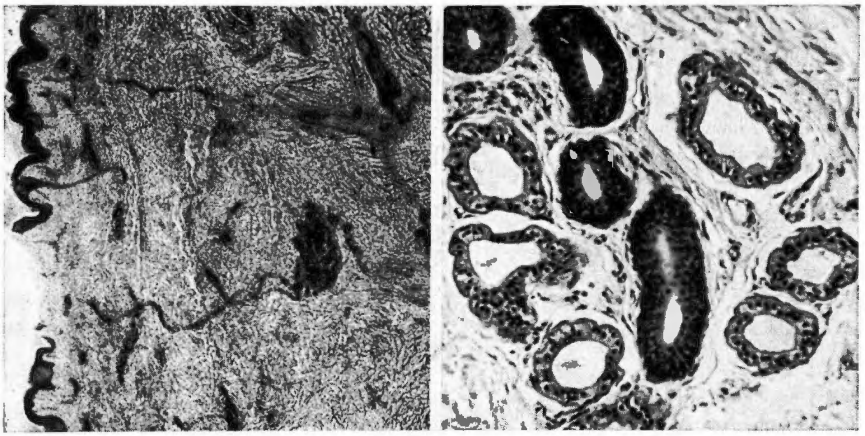


FIG. 310. Photomicrograph showing the wall of a dermoid cyst which is undergoing malignant change.

tumors resembling the sweat glands. Metaplasia in mammary epithelium or degenerative changes in secreting cells may simulate the structure of the sweat glands. Despite the absence of satisfactory distinguishing features, numerous observers have attempted to separate a group of tumors of the breast that may be classed as "sweat gland in origin" (Krompecher, Creighton, Lee, Pack and Scharnagel).

The sweat glands are divided into two types, the large apocrine glands and the small eccrine glands. The large apocrine variety is

FIG. 311 FIG. 312



Normal Sweat Glands.
FIG. 311. Small coiled glands of the eccrine type.
FIG. 312. Large apocrine sweat glands.

prominent in the axilla, pubis, anus, external ear and in the areola of the breast. The eccrine glands are most frequent in the derma and are also found in a superficial location in the areola. The eccrine glands are easily distinguished by their small alveoli, lined with several layers of small oval cells, although transitional types between this and the apocrine glands with large alveoli lined by cuboidal or columnar cells with eosinophilic cytoplasm are found (Figs. 311, 312).

Eccrine-Gland Tumors. Benign adenomas of eccrine glands may occur superficially in the region of the areola. These are small circumscribed nodules which grow slowly and are painless. They are found also in the skin and subcutaneous tissues overlying the mammary gland, and in some of the reported cases similar tumors co-existed in the region of the scalp and elsewhere in the skin. Infection or irritation is usually the only reason for their removal.

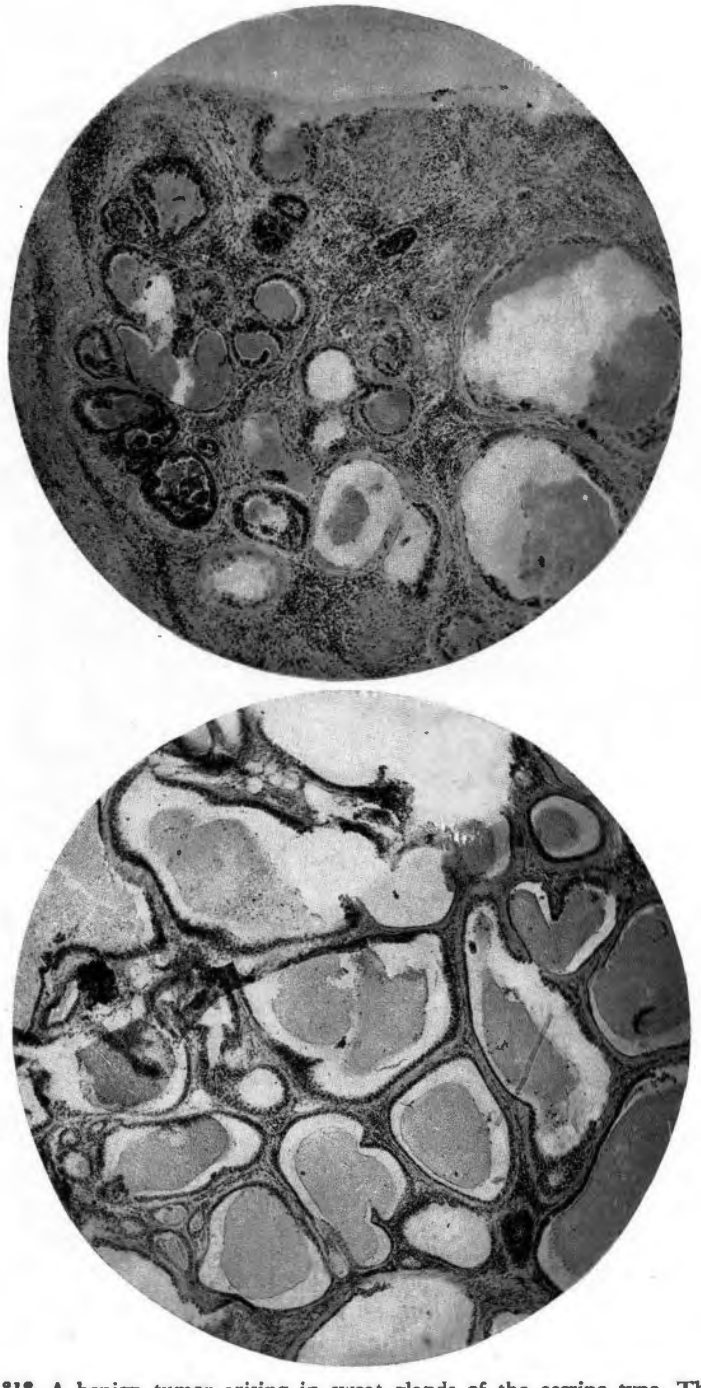


FIG. 313. A benign tumor arising in sweat glands of the eccrine type. The photomicrographs show the structure of a small adenomatous tumor occurring just beneath the areola that produced retraction of the nipple. The unusual microscopic appearance and the retraction of the nipple led to an erroneous diagnosis of adenocarcinoma.

Papillary formation or malignancy is excessively rare. The gross pathology of these tumors is quite uniform. They are small, white, circumscribed growths faintly lobulated in appearance and are often multiple. Microscopically, the adenomatous change is characterized by the reduplication of well-formed acini lined by several layers of small cylindrical cells with an intact basement membrane (Fig. 313).

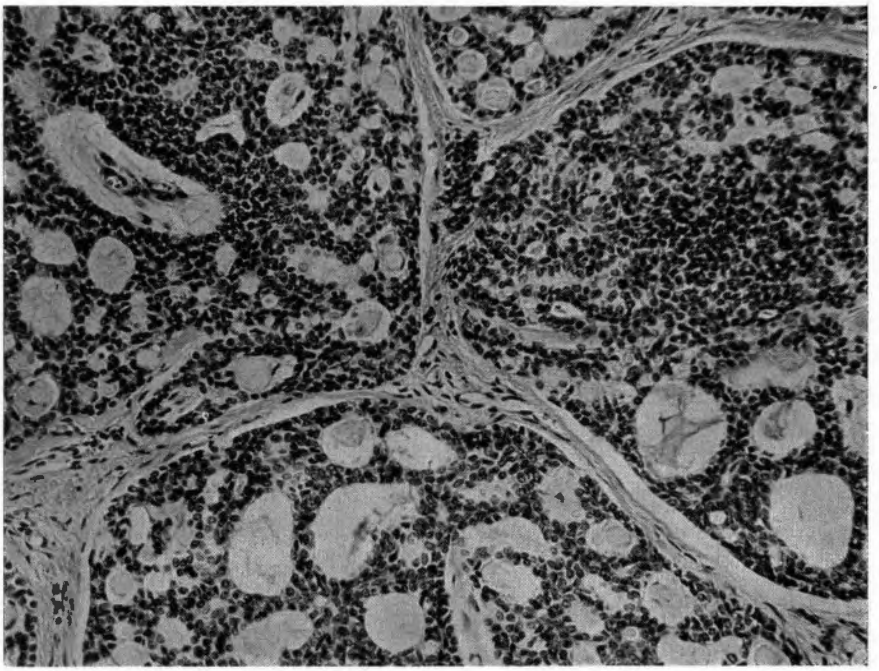


FIG. 314. Adenocystic basal cell cancer, probably of sweat gland origin. This type of cancer is rare in the breast but resembles the more common adenocystic basal cell cancers of the skin which arise in the eccrine glands.

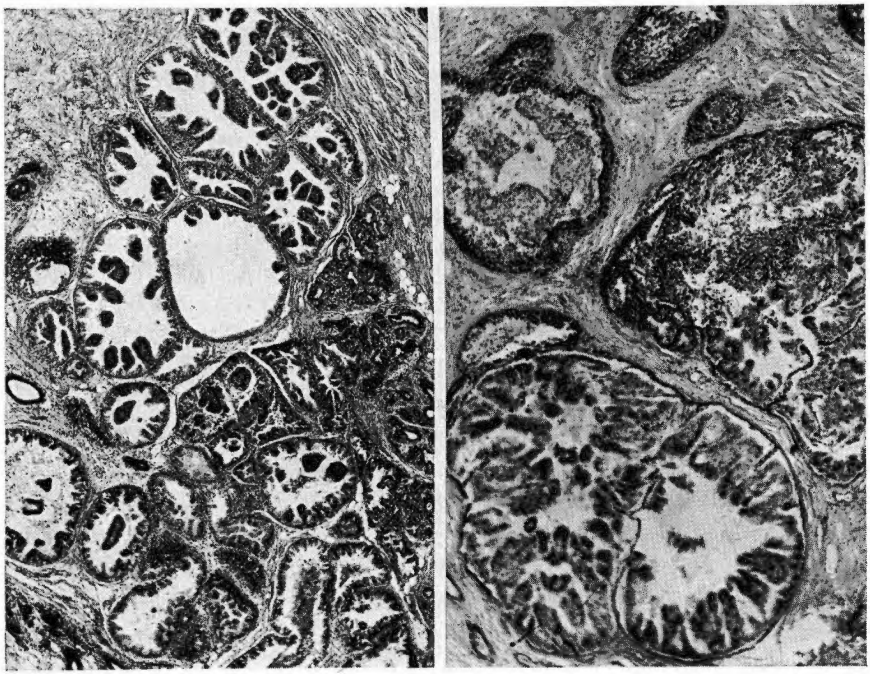
Slowly growing malignant tumors of this type have been described. The rare adenocystic basal-cell cancers of the breast probably belong to this category. These are as a rule nonmetastasizing lesions resembling adenocystic basal cancers of the skin. Such a tumor is illustrated by Lee et al., as of sweat-gland origin. There are four such cases in the author's series (Fig. 314).

Apocrine-Gland Tumors. Benign and malignant tumors of the apocrine sweat glands may occur in the subcutaneous tissues of the body particularly in the region of the neck and back of elderly adults. These take the form of papillary cystadenomas and papillary adenocarcinomas. The latter are often extremely vascular.

Tumors of this variety are apparently rare in the mammary gland. This, however, is not the opinion of some authors who find a close relationship between the pale-staining duct cells (so-called pale epithelium) of benign and malignant tumors and that of the apocrine glands (Lee, Pack and Scharnagel).

In the author's opinion, an attempt to separate some of the smaller blue-dome cysts with pale, columnar epithelial lining into

FIG. 315 FIG. 316



FIGS. 315-316. Benign tumors of the aprocrine sweat-gland type. The photomicrographs show the character of two small encapsulated mammary tumors with a histologic structure resembling the aprocrine sweat glands.

a separate class, distinct, from cystic disease, is without clinical significance. That the majority of these are physiologic or metaplastic changes in mammary epithelium (as suggested by Dawson) is indicated (1) by the finding of both mammary-duct epithelium and cells of the "pale" type in the lining of the same dilated acinus or duct (2) by the production of such cysts in normal mammary structures in the rat and monkey by the administration of estrogen (Figs. 317-319) and (3) by the marked increase in the type of epithelium in mammary fibro-adenomas of long standing. Menville,

in going over the sections of the cases of cystic disease which are reported in Chap. 10, found 32 cysts of small size which he believed were of the apocrine variety. These originated deep in the breast, apparently from basal cells of the mammary tubule which had undergone sweat gland metaplasia. Aside from their microscopic appearance, there were no clinical or pathologic distinguishing features. However, a group of five cystic adenomas near the nipple, because undoubtedly of sweat-gland origin, are worth reporting.

These were small cystic tumors, 0.5 to 1 cm. in diameter, situated just beneath the areola. The patients were in the childbearing period, 20 to 44 years of age, and had noted the presence of a painless swelling for periods varying from two to four years. The lesions were treated by simple excision and did not recur. In the gross they were encapsulated cystic nodules with one or more papillary infoldings. Under the microscope one or more layers of characteristic large eosinophilic columnar cells rested on a membrane of smooth muscle fibers (Figs. 315, 316).

Lee, Pack and Scharnagel who have sought to widen the category of sweat-gland cancers, have included in this group cases of every variety of mammary cancer, such as "bulky adenocarcinomata; the papillary, intraductal and intracystic carcinomata; the medullary carcinomata; the carcinoma simplex; and even scirrhous carcinomata of the breast."

The classification of duct cancers with large clear cells, of comedo cancers, and of papillary adenocarcinomas with columnar eosinophilic cells among so-called sweat-gland cancers would mean, according to Ewing, that approximately 25 per cent of all mammary cancers originate from sweat-gland structures. In the author's opinion true sweat-gland cancers of the breast are rare and have more sharply delimited pathologic features.

Sweat-gland cancers of the breast are papillary or alveolar carcinomas with large eosinophilic or pale cells often with swollen bizarre nuclei (Fig. 509). The cells rest on a basement membrane which may be composed largely of smooth muscle. As pointed out by Lee and his co-authors, these tumors often have a yellowish color in the gross, occur in the region of the axillary prolongation of the breast, in the submammary fold, or beneath the nipple and are more frequently seen in swarthy brunettes or in the colored race. In the cases studied by the author there was no characteristic age distribution. The duration of the tumor varied from several months to one or more years and in size from 2 to 6 cm. in diameter.

The tumor was usually described as freely movable, circumscribed

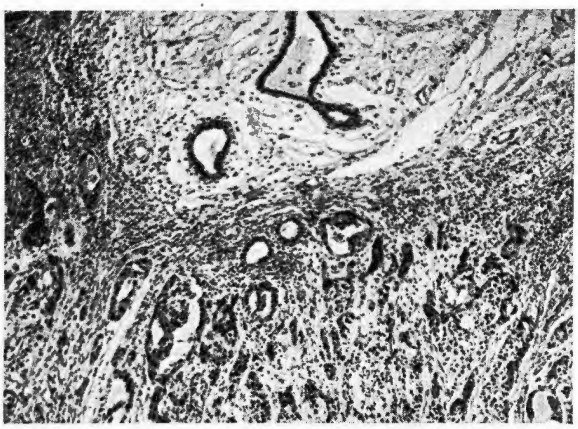


FIG. 317. Photomicrograph of sweat-gland cancer of the breast. The tumor cells have a glandular arrangement and the adjacent mammary tissue has a characteristic fibromyxomatous hypertrophy.

FIG. 318

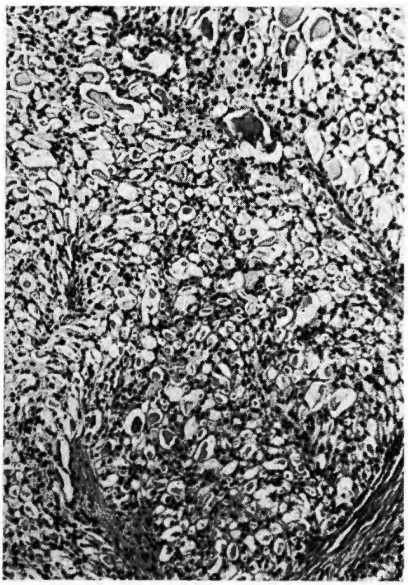


FIG. 319

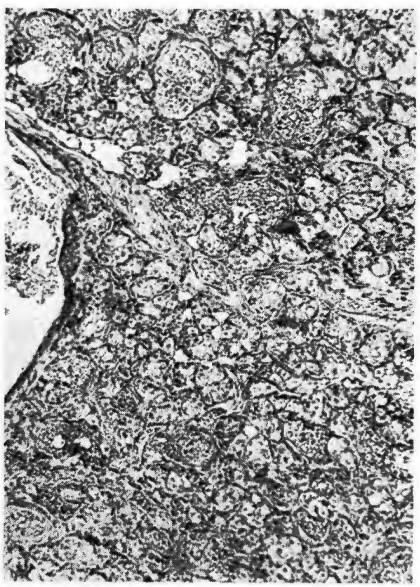


FIG. 318. Photomicrograph of a sweat-gland cancer arising in the apocrine glands of the axilla in a woman 54 years old.

FIG. 319. Cancer of the sweat-gland type experimentally produced in the rat by combined injections of estrogen and testosterone propionate (compare with Figure 318).

but not encapsulated, with dimpling or attachment to the overlying skin. The consistency varied from firm to cystic or fluctuant. The characteristic microscopic features include a papillary or alveolar structure with varying degrees of vascularity, papillary tufts or alveoli composed of large cuboidal or columnar cells with pale staining or eosinophilic cytoplasm, and a stroma containing fibers of smooth muscle, or a surrounding zone of pale-staining fibroadenomatous tissue (Fig. 317). The tumor cells have large dusty nuclei and there are many large, degenerating forms with frequent mitotic figures. Strands of smooth muscle may traverse the tumor right next the epithelium. In about one-third of the cases the original microscopic note stressed the resemblance to so-called hypernephroma of the kidney. In the more slowly growing tumors characteristic sweat-gland structures were visible at the margin. (See Figs. 507, 508, Chap. 26.) Although the large size of the cancer cells gave the impression of a Grade-IV malignancy when the sections were first examined, 67 per cent of the patients survived the five year period following radical mastectomy. These tumors are described in more detail in Chapter 26.

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PART V

MALIGNANT MAMMARY TUMORS

ORIENTATION

Following the childbearing period in women, the probability of the development of mammary carcinoma steadily increases, approaching 1 per cent beyond the sixth decade. Once the disease becomes manifest the average duration of life is four years. Radical surgery as practiced since the end of the 19th century has enabled one-third of those afflicted to survive treatment by more than five years and modern methods of irradiation have added to the number of favorable results. With the accumulation of additional information, it has become possible to demonstrate from clinical and experimental data conditions which predispose to the development of the disease and factors which influence its rate of growth and spread. Follow-up studies have made available data by which to judge the relative merits of the various accepted modes of treatment. It has become increasingly evident that mammary cancer comprises not one, but a group of carcinomas and that the various stages of development required for the mature functioning gland provide a series of separate conditions for the origin of different forms.

In Part V, devoted to malignant mammary tumors, sarcoma of the breast which behaves quite differently from mammary carcinoma is first considered. This is followed by chapters on the general nature of mammary carcinoma, by a chapter on the pathology of the disease, and by chapters devoted to the individual forms of mammary cancer. Treatment is discussed in detail in the chapters of Part VI.

Generalizations in regard to mammary carcinoma are usually predicated upon a single form of the disease, infiltrating or lobular cancer, which is referred to as scirrhous in the older literature. As will be seen from a comparison of the charts shown in Figures 373 and 384, in Chapters 19 and 21, respectively, and in Table XLIX, the circumscribed forms of adenocarcinoma, which are one-fifth as frequent as the infiltrating form, have entirely different growth characteristics and hence different clinical features with a decidedly better prognosis. These circumscribed adenocarcinomas which include the comedo, papillary and mucoid forms arise from the same lobular epithelium as the more malignant infiltrating form but have reduced potentialities for growth because of the limitations imposed on their vascular supply. On the other hand, the groups of stratified epithelial carcinomas which include Paget's disease, pagetoid duct cancer and neomammary carcinoma arise usually from a more primitive type of epithelium lining the larger ducts which

are derived from the nipple pouch (an embryonic structure). The stratified epithelial forms differ in their diagnostic features both clinically and pathologically from the other two major groups of mammary carcinoma, but in their prognosis are similar to the infiltrating group. The rare forms of mammary carcinoma (which are of pathologic rather than clinical interest) include squamous cell, adenocystic basal cell and sweat gland carcinomas. Mammary carcinoma may arise in accessory breast tissue or in the male breast. In men the incidence of mammary carcinoma is only slightly over 1 per cent of that of women.

Although between 30 and 40 per cent of all forms of mammary carcinoma survive the 5-year period, approximately one-third of these surviving cases succumb before the end of the tenth year. Thus, about three-fourths of all cases are seen sooner or later in the hopeless, recurrent, or metastatic stage. To these must be added the acute or inflammatory forms of carcinoma often seen in pregnancy or lactation which are hopeless from their outset. Chapter 20 is devoted to this important aspect of the disease and Chapter 31 in Part VI discusses the therapy of these advanced cases. The detailed study which has been given to this phase of mammary carcinoma only serves to emphasize the importance of the application of proper diagnostic and therapeutic measures to the earlier and more hopeful stages. The advanced stages of untreated mammary cancer formerly seen could be diagnosed without recourse to microscopic studies but with the emphasis which is now placed on early recognition, microscopic study is essential to confirm and to record the presence of malignancy. For this reason, Chapter 25 has been included on the microscopic diagnosis of mammary carcinoma.

16

Mammary Sarcoma

If the epithelial and mesenchymal elements of the breast were equally susceptible to malignancy, sarcoma rather than carcinoma would be the most frequent, since the latter exceeds in amount the former except during the periods of late pregnancy and lactation.

While the total number of sarcomas of the breast is small, the pathologic variety is great. Those originating in the fibrous stroma of the gland are varieties of fibrospindle-cell sarcoma which grow to immense size and metastasize relatively late. They are of two forms: (1) mammary fibrosarcoma which is primary in the connective tissue, and (2) mammary adenosarcoma which is secondary to fibro-adenoma and contains scattered epithelial elements. Approximately one-half of all the sarcomas in the mammary gland are of these two varieties. (Table XLIII.) The other forms are sarcomas arising from fat, from vascular structures, other mesenchymal derivatives or from the nerve sheaths and mixed tumors, highly malignant

carcinosarcomas. Their variety and relative incidence is shown in the table just referred to.

Fox, who was able to find 510 mammary sarcomas in the literature, estimated their frequency as 1.6 per cent of mammary tumors. Wellbrock reported 29 sarcomas in a series of 7,763 mammary lesions from The Mayo Clinic. Sailer estimated the proportion as one sarcoma to one hundred mammary carcinomas.

In recent studies the ratio of mammary sarcomas to cancer is less than in the older literature. This is because of the exclusion of benign giant intracanalicular myxomas, formerly classed as cystosarcomas, and a group of so-called endotheliomas, now classed as highly cellular carcinomas.

The only form of sarcoma peculiar to the breast is the fibro-spindle cell form which often includes surviving epithelial elements from compressed mammary tubules. The other malignant connective-tissue tumors (lympho-, myelo-, lipo-, and myosarcoma) more frequently affect other organs or regions of the body.

FIBROSARCOMA AND ADENOSARCOMA

Mammary fibrospindle-cell sarcomas were found in 29 cases. In 18, the lesion was primary in the stroma and in 11 the growth was secondary to a pre-existing fibro-adenoma. If care is taken to exclude the so-called cystosarcomas or giant myxomas, the age incidence and degree of malignancy are within the range found in mammary carcinomas. The majority of these growths occur after the age of 40 years and the peak of incidence is between 45 and 55 years. Three patients were in their thirties, one was 13 years and another seventeen years old. Among the primary fibrosarcomas adequately followed, 10 are dead of the disease, and four well beyond the five-year period. Among the sarcomas secondary to fibro-adenoma, eight are dead and three have remained well.

Clinical Features

The distinguishing clinical features of mammary fibrospindle-cell sarcomas are the large size, the rapid growth, and the firm consistency of the tumor. Involvement of the skin or the axillary nodes is usually absent.[1] Ulceration and fungation may occur, however, usually in cases where local recurrence has followed an incomplete removal (Fig. 322). In the circumscribed mammary cancers of large size, the growth is slow, and the tumor is softer than a fibrosarcoma. In the infiltrating carcinomas with rapid growth, extension to the skin and to the axillary nodes is the rule.

1 Tumors of large size and long duration without extension to the skin or axillary glands with soft cystic portions within a firmer mass are usually benign giant myxomas.

Pain and rapid growth are the symptoms most frequently noted by the patient. In sarcomas secondary to fibro-adenoma, the patient will have noted the existence of a tumor of stationary size in the

FIG. 320

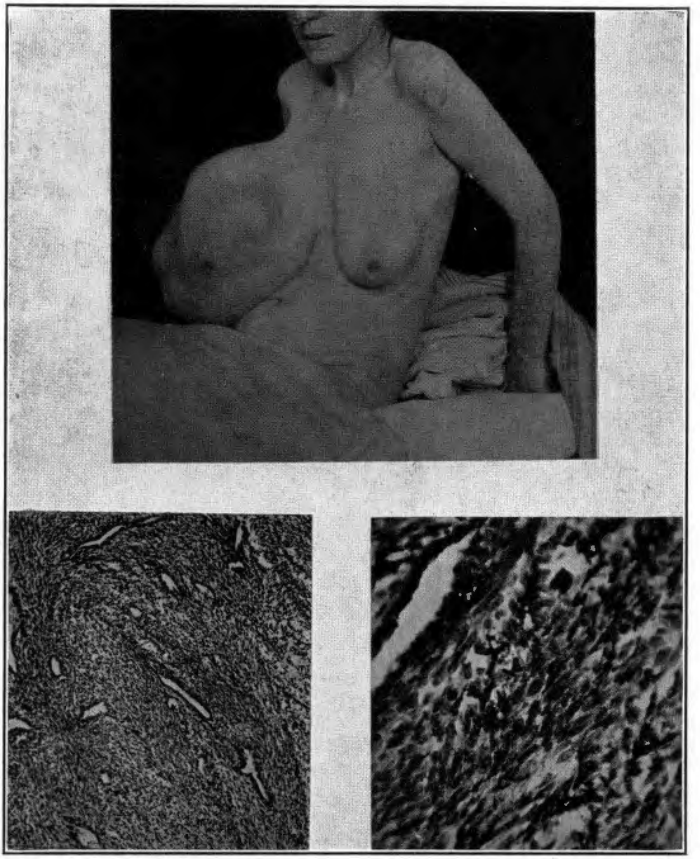


FIG. 321, A and B

FIG. 320. Photograph of a patient with fibrosarcoma.
FIG. 321 (A and B). Low and high-power photomicrograph; the growth was secondary to a pre-existing fibro-adenoma.

breast for a period of several to 10 or more years. Then a period of rapid and painful growth occurs, the tumor at the time of examination usually exceeding 5 cm. in size. The period of acute symptoms varies in duration from several months to a year.

Pathology

These tumors in the gross may be circumscribed or, more rarely, infiltrating. Usually, they are composed of dense, solid, fleshy tissue

which grows in interlacing bands which enclose softer myxomatous material. Since sarcomatous change may occur in giant myxoma, large cysts may be found within the tumor and on macroscopic examination it may be impossible to differentiate between benign

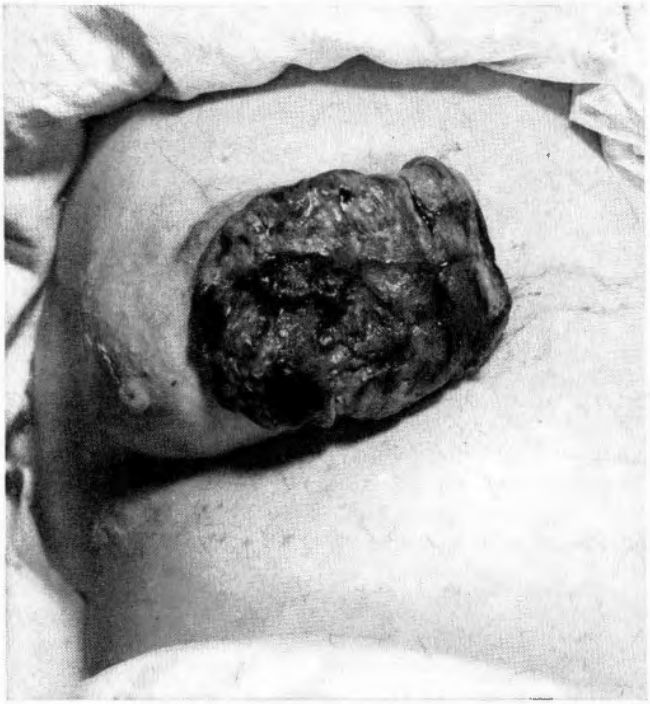


FIG. 322. Photograph of a case of fungating fibrosarcoma.

giant myxomas and similar growths which contain sarcomatous tissue. If cellular solid or infiltrating areas are found, it is important to have these examined by frozen section in order to confirm the diagnosis of malignancy.

On microscopic examination, the malignant tissue is composed of interlacing bands or whorls of fibrospindle cells with large dusty or dense nuclei. If the tumor is of the adenosarcoma type, scattered mammary tubules are found in the dense spindle-cell tissue. Occasional binucleated forms are seen. In some of these growths there is myxomatous degeneration, and pleomorphic cells with bizarre nuclei are found embedded in a loose, pale, lightly staining matrix. Sailer has classed the various microscopic forms as fibrospindle-cell, fibromyxomatous and polymorphous-cell fibrosarcoma.

TABLE XLIII

INCIDENCE AND VARIETY OF MAMMARY SARCOMA

SARCOMAS OF THE MAMMARY GLAND—62 CASES

MAMMARY FIBROSARCOMA—29 CASES

Primary in Stroma	Fibrosarcomas —18
Secondary to Fibro-adenoma	Adenosarcomas—11

NONINDIGENOUS SARCOMAS—28 CASES

Mesenchymal	Osteogenic sarcomas	3
	Liposarcomas	3
	Myosarcomas	3
Vascular	Lymphosarcomas	8
	Myelosarcomas	4
	Angiosarcomas	2
Neurogenic	Sarcomas of Nerve Sheath	4
	Melanosarcomas	1

MIXED TUMORS—CARCINOSARCOMAS—5 CASES

The microscopic differentiation between giant myxoma and fibrosarcoma is not an easy one, and cannot be made from a single section as a rule. The hard, firm areas may show characteristic fibrosarcoma with tightly packed dense and malignant nuclei, while areas of less consistency frequently show only benign myxomatous tissue. If the tumor is large, the mastectomy should be thoroughly performed, on the assumption that sarcoma may be present. This advice is based upon experience in cases where the microscopic diagnosis was in dispute and in which local recurrences took place because of an inadequate dissection.

Treatment

The treatment of choice in mammary sarcoma is simple mastectomy including removal of the pectoral fascia. The pectoral fascia should be stripped from the entire surface of the pectoralis major muscle in order to avoid the possibility of local recurrence. To insure adequate removal of this fibrous tissue, Bloodgood recommended that the pectoralis major muscle be taken as in the radical mastectomy. Axillary dissection, however, is not indicated since metastasis to this region seldom occurs. If a palpable and large gland is found, however, this may be taken for biopsy. If a sarcomatous deposit is found, the prognosis is grave but the axillary dissection does not add to the probabilities of cure and should not be performed. The fibrospindle-cell sarcomas of the breast are radio-

resistant and irradiation, except in palliative form, is not recommended.

Prognosis

Among the 25 cases of fibrospindle-cell sarcoma adequately followed seven remained well beyond the five-year period (28 per cent). Five cases suffered local recurrence following excision or radical

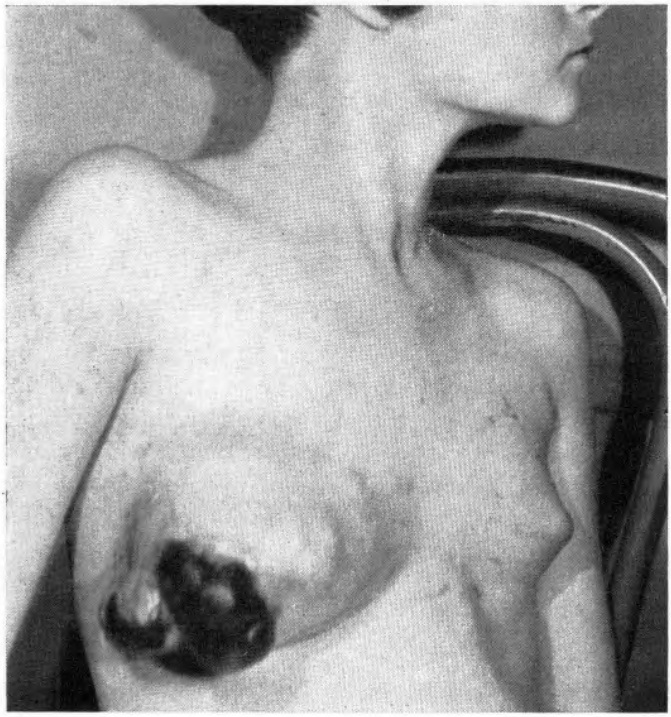


FIG. 323. Fibrosarcoma in the breast of a girl of thirteen years. Symptoms had been present for only five weeks. This was an infiltrating growth.

mastectomy, and only one of these cases remained well following a second operation. Among the fatal cases, metastasis to the lungs was usually the cause of death. One patient died from metastasis to the spinal cord, and another with brain metastasis. Extension of the disease to the opposite breast was not reported. The axillary lymph nodes were involved in one case, and in another there were metastases to the skin of the back, and in still another case sarcomatous nodules were removed from the hand. In cases of sarcoma secondary to intracanalicular myxoma, the metastasis may show a more compact and cellular tumor than the primary growth. Freedom from the disease beyond the five-year period does not assure a permanent

cure, since deaths from the disease have been reported in the sixth, seventh, eighth and ninth years.

OSTEOGENIC SARCOMA

Osteogenic sarcoma is a rare form of malignancy in the mammary gland. It was noted three times in the present series. Similar cases have been reported by Sailer, by Kurosu, and by Schreiner and Thibaudeau.

These tumors occur in elderly adults. Two of our patients were 70 and another 65 years of age. Sailer's case was 59 and the one reported by Kurosu was 80 years old. Clinically the tumors resemble mammary fibrosarcomas. They are firm, large growths (usually 8 cm. or more in diameter) and may be of several years' duration. As a rule they remain circumscribed and freely movable. In the gross, with the exception of the firm ossified portions, they resemble fibrosarcoma. Microscopically, these tumors are composed predominately of malignant spindle cells of the fibroblastic series with varying amounts of osteoblastic tissue surrounding osteoid or bone spicules. Small areas of precartilaginous connective tissue and cartilage may be seen. Apparently these sarcomas with osteogenic tissue are examples of osseous metaplasia occurring in fibrosarcoma. Kurosu's patient died shortly after discharge from the hospital, but Sailer's patient was living two years later. Occasionally in mammary fibrosarcoma, strands of precartilaginous connective tissue surrounding small islands of hyalin cartilage are seen without signs of osteogenesis. Some authors have chosen to separate these as teratomatous or mixed tumors. Like the tissue in mammary osteogenic sarcoma, however, these cells which vary in their mode of differentiation in the adult state originate from the same primitive mesenchymal elements which furnish the tissue of origin for the more common fibrosarcomas.

Treatment

Mastectomy performed in the same manner as that practiced for other mammary sarcomas is the treatment of choice for these neoplasms. (See Part VI.)

LIPOSARCOMA

Liposarcoma, which is rare in any location, has been reported in the fatty tissues of the breast by Lifrendahl and by Schreiner and

Thibaudeau. Among our cases there were three mammary liposarcomas. These occurred in women past the menopause between the ages of 52 and 65 years. At the time of examination they were rapidly growing tumors which measured 8 cm. or more in diameter. Skin changes and involvement of axillary glands were noted in two cases. As the tumor increases in size, the overlying skin becomes red, indurated, and may ulcerate as in carcinoma. Secondary nodules extending to the fat may surround the main mass or invade the opposite breast. All of the recorded cases had a rapidly fatal termination.

Liposarcoma shows extremely variable microscopic features. The spindle-cell portions of the tumor, which may be relatively prominent or sparse, have a loose myxomatous appearance. Malignant lipoblasts with foamy or granular cytoplasm and with bizarre and often immense nuclei are conspicuous features. Degenerating and binucleated forms may occur.

Treatment

Irradiation is preferable to radical surgery in liposarcoma. These tumors often respond rapidly to deep roentgen-ray therapy, administered in divided doses, but arrest rather than cure is accomplished. Since these liposarcomas may metastasize to the regional lymph nodes such regions should be included in the fields irradiated. If possible, deep roentgen therapy should be applied through multiple ports on successive days using 200 r daily for a total dose of 2,400 to 3,000 r to each field.

LYMPHOSARCOMA AND MYELOSARCOMA

The classification of mammary sarcomas as lymphoid and myeloid in character has supplanted the less accurate classification of round-cell sarcoma. These two forms of highly malignant tumors are next in frequency to the fibrospindle-cell group.

Of eight mammary lymphosarcomas, four were between the ages of 15 and 32 years and four between the ages of 42 and 63 years. The duration of the symptoms was brief in comparison with the long duration of symptoms often noted in fibrosarcoma, since they varied from six weeks to eight months only. These tumors grow rapidly, are soft or doughy in consistency and for a time remain freely movable. Rapid enlargement or multiple nodules in one or both breasts soon follows (Fig. 324). In two cases (patients 29 and 32 years old) both breasts were enlarged, tense and swollen and had a bluish tint within three months of the onset of the symptoms. The

axillary, inguinal or mediastinal lymph nodes may become enlarged and ascites and edema in the lower extremities may occur with extension of the disease to the mediastinal and abdominal lymph nodes.

In the four cases where irradiation was tried there was a response in only one. In six of the eight cases the course of the disease was rapidly fatal. One patient from whom a small nodule was excised early, followed by thorough irradiation, is alive two years after treatment. Within a period of 20 months six of the patients died

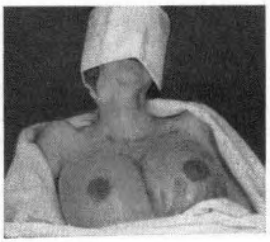


FIG. 324. Lymphosarcoma of the mammary gland.

with widespread metastatis, and one is lost. There were no significant changes in the white blood-cell count in these cases. In the two patients where both breasts were diffusely involved one had involvement in the region of the parotid gland and the other, in the submaxillary gland suggesting the onset of a Mikulicz syndrome. In both of these cases the disease developed during or shortly after pregnancy and both patients died within four months after diagnosis was established.

There were four cases of myelosarcoma. The ages of these cases varied from 30 to 61 years. The duration of symptoms varied between one and 18 months. The mammary tumor was circumscribed and protuberant when first noted, varied from 3 to 9 cm. in diameter and grew rapidly. One case responded to irradiation, another did not, in the two instances where it was tried. In two cases the axillary nodes were palpable. In a third the inguinal lymph nodes were enlarged, the patient had gastric distress, and at autopsy the intestinal tract and both ovaries were involved. There was no leukemic blood picture in these cases and the course was rapidly downhill, death occurring in less than a year.

On section, lympho- and myelosarcomas are homogeneous, cellular growths. Microscopic study shows little or no stroma. The sarcomas are composed of tightly packed lymphoid or myeloid cells of varying sizes with numerous mitotic figures. (Fig. 325.)

ANGIOSARCOMA

In nearly every instance, vascular tumors of the breast are either benign hemangiomas or highly cellular and vascular forms of mammary carcinoma. Nevertheless, malignant angiomatous tumors have been described in this organ. Borrmann reported a metastasizing

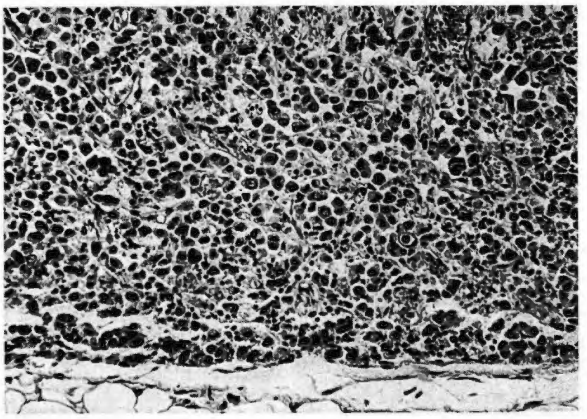


FIG. 325. Myelosarcoma of the mammary gland. The photomicrograph shows the highly cellular character of the new growth.

hemangioma of the breast, which recurred repeatedly after operation and ultimately involved the lungs. Ewing and Onsy have reported similar cases. In the present series an angiosarcoma occurred in the breast of a woman, 53 years old. This was a slowly growing cystic tumor, with involvement of the axillary lymph nodes. The second case was a large growth in an elderly woman, which had fungated and had given rise to widespread metastases.

Treatment

Deep roentgen-ray therapy is indicated in lymphosarcoma, myelosarcoma, and angiosarcoma. If the cases are seen sufficiently early the reaction may be favorable, but in the later stages there is no improvement.

MYOSARCOMA

In recent years, myosarcoma of both smooth and voluntary muscle has been recognized with increasing frequency in the mammary gland and distinguished from the so-called pleomorphic-cell sar-

comas with which they were formerly classed. Tumors of this type have been reported by Sailer, Schreiner and Thibaudeau, Leroux and Chanton, Gaudier, etc. Both the leio- and rhabdomyosarcomas are highly malignant growths which recur and metastasize with a rapidly fatal termination. The tumors are usually large solid growths occurring in middle-aged adults. In the author's series there were two rhabdomyosarcomas and one leiomyosarcoma. The leiomyosar-

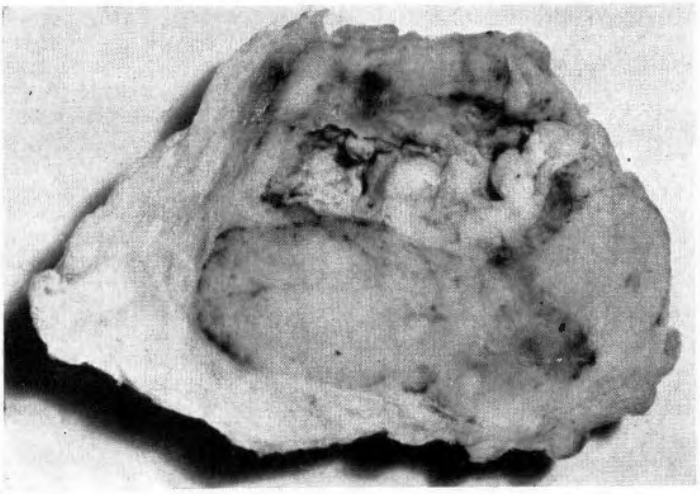


FIG. 326. Gross specimen of a case of rhabdomyosarcoma of the breast. The patient died seven months after mastectomy with metastasis to the lungs.

coma was the largest of the three, measuring over 26 cm. in diameter. The rhabdomyosarcomas have characteristic elongated spindle cells with heavy, beaded fibers; numerous tumor giant cells with bizarre nuclei and a granular cytoplasm; characteristic spider cells with dendritic processes and occasional fibrils with cross striation. (Figs. 327, 328.) The leiomyosarcomas are composed of clumped spindle cells, with heavy fibrils and occasional tumor giant cells. These tumors apparently are derived from undifferentiated mesenchyme in the stroma of the mammary gland with a predetermined tendency to differentiate into muscular structures.

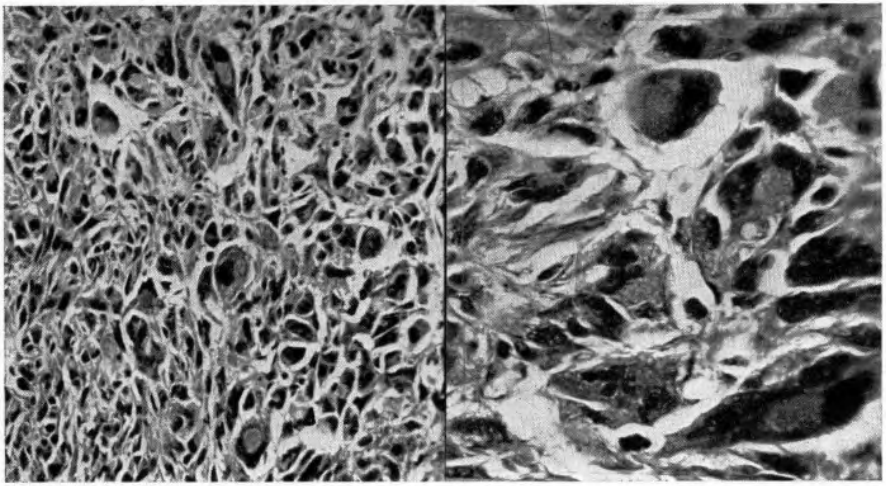
Treatment

Amputation of the breast with removal of the pectoral muscle and fascia is the treatment of choice for these growths, which are more rapid in their mode of spread than the mammary fibrosarcomas.

NEUROGENIC AND MELANOSARCOMA

In rare instances highly malignant spindle-cell tumors that are rapidly fatal are found in the breast. Some of these have the histologic characteristics of sarcoma of the nerve sheath and others may contain melanin pigment. In the present series, four cases were classified as nerve-sheath sarcoma and one as melanosarcoma. None of these patients survived the five-year period, although all were treated by radical mastectomy.

FIG. 327 FIG. 328



FIGS. 327-328. Low and high-power photomicrographs from the case shown in Figure 326.

Treatment

In these cases the axillary dissection should be included in the mastectomy in the same manner practiced for mammary carcinoma because of the tendency of the tumor to involve the axillary nodes.

CARCINOSARCOMA

Malignant tumors with a dual histogenesis comprising the characteristics of both carcinoma and sarcoma have been reported and discussed by pathologists since the time of Virchow, who termed them carcinosarcoma. In this rare group of tumors either the sarcoma or the carcinoma may be primary and stimulate the other tissue to undergo malignancy. A different interpretation of these tumors has been advanced by those who believe that a primary carcinoma

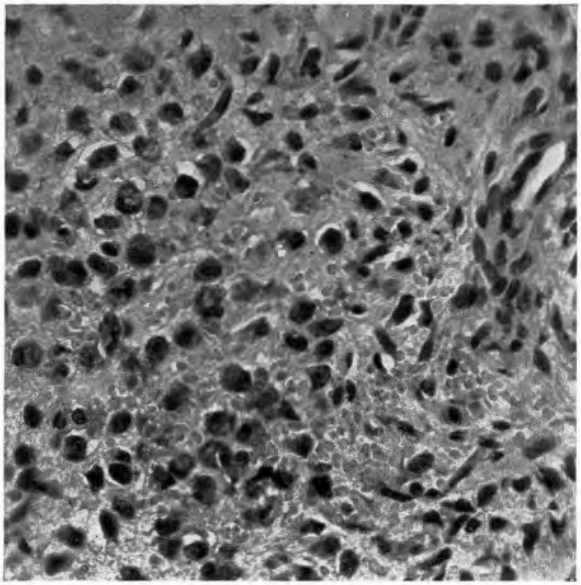


FIG. 329. Photomicrograph of a case of mammary osteogenic sarcoma.

FIG. 330 FIG. 331

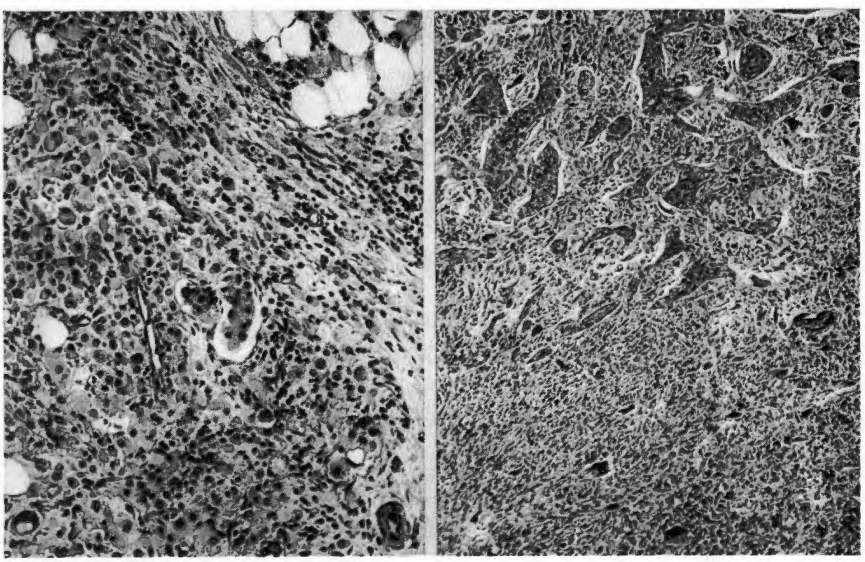


FIG. 330. Photomicrograph of a case of mammary liposarcoma.
FIG. 331. Photomicrograph of a case of so-called carcinosarcoma. Islands of mammary carcinoma undergoing degeneration and spindle cell compression are penetrating the adjacent stroma, the invading cells resembling fibrosarcoma.

may be so altered in its histologic appearance in certain portions as closely to resemble sarcoma. This is the opinion of Saphir and Vass who doubt if the carcinosarcomas are examples of compound malignancy. These authors give the following explanation for the presence of both carcinomatous and sarcomatous features in these neoplasms: Variations in the form of the carcinoma cells occur. Some assume spindle shapes and may be interpreted as cells of spindle-cell sarcoma This is particularly true in cases of squamous-cell carcinomas with transitional features; in cases with marked anaplasia of carcinoma cells; and with chronic inflammation which either leads to morphologic changes in the tumor cells or produces a connective tissue reaction, which may be regarded as the sarcomatous part, or a lymphocytic reaction, regarded as the lymphosarcoma component, of some of these tumors. The invasion of a benign connective-tissue tumor by a carcinoma is another source of error. Other instances of so-called carcinosarcomas are believed to be sarcomas which have invaded normal or metaplastic epithelial structures, the latter being interpreted as the "carcinomatous" elements.

In the five carcinosarcomas in the present series, microscopic study of the tumor showed in each case a transitional zone in which islands of cancer cells were undergoing compression or degeneration where they were invading cellular, but benign, reactive fibrous tissue. In the last analysis, therefore, these growths were interpreted as pleomorphic carcinomas with areas simulating sarcoma. (Fig. 331.)

In spite of the above observations, two separate malignancies in the same organ, one carcinoma and the other sarcoma, may and do occur. Cancer and sarcoma of the skin are seen side by side in cases of xeroderma pigmentosum, and the author has described both in the parotid gland.

TERATOMATOUS GROWTHS

Mixed and teratoid tumors of the breasts are described in the older literature, but growths containing derivatives of more than one germ layer, true teratomas, are practically unknown. In addition to the carcinosarcomas described above, fibro-adenomas or adenocarcinomas with squamous-cell metaplasia were formerly classed as teratoid growths (see Chap. 26).

Coues reported a case of teratoma of the breast which is unique. The tumor was the size of a baseball and developed in the right breast in a woman 60 years old. Gross examination showed a tumor which in places was fibrous and of bony hardness. Elsewhere, there were cystic areas and in one place alveolar processes with teeth.

SO-CALLED GIANT-CELL TUMORS

In rare instances both benign and malignant lesions of the breast have been reported as giant-cell tumors. The benign growths referred to have nothing in common with giant-cell tumors of bone but are examples of fat necrosis or xanthomatous degeneration and the giant cells in the tumor are associated with the process of lipoid phagocytosis. The malignant growths in the breast which are erroneously referred to as giant-cell tumors are examples belonging to the group of carcinosarcomas referred to above. They are usually carcinomas with areas of degeneration, having an atypical fibrous reaction. The giant cells apparently are associated with the degenerating cancerous tissue and are not part of the neoplastic process.

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17

Mammary Cancer

(Incidence and Predisposing Factors: Prognosis)

FACTORS INFLUENCING THE INCIDENCE

Predisposing Factors

Cancer of the breast ranks with cancer of the stomach, the uterus, the skin and oral mucous membranes as a leading cause of death from malignancy. Approximately 11 per cent of all forms of cancer arise in this organ. The frequency of mammary cancer in the United States, based upon the vital statistics of 1940, is shown in Table XLV. Bevan, in discussing the frequency of malignancy as compared to other mammary lesions, stated that of 300 women who, during a year, will present themselves to a general surgical clinic for examination for tumor of the breast, 100 will not have any tumor at all, 100 will have a benign tumor, and 100 will have a malignant tumor. Thus, benign and malignant tumors of the breast, in the practice of general surgery, occur with about equal frequency. This is corroborated by the data presented in Table XLIV. During the period when 2,303 benign tumors of the breast were examined, 2,554 cancers were treated. There were in addition, 971 benign lesions of the breast

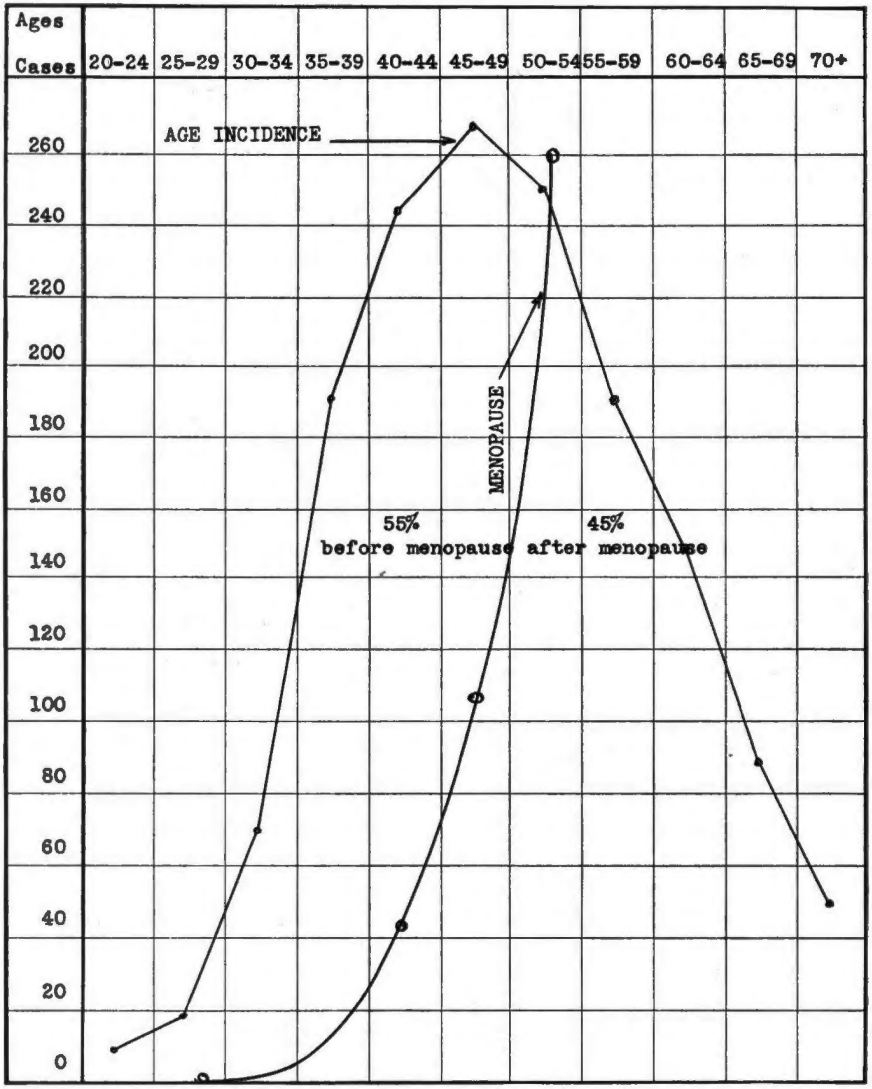

FIG. 332. Chart showing the menopausal age and the age incidence of mammary cancer. 55% of women with mammary cancer have not passed the menopause.

TABLE XLV

THE INCIDENCE OF BENIGN AND MALIGNANT LESIONS IN 6,044 BREAST CASES

TYPE OF TUMOR			TOTAL CASES
3,274 Benign Lesion of the Female Breast			
Benign Tumors and Mammary Dysplasia			2,303
Chronic cystic mastitis		1,176	
Mastodynia	375		
Adenosis	212		
Cystic disease	589		
Fibro-adenoma		600	
Giant myxoma (Cystosarcoma of Müller)		58	
Intracystic papilloma		203	
Bleeding nipple		68	
Non-indigenous benign tumors		117	
Lipomas	30		
Dermoid cysts	28		
Fat necrosis, angioma, myoblastoma, leiomyoma, etc.	59		
Galactocele		9	
Dilated ducts beneath the nipple		72	
Other Benign Lesions			971
Infectious mastitis		211	
Acute lactation mastitis	60		
Chronic lactation mastitis	64		
Plasma-cell mastitis	15		
Tuberculosis	56		
Boeck's sarcoid	4		
Syphilis	8		
Typhoid mastitis	4		
Infantile hypertrophy		6	
Virginal hypertrophy		27	
Miscellaneous mammary complaints		727	
Retracted and warty nipples			
Discharge of nipple, other than bloody			
Hypertrophy, neuralgia, cancerphobia, etc.			
2,623 Malignant Tumors of the Female Breast			
Carcinomas			2,561
Infiltrating form—lobular cancer		1,906	
Circumscribed forms: Papillary adenocarcinoma		197	
Circumscribed forms: Comedo adenocarcinoma		106	
Circumscribed forms: Mucoid adenocarcinoma		83	
Transitional cell forms: Cancer cysts and medullary cancers (Neomammary)		135	
Transitional cell forms: Duct cancers		35	
Transitional cell forms: Paget's disease		62	
Rare forms—Squamous cell, basal cell, sweat gland cancers		30	
Cancer in axilla		7	
Sarcomas			62
Mammary sarcoma		62	
Fibrosarcoma and adenosarcoma, liposarcoma, myosarcoma, osteogenic sarcoma, lympho- and myeloid sarcoma			
147 Lesions of the Male Breast			
Gynecomastia (Fibro-adenoma of male breast)		108	
Cancer in male breast		30	
Infections of male breast		9	

which did not give rise to a palpable tumor. Therefore, in a woman with a palpable nodule of the breast, the probabilities of cancer are 50 per cent.

Age

The age distribution of cancer of the breast has been computed by various observers from both hospital records and mortality statistics. On the basis of hospital records, the highest incidence is in the decade from 40 to 49 years. Taylor has estimated that 73.5 per cent of mammary cancers occur in women past the age of 40 years. As pointed out by Nathanson and Welch the "hospital population of mammary cancer shows a lower age incidence than that of the community at large." (Fig. 332.) These authors find that there is an increasing susceptibility with advancing age. The curve rises steadily, reaching a maximum in the highest age group. The probability of mammary cancer in women between the ages of 75 and 79 years is more than ten times as great as between the ages of 35 and 39 years. (Table XLVI.) Age, in itself, therefore, is a predisposing factor.

Hawkins found that mammary cancer occurs on an average of about 5 years earlier in negro women than in white women. The mean age of white women in his series was 53.7 years, and in colored females, 48.3 years.

TABLE XLIV

FREQUENCY OF CANCER IN THE VARIOUS ORGANS

(Based on United States Vital Statistics, Bureau of Census, Department of Commerce)

ORGAN	PER CENT—ALL FORMS
Stomach	21.7
Bowel	18.5
Uterus	12.0
Breast	11.2
Skin and oral cavity	10.2
Other gastro-intestinal organs	4.4
Other gynecologic organs	2.1
Male organs	4.7
Urinary organs	4.8
Respiratory tract	1.9
Nervous system	1.7
Vascular and lymphatic tissues	1.4
Bones and supporting tissues	1.2
Embryonal tumors	0.1
Miscellaneous metastatic tumors (source undetermined)	4.1

TABLE XLVI

DEATHS AND DEATH RATES

Per 100,000 from Cancer of the Breast
White Females in the United States, 1934–1936

AGE GROUP	DEATHS	DEATH RATES PER 100,000 WHITE FEMALES
30 to 34	646	5.0
35 to 39	1,633	13.5
40 to 44	2,817	24.1
45 to 49	4,046	39.5
50 to 54	4,875	55.6
55 to 59	5,080	69.2
60 to 64	4,925	86.0
65 to 69	4,337	99.0
70 to 74	3,486	114.0
75 to 79	2,655	141.0
80 to 84	1,493	164.4

Ovarian Function

The importance of ovarian function in relation to cancer of the breast is stressed by Olch. He computed from a study by various authors that 71.7 per cent of normal women pass through the menopause between the ages of 40 and 50 years. In 342 cases of cancer of the breast he found that 54.7 per cent passed through the menopause after the age of 50 years. His figures for the menopausal age in women with cancer of the breast are:

Under 40	10
40 to 44 years	41
45 to 49 years	104
50 and over	187
Total	342

When the menopausal ages found by Olch are plotted against the age distribution of mammary cancer in our series it is found that slightly more than 55 per cent of women with cancer of the breast have not yet reached the menopause (Fig. 332). The importance of continued ovarian function for mammary cancer is also emphasized by Herrell, who found that only 1.5 per cent of women with mammary cancer were castrates, whereas in the control group of the same age 15.4 per cent had been sterilized. The influence of ovarian function is also apparent in the sex distribution of mammary cancer. Compared with its frequency in the female, carcinoma is exceedingly rare in the male. It occurred in about 1 per cent of our series of 2,600 cases of mammary cancer. Nathanson and Welch found 1.1 per cent of males in their series and Pack and LeFevre, 1.5 per cent.

Marriage, Childbearing and Lactation

Whether cancer of the breast is relatively more common in single than in married women is not thoroughly established, but most reports indicate that the reverse is not true. Lewis and Rienhoff, in going over the same material as that studied by the author, found 87.3 per cent married and 12.4 per cent unmarried women. For women in the normal population they found 90 per cent married and 10 per cent single in the same age groups and concluded that this was an insignificant difference. This is in accord with our own findings. (Table LVII.) On the other hand, Warren states that in the statistics of Massachusetts, the mortality rate for mammary cancer is 78.1 per 100,000 for single women over thirty years as compared to 55.5 for those not single. Lane-Claypon and also Semb noted similar findings. Lane-Claypon found 18.3 per cent of cancers in single women over 40 years, yet these constituted only 11 per cent of the normal population. These figures are supported by Pikkarainen, who found 23.3 per cent single and 76.1 per cent married women in 1,105 cases.

There is evidence to indicate that in married women who have mammary cancer there is a relatively low percentage who have borne children or who have nursed them. Antoine and Pfab found that only 576 (50.9 per cent) of 1,131 cases had borne children. Of these only 241 (21.3 per cent) gave a history of lactation. Wainwright found 28.2 per cent of married women with cancer had never lactated compared with 15.7 per cent among a control group. In Semb's material 16.5 per cent of the married women were childless, and in the remaining cases the number of women with relatively few children was significantly high. MacDonald found that 59.2 per cent of women with mammary cancer had borne children compared to 66⅔ per cent for those in the general population. Among the parous group 42 per cent had had abnormal lactation, compared to 20 per cent in a control group. Wainwright found failure of lactation in 40 per cent; twice that among the control group. The fertility of married women with mammary cancer was lower than that in the normal population in our records. (Table XLVII.)

Previous Benign Tumors

Cancer of the breast is more common in women who have had a previous benign mammary tumor, such as intracystic papilloma or forms of chronic cystic mastitis or fibro-adenoma. Warren found "the cancer rate for women with pre-existing breast lesions is 4.5 times as

TABLE XLVII

MARITAL DATA IN 1,041 CASES OF INFILTRATING MAMMARY CANCER

Single		125
Married		916
Per cent single	12%	
Percentage of single women over 20 in population 1920 census	10.3%	
Married, no children		192
Married, miscarriages		34
Married, one child		192
Married, two or more children		498
Average number of children per family		2.30
Average number of children per family (1920 U. S. Census)[1]		3.75

[1] Control figures from the 1920 U. S. census were chosen since the number of cancers in our series prior to and subsequent to 1920 were approximately equal. The figure 3.75, thru Courtesy of Dr. L. I. Dublin.

great as for all women; and this predominance is especially marked in the decades below fifty years of age." This was in a series of 604 cases with cystic mastitis, intracystic papilloma, and fibro-adenoma, traced for an average period of 9.3 years. Among this group there were 513 patients with forms of chronic cystic mastitis who developed 25 mammary cancers; 21 with intracystic papillomas, in whom 3 mammary cancers developed; and 70 with fibro-adenomas in whom 2 developed mammary cancers.

The findings of Warren are similar to those in our own series. In 54 cases of benign intracystic papillomas, treated by excision and followed on an average of ten years, the incidence of mammary cancer was 6 per cent; and in 192 cases of adenosis selected from chronic cystic mastitis and followed for a similar time, the incidence of mammary cancer was 3 per cent. In 201 fibro-adenomas, similarly followed, the incidence of mammary cancer was 1 per cent. Dublin has calculated the risk of mammary cancer in the normal population of the same age groups for a period of ten years as 0.42 per cent. This corresponds closely with the figure of Warren[1] for the normal population of the state of Massachusetts, which is 0.58 per hundred for a 10-year period for women in this age group.

Virginal Hypertrophy and Excessive Mammary Development

The relation of excessive mammary development at puberty to the subsequent development of mammary carcinoma in the affected breast in later life is seldom discussed in the literature. In 24 cases of virginal hypertrophy with an onset during adolescence, in the author's series, two subsequently developed mammary carcinoma 17 to 20 years after the onset of the enlargement (Chap. 4, p. 116).

[1] Dublin's figure is based on the actual number of cancers recorded; Warren increased the figure to allow for undiagnosed cases.

On the other hand, in 1400 cases of infiltrating mammary carcinomas in which a reasonably complete clinical history was recorded 16 cases gave a history of virginal hypertrophy or excessive breast development dating from puberty (Chap. 18, p. 422). A relationship between excessive development and mammary carcinoma has been noted by other authors in regard to carcinoma of the male breast. Gilbert in 47 cases found cancer associated with hypertrophy in nine patients. Ewing believes that unusual development in the male breast, regardless of its inciting cause, may predispose to cancer (Chap. 27, p. 628).

Previous Mastitis

Kilgore has stressed the importance of residual lactation mastitis in the etiology of mammary cancer. Prass found a history of puerperal mastitis in 6 per cent of 617 mammary cancers. This is about the incidence in our cases (Chap. 20). He also found that in approximately 2 per cent of the cases the cancers developed at or near the site of excision of a benign breast tumor.

TABLE XLVIII

FREQUENCY OF CANCER OF THE BREAST AMONG RELATIVES OF CANCER PATIENTS AND RELATIVES OF CONTROL POPULATION[1]

	RELATIVES OF CANCER PATIENTS (a)		CONTROL POPULATION	
	HEALTHY	DISEASED	HEALTHY	DISEASED
Mothers	128	6 (4.48%)	768	2 (0.26%)
Sisters	274	6 (2.14%)	395	..
Aunts	158	6 (3.65%)	..	..
Cousins	218	4 (1.80%)	..	..
Grandmothers	65	1 (1.52%)	..	..
Total	843	23 (2.65%)	1,163	2 (0.17%)

[1] After Martynova.

Heredity

Mammary cancer, like other forms of malignancy, occasionally affects several members in the family of one or more generations. Whether this is coincidence in a disease which is relatively common or whether it has a genetic significance is yet to be established. MacDonald found that among patients with the disease who gave a family history of cancer there were three times the expected number with relatives who had breast cancer. Martynova studied the family histories in 201 patients with cancer of the breast. In all categories

of female relatives of these patients, mammary cancer was more common than in the control population. In the mothers of these patients the frequency was 18 times that of mothers of a similar age in a control group. (Table XLVIII.) Martynova found that not only mammary cancer but other forms of malignancy were more common in these relatives.

Sampson Handley reports a family of five sisters. Three sisters had carcinomas in both breasts. The fourth had an incipient cancer following cystic mastitis, and the fifth remained well after irradiation of the breast for cystic mastitis. Munford and Linder report twin sisters who, at the age of 91 years, both developed cancer in identical locations in the left breast. Three other cases of breast cancer occurred in the two preceding generations in this family. We have selected a typical family from our own series, illustrating the occasional marked family tendency to carcinoma of the breast. The mother's sister had died of mammary cancer at the age of 48, and the mother died of metastatic cancer of the liver and spleen at the age of 75 years, the primary source not determined. In the present generation there were six brothers, four well, one died of cancer of the bladder, and the other of cancer of the larynx. There are three sisters—all three of whom have had operations for mammary cancer, microscopically verified. Two of these have died, one with metastasis to the lungs, and the other with metastasis complicated by primary cancer in the large bowel. The third sister is well, three years after a radical mastectomy.

Cancer of the Other Breast

Women with cancer of one breast develop cancer of the opposite breast in 7.5 per cent of the cases according to Kilgore. Leo states that in Italian clinics the cases of bilateral mammary cancer are between 1 and 2 per cent of the total at the time of examination, but in a large autopsy material 7.8 per cent have bilateral involvement. Lewis and Rienhoff, in reviewing the material studied by the author, found that 4.7 per cent of mammary carcinomas ultimately become bilateral and 1.5 per cent were bilateral on admission. Our own figures correspond to those of Kilgore and of Leo (see Chap. 20).

ETIOLOGY OF MAMMARY CARCINOMA

In America there are 15,000 deaths annually from mammary carcinoma and since the disease has an average duration of 4 years there are approximately 60,000 cases under observation at any one time. The relative frequency of malignancy in this organ as compared to other structures such as the muscles, bone, liver, etc., throws

some light on the etiology of the disease. Not only is malignant disease prevalent in the breast but benign hyperplasia in the form of cystic mastitis and benign neoplasia in the form of fibro-adenoma and papilloma is likewise common. Thus, the three major clinical conditions in the breast are mammary dysplasia or cystic mastitis, benign tumors, and mammary carcinoma.

These forms of hyperplasia and neoplasia are all disturbances of the regenerative capacity of the affected tissue. Therefore, one would expect such disturbances to be most common in the organs in which tissue regeneration is continued into adult life, and in which this capacity is repeatedly stimulated either by external influences in direct contact with the involved structures or by hormonal influences from within. A brief consideration of the facts indicates that this is so. Thus, hyperplasia and neoplasia are frequent in the epidermal tissues of the skin and oral cavity and in the epithelial lining of the digestive tract which are exposed to the wear and tear of outside influences which come into direct contact with these tissues. The same conditions are also prevalent in the accessory sexual organs, the breast, the uterus and the prostate which are regulated in their growth and development throughout sexual maturity by the glands of internal secretion (Table XLIV).

While regenerative capacity and its repeated stimulation are controlling factors in hyperplasia and benign neoplasia, additional factors are concerned in the development of malignancy. The degree of specialization in the affected tissue conditions its susceptibility to cancer. Thus, in the relatively undifferentiated mesenchymal stroma of the breast and uterus benign tumors are common but malignancy is relatively rare. Malignancy is also relatively rare in the epithelial lining of the small intestine which in its development represents a continuation of the lining cells of the primitive digestive tube, while it is more common in the highly differentiated glandular tissue of the pylorus and rectum.

The susceptibility of the breast to hyperplasia and benign neoplasia, therefore, is an expression of its regenerative capacity and the repeated stimulation of this capacity by endocrine influence. The susceptibility of this organ to malignancy is dependent upon both of these factors, and, in addition, upon the degree of specialization in the mammary epithelium. Apparently specialization imposes a definite restriction on the capacity for continuous regeneration in mammary epithelium. However, a study of the embryology of the breast (Chapter 1) and the experimental production of mammary carcinoma with endocrine substances (Chapter 34) indicates that this restriction brought about by specialization is not placed upon

the most highly differentiated structures of the organ but rather upon their immediate predecessors, which represent more primitive stages in the process of development. Thus, in the breast the regenerative capacity of the lobules or milk secreting units is relatively unlimited, but the more primitive structures, the mammary ducts, and the larger milk channels derived from the nipple pouch have more abbreviated capacities (perhaps to conserve epithelial elements for the more recently developed lobular structures). This observation is readily proved experimentally. Luteal or luteal-like hormones such as progesterone and testosterone which are primarily stimulants of lobular development can not be used for the production of mammary carcinoma. On the other hand, estrogen which acts primarily on the ducts and tubular structures is a potent carcinogenic agent for the mammary gland when applied in intense, prolonged doses.

As far as can be determined from clinical and experimental evidence, any influence which activates regeneration in the mammary tissue diminishes the normal margin of safety in the gland and brings the tissue nearer to the end point where normal regeneration and repair are no longer possible. Thus, chronic lactation mastitis, mammary hyperplasia, benign neoplasia and age itself may ultimately exhaust normal regeneration and aid in the precipitation of a malignant growth. The clinical evidence indicating that these factors predispose to mammary carcinoma has been summarized in the preceding pages of this chapter.

In the past decade experimental cancer research has demonstrated several factors involved in the development of spontaneous and induced mammary carcinomas in mice and rats. An inherited susceptibility to the disease in mice has been demonstrated by the inbreeding of so-called cancer strains. This inherited susceptibility has been demonstrated in human carcinoma as pointed out above. An estrogenic hormonal influence also has been repeatedly demonstrated in mice and rats, and also in rabbits. (See Chapter 34.) This estrogenic influence which predisposes to mammary carcinoma explains the increased prevalence of mammary carcinoma in women with delayed menopause; the low percentage of women with mammary cancer who have a history of surgical castration; and the relatively high incidence of mammary cancer in women as compared to men (a ratio of 100-1). A further estrogenic influence, predisposing to mammary cancer, is found in single or childless women. In these individuals the intense luteal hormonal influence of pregnancy which counteracts the action of estrogen on the breast is lacking. Moreover, in such cyclic women there is a premenopausal decline in the ovulatory function with absence of corpus luteum formation and a resulting hyperestrinism. These are the women, as pointed out in Chapter 11,

who are prone to develop the various forms of cystic mastitis or mammary dysplasia.

It can be shown experimentally that either previously intense estrogenic stimulus in early life or a continuous moderate overstimulation over many months will render the rat's breast more susceptible to mammary carcinoma if a high dose of this hormone is given for a short period in later life. In similar fashion it is probable that in women whose breasts have been subjected years previously during adolescence to intense estrogenic influence or during the years of sexual maturity to a more moderate hyperestrinism, the intense hormonal influence of the menopause may precipitate mammary carcinoma. In confirmation of this the incidence of mammary carcinoma, as we have seen, is higher than the expected figure in patients with virginal hypertrophy or those with forms of cystic mastitis.

A third factor which has been demonstrated for mammary carcinoma in mice is the so-called milk influence or milk inciter of Bittner. In mice of a non-cancerous strain which are allowed to nurse from mothers of a high cancer strain, the incidence of mammary carcinoma is increased through some factor present in the milk. The identity of this substance is obscure. It has a high molecular weight, it is water-soluble, and probably a protein. Whether it is similar to the mammogenic protein hormonal substance which Turner and his associates have isolated from the pituitary gland is uncertain. It is significant, however, that the milk influence is only effective during the early development of the mammary ducts, and like estrogen, it probably acts to curtail or limit the ultimate regenerative capacity of the duct epithelium. There is very little clinical evidence on this point. However, Wood and Darling have traced a family through four generations in which a number of the female members developed bilateral carcinoma of the breast. One female sibling of the fourth generation at the age of 18 years had a cancer of the breast. The predisposition was apparently transmitted in the maternal line of descent and mammary carcinoma occurred only in those women who had been nursed by their mothers.

FACTORS INFLUENCING THE PROGNOSIS

Dublin[1] has estimated that the average duration of life of cases with cancer of the breast is four years. This is based upon data in the article by Nathanson and Welch who found the average duration of the disease 4.6 years in treated patients, and 3.4 years in untreated patients (Fig. 333).

[1] Dublin states that "the figure of 3.5 years used by Nathanson and Welch for the average length of life after onset is actually not this quantity, but is the duration after which half of the treated cases have died. For this reason, and also because the figure relates only to treated cases, our judgment is that the figure of 4.0 is preferable to Nathanson and Welch's figure of 3.5."

Age

Nathanson and Welch found that patients with cancer of the breast beginning before the age of 40 years had a distinctly poorer prognosis than those in which the disease had its onset in the ages of from 40 to 60 years. These findings were also corroborated by Lee, who emphasized the high mortality of such cancers in young women. Braine has emphasized the comparatively mild course of cancer in women over 60 years, pointing out the lateness of involvement of the axillary nodes and the pectoral fascia in elderly women. In our own series of cases, the average duration of life for patients younger than 40 years was 3.45 years, compared to 5.5 years for those 40 or more years of age. Sistrunk and MacCarty found that 41.7 per cent of women over 50 years of age were living from five to eight years after operation, as compared with 31.8 per cent of women less than 50 years of age. The longer postoperative life in elderly patients is shown graphically in Fig. 334.

However, the consensus of recent reports does not indicate that the five-year survival is lower in women under 50 years than those over this age. MacDonald found the best results of treatment were obtained in patients between 35 and 50 years and stated: "that an especial virulence exists for mammary carcinoma in the young cannot be verified." De Cholnoky studied 73 cases of mammary cancer under 30 years of age and found 40.8 per cent of five-year survivals. He concluded that the disease was not more fatal in the young. Hawkins found a five-year survival rate of 31.4 per cent in women under 49 years; of 26.1 per cent in the group 50 to 59 years old, and 27.4 per cent in those 60 or more years of age.

The apparent conflicting viewpoints in the literature can be reconciled if the influence of age on the prognosis of mammary carcinoma is more carefully analyzed. In younger women, pregnancy and ovarian function both exert an unfavorable influence on the growth of the tumor. However, these factors are partially offset by the recent tendency for those in the younger age group to come to the hospital sooner for treatment than older patients, since the latter are not as responsive to the modern educational campaign against cancer as the younger group. On the other hand, the tendency on the part of many surgeons to shorten the time of the operation and to curtail the dissection in elderly patients lowers the five-year survivals in this group. Thus, while the number of five-year survivals in the younger age group compares favorably with those in the older group, the average duration of life for both cured and non-cured patients is less in the younger group. This is because of the rapid termination of fatal tumors in the young, particularly during pregnancy and lactation.

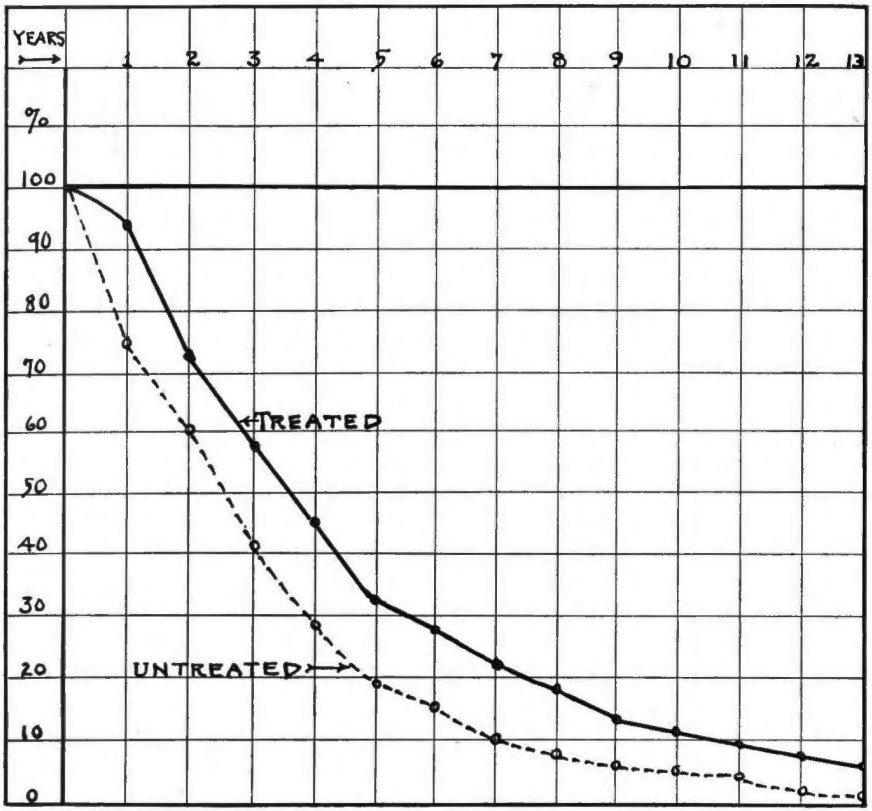

FIG. 333. The life expectancy in cancer of the breast. The chart shows the percentage of living cases in the years following the onset of symptoms. (After Nathanson and Welch, Amer. Jour. Cancer, 28:40, 1936.)

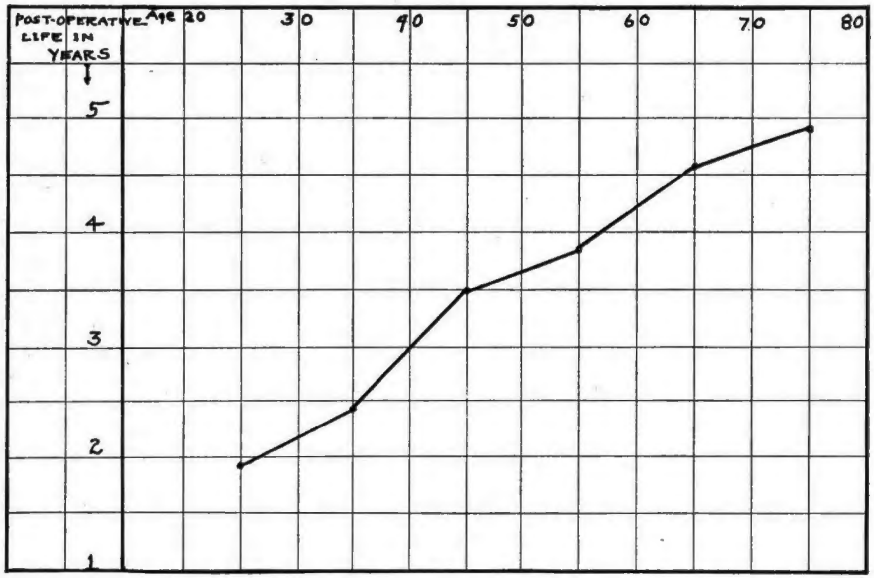

FIG. 334. Chart showing average length of post-operative life in years for patients of various ages with mammary cancer (patients known to be dead). (After Lewis and Rienhoff, Ann. Surg., 95:336, 1932.)

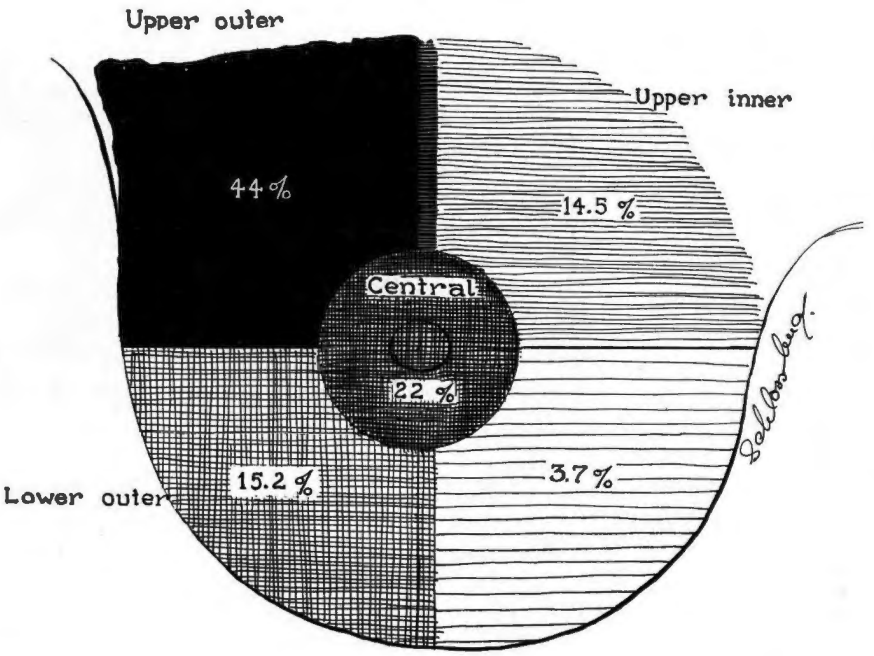

FIG. 335. Chart showing the distribution of 1000 infiltrating mammary cancers. The black and more darkly shaded areas show the most common sites.

Duration of Symptoms

The duration of symptoms is an important factor in prognosis. In 1,000 cases of mammary cancer studied by Wevill, the average duration of symptoms was 14.74 months and the three-year survivals were 30 per cent. In a large series of cases studied by Dahl-Iversen, the average duration of symptoms was 9.5 months and the three-year survivals were 45 per cent. In general, it is impossible to estimate the influence of delay on prognosis unless the more malignant infiltrating cancers are separated from the more slowly growing, circumscribed forms. Nathanson and Welch found that the average duration of symptoms of 690 cases was 1.05 years, and state that patients with the shortest delay in treatment have the worst prognosis, because patients with a slowly growing tumor seek medical aid much later than those with a rapidly growing one. Hawkins also found that "duration per se contributed little to the determination of prognosis." If, however, the duration of symptoms and percentage of five-year survivals is calculated separately for individual pathologic types of cancer, the unfavorable effect of delay is apparent.

In our own cases we have separated the infiltrating from the circumscribed forms. (Table XLIX.) The more circumscribed and slowly growing cancers have a longer duration of symptoms, averaging 17.5 months. In this group, the five-year survival rate is from 55 to 76 per cent. On the other hand, in the more rapidly growing, infiltrating cancers, the average duration of symptoms is 10.0 months, and the five-year survivals 32.6 per cent. Among these cases, women with cancer measuring 1 to 5 cm. in size had an average duration of symptoms of 8.5 months, with 42.8 per cent of five-year survivals; whereas those with larger tumors of the same type had an average duration of 14 months and a five-year survival rate of only 9.3%.

TABLE XLIX

DURATION OF SYMPTOMS AND PROGNOSIS IN MAMMARY CARCINOMA[1]

AVERAGE DURATION	AVERAGE SIZE	FIVE-YEAR SURVIVALS
966 Infiltrating Cancers, Average Duration—10.0 Months; Survivals—32.6%		
8 months	2.7 cm.	55%
15 months	8.2 cm.	7%
386 Circumscribed Cancers, Average Duration—17.5 Months; Survivals—62%		
8 months	3.4 cm.	76.5%
15 months	5.6 cm.	65.6%

[1] Based on graphs shown in Figs. 336 A and B.

Location

The distribution of 1,000 cancers of the mammary gland in relation to the nipple and the various quadrants of the breast is shown diagrammatically in Fig. 335. It will be seen that approximately 60 per cent of cancers occur in the outer hemisphere, 18 per cent in the inner hemisphere, and 22 per cent in the central zone. Taylor, after reviewing the conflicting experience of various authors, believes that the prognosis is poorer for tumors in the inner hemisphere. He believes it is fair to assume "that any surgically treated series of cases contains a relatively high proportion of late operable cases of growths in the outer quadrant, and that correspondingly advanced states of disease in the inner quadrants might be considered already inoperable." This is the experience of Bartlett who states that tumors of the medial half of the breast tend to metastasize to the mediastinal lymph nodes. He gives the following table, based upon 167 radical amputations for mammary cancer.

TABLE L

RELATION OF TUMOR SITE TO METASTASIS

LOCATION	5-YEAR CURES
No axillary metastases, outer hemisphere	77%
No axillary metastases, inner hemisphere	47%
Axillary metastases, outer hemisphere	29%
Axillary metastases, inner hemisphere	4%

Hawkins found the five-year survival rate for cancer in the inner quadrants to be 52.1 per cent compared to 64.6 per cent for the outer quadrants.

Pregnancy and Lactation

Pregnancy and lactation exert an unfavorable influence on the prognosis of mammary cancer. Sistrunk and MacCarty state that cancers developing during pregnancy are usually fatal within five years of operation. Lee found that in 11 mammary cancers complicated by pregnancy in women younger than 40 years there were no cures—the longest postoperative survival being five years and 10 months. In 14 cases developing during lactation, the results were similarly unfavorable. In 92 cases of cancer in pregnancy and lactation reported by Harrington, 84.8 per cent had axillary metastasis, compared to 63.8 per cent for the entire group of mammary cancers. Taylor and Meltzer have emphasized the frequency with which hopeless inflammatory carcinoma of the breast develops during pregnancy or lactation. From a survey of the literature and their own cases, they found that in 205 cases of mammary cancer which had an onset just

before pregnancy, during pregnancy or during lactation there were 45 (22 per cent) inflammatory carcinomas. On the other hand, the incidence of inflammatory carcinoma in any large series of cases is usually given as from 1 to 4 per cent.

In our own series of 58 cancers in pregnancy and lactation, the five-year survivals were 19.4 per cent compared to 32.6 per cent for infiltrating cancers and 34.2 per cent for all forms of mammary carcinoma. Our only five-year survivals in cancers developing during pregnancy were two cases associated with miscarriages rather than full term gestation.

Size

The relation of the size of the tumor to prognosis is seldom discussed, although it is usually stated that cancer occupying the entire breast is most frequently hopeless. Dahl-Iversen noted that when the cancer is 2 cm. or less there are 83 per cent of three-year cures; whereas if it is more than 2 cm., the three-year survivals are only 13 per cent. The size of the tumor is a reliable index of prognosis only if the pathologic type is taken into consideration. Grouping together the infiltrating forms of cancer in our own series, it was found that when the survival rates were plotted against the size of the tumor and the duration of symptoms they were practically inversely proportional to both (Figs. 336 A and B). The same finding also held for practical purposes for the individual forms of adenocarcinoma (Table XLIX). Among patients with an infiltrating form of mammary carcinoma who survived five years or more the average size of the tumor at the time of treatment was 2.5 cm.

Incomplete Operation

It is well recognized that a preceding incomplete operation markedly reduces the patient's chance of surviving beyond the five-year period. In carcinomas recurring in the scar of a previous excision, the five-year survivals were less than 5 per cent in our series. The dangers of a biopsy preceding radical therapy for the treatment of mammary cancer have been much discussed. Siemens believes that the danger of biopsy is overestimated. Ewing advises the greatest of caution in carrying out this procedure. He recommends that big tumors should be incised, the wound packed with a sponge soaked in 10 per cent formalin and that both gloves and instruments be changed if the biopsy reveals cancer. Small tumors should be excised with a margin of normal tissue and without squeezing. Where the technic has been perfected, aspiration biopsy is preferable on the larger tumors.

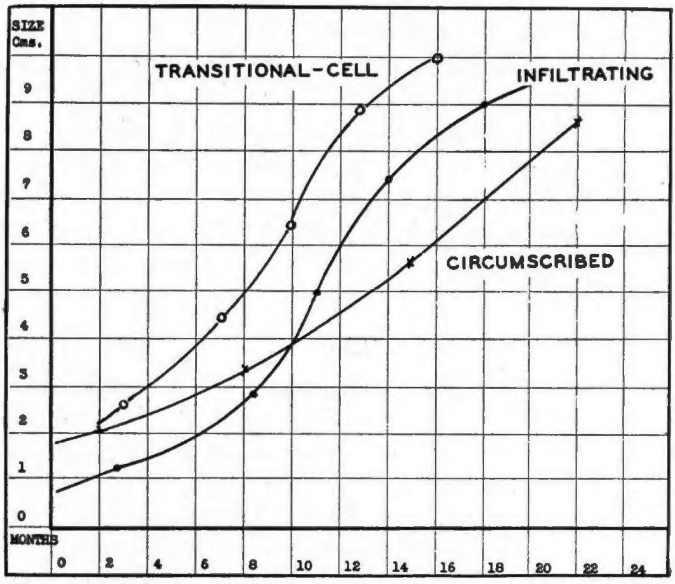

FIG. 336 A. Increase of size in the different forms of mammary carcinoma in relation to the duration of symptoms.

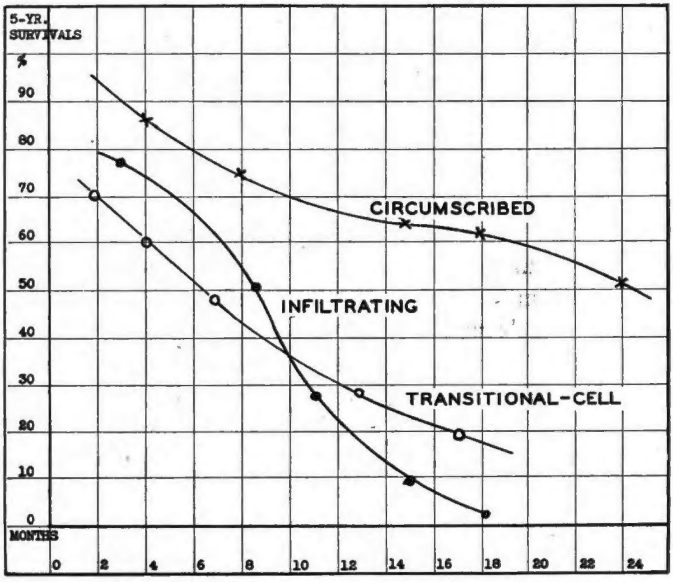

FIG. 336 B. Decrease in percentage of five-year survivals in the different forms of mammary carcinoma in relation to the duration of symptoms.

Lymph-Node Involvement

It is generally agreed that the extent of the disease at the time of treatment is the most important factor in the prognosis of mammary cancer. This is the basis of the Steinthal classification of cancers into Groups I, II and III. In Group I, the tumor is limited to the breast, is freely movable and the axillary nodes are uninvolved. In Group II, the larger part of the breast is involved, the tumor is adherent to the skin and the axillary nodes are palpable. In Group III, practically the entire breast is involved. There is fixation to the skin and underlying muscle. The supraclavicular nodes are often involved and there may be extension to more distant organs, such as bone, lungs, liver, etc. The following table shows the five-year survivals following the radical mastectomy for the various stages of mammary cancer in the Steinthal groups and also the relative percentage of cases which fall into each group. As will be seen from Table LI, approximately two-thirds of the cases of mammary carcinoma will survive the five-year period when the disease is confined to the breast, whereas, extension of the disease to the axillary lymph nodes reduces the survivals to about one-fourth of the total. When the disease is more widespread than this five-year survivals vary from 3 to 8 per cent.

TABLE LI

FIVE-YEAR SURVIVALS IN MAMMARY CARCINOMA

Stage of Disease	*1 Radical Surgery 1916-1927*		*2 Radical Surgery 1925-1935*		*3 Radical Surgery 1890-1935*		*4 Surgery and Irradiation 1929-1936*	
STEINTHAL GROUP	850 CASES		8585 CASES		1957 CASES		1953 CASES	
	PER CENT TOTAL	PER CENT SURVIVAL	PER CENT TOTAL	PER CENT SURVIVAL	PER CENT TOTAL	PER CENT SURVIVAL	PER CENT TOTAL	PER CENT SURVIVAL
I-III	100	30.6	100	36.9	100	34.2	100	30.0
I	25	63.6	32	66.7	32	66.0	28	61.0
II	75	19.6	68	23.0	45	25.0	52	24.0
III					23	8.0	20	3.0

Group I. Tumor limited to breast, movable, nodes negative.

Group II. Larger part of breast involved, skin adherent, palpable axillary nodes.

Group III. Almost entire breast involved, fixation to skin and muscle, supraclavicular nodes often involved.

[1] Summarized from Taylor, 1932.
[2] Summarized from Table LXXXVIII. Chap. 29.
[3] Author's Cases.
[4] Summarized from Hawkins, 1944.

Pathology

As a determining factor in prognosis, the pathologic character of the cancer ranks with the extent of the disease. Unfortunately, there is no general agreement regarding the definition of the separate pathologic groups of mammary cancer. It is, however, possible from the standpoint of prognosis to group mammary cancer into three major types: (1) the common infiltrating form; (2) circumscribed adenocarcinomas, and (3) transitional cell forms. The infiltrating form includes three-fourths of all mammary cancers and is variously referred to as carcinoma simplex, spheroidal cell cancer, scirrhous carcinoma, etc. The cancers of this group are characterized by their hardness, their stellate infiltrating shape, and their microscopic features, namely, cords, islands or occasionally alveoli of cells of moderate size infiltrating the fat and fibrous tissue. The second group comprises the major portion of the remaining cancers and includes the circumscribed forms, such as papillary adenocarcinoma, mucoid adenocarcinoma and the comedo form of adenocarcinoma. These usually are soft tumors which show marked degeneration when attaining large size and which metastasize relatively late.

The third group is composed of the transitional-cell forms of mammary carcinoma and includes Paget's disease of the nipple, duct cancer and neomammary cancers. These carcinomas are distinguished microscopically by the large transitional cells growing in sheets and resembling squamous epithelium. In Paget's diseases the cells are found at the base of the epidermis of the nipple and lining the large ducts; in duct cancer they are confined for the most part to the ducts; and in neomammary cancer they are found deep in the breast, often lining a thick-walled cavity, partially filled with necrotic material—the so-called cancer cysts of the older literature. The pathologic basis for this classification is discussed in Chapter 18.

The five-year survivals for the largest group—the infiltrating carcinomas—was 33.7 per cent in our cases. Among the cases with transitional cell carcinoma, 39.5 per cent survived the five-year period, while among the circumscribed adenocarcinomas, the rate was 62 per cent (see Fig. 336 B and Tables LXXVII, LXXVIII, and LXXIX, Chap. 25). The correlation of the microscopic grade of the disease with the rate of survival is discussed in Chapter 25.

INFLUENCE OF FORMS OF THERAPY

When mammary carcinoma is confined to the breast, radical mastectomy when properly performed will arrest the disease for five

or more years in 65 to 70 per cent of the cases. The addition of post-operative irradiation does not increase significantly the percentage of survivals in this group, but rather adds to the discomfort and financial burden of the patient and to the risk of pulmonary fibrosis, skin damage, lymphedema of the arm and radiation neuritis or bone necrosis (Chap. 30). Simple mastectomy followed by irradiation in these cases reduces the survivals to about 54 per cent (Table LXXXIX, Chap. 30). Pre-operative irradiation, because it delays radical surgery and renders proper performance of the procedure more difficult, likewise reduces the survivals to about 54 per cent. In other words, when radical mastectomy for localized mammary carcinoma is preceded by irradiation, or when the axillary dissection is omitted and reliance is placed on post-operative irradiation, one patient in every six that might have been added to the group of five-year survivals is lost.

When mammary carcinoma has extended to the axillary nodes radical mastectomy will arrest the disease for five or more years in approximately 25 per cent of the cases. Adequate post-operative irradiation will raise this figure to over 30 per cent, hence this form of irradiation should be adopted as a routine in such cases. Again, pre-operative irradiation, even when combined with post-operative irradiation, does not increase the number of survivals. When mammary carcinoma has extended beyond the breast and axillary nodes, the disease is inoperable and irradiation only is the treatment of choice. About 5% of patients thus treated survive 5 or more years.

Irradiation alone, without radical mastectomy, whether in the form of x-ray or radium, must be looked upon as a palliative measure. Attempts to substitute it for the radical operation in operable cases (Steinthal Groups I and II) reduces by half or more the number of five-year survivals. Moreover, irradiation in inadequate dosage (less than 3500 r) like inadequate surgery, is a deleterious procedure and as shown by Hawkins has an adverse effect on the curability of the disease. Surgical or x-ray castration of cyclic women with mammary carcinoma also is a palliative treatment that may relieve the symptoms of metastatic disease. However, there is no proof to date that the procedure increases the number of five-year survivals. Roentgen-ray castration may be used in young women following operation to avoid the complications of pregnancy.

CRITERIA OF OPERABILITY AND IRRADIATION

Since radical mastectomy is the most effective form of therapy for proved cases of mammary carcinoma, the criteria employed to

classify operable and inoperable cases have an important bearing on the ultimate results achieved. If too rigid criteria for operability are used in selecting cases for radical mastectomy (such as the exclusion of cases with large, firm axillary nodes) there will be excluded about 10 to 15 per cent of patients from the operable group. The patients thus excluded are taken from a group in which the five-year survival rate is 12 to 15 per cent, and placed instead in a group where the survival rate is only 5 to 8 per cent.

To date the following are the most reliable criteria of inoperability:

1. Lymph node metastases which extend to the supra-clavicular region.
2. Skin metastases beyond the area immediately adjacent to the tumor.
3. Acute or inflammatory carcinoma.
4. Carcinoma developing in full-term pregnancy.
5. Evidence of internal or visceral metastases.
6. Extensive fixation of the tumor to the chest wall or tumor nodules in the chest wall.
7. Extensive edema of the skin over the breast or of the arm.
8. Considerations in regard to the general condition of the patient, such as severe hypertension, cardiac or renal disease, advanced age, etc.

Routine irradiation[1] is indicated for:

1. Inoperable mammary carcinoma, as defined above.
2. Recurrent carcinoma.
3. Post-operatively for operable carcinomas with metastases to the axillary lymph nodes or more extensive disease, clinically unsuspected before operation.

INFLUENCE OF POPULAR TRENDS AND CANCER PROGRAMS

Statistics obtained by national surveys indicate that the incidence and number of deaths from mammary carcinoma (as well as other forms of cancer) are steadily increasing, but there are no corresponding figures by which to judge improvement or decline in the national cure-rate for the disease. The only figures available are those obtained from large clinics in densely populated districts, and a break-down of these statistics is extremely difficult. In most reports of five-year results, there is a separation of cases without lymph node involvement from those with such involvement; but in the latter group there is no way to determine whether only the operable

[1] For special indications for irradiation see Chap. 30.

cases are included or whether patients with more extensive disease have been treated.

Taylor in 1932 found the five-year survivals in 7974 cases of mammary carcinoma treated by radical mastectomy* to be 30.6 per cent. The author reviewed the results reported from 1932 to 1944 in 8585 cases similarly treated and found the survival rate to be 36.9 per cent (see Chapter 29). On the basis of these figures it would appear that there has been a definite improvement in the results obtained in cases treated *surgically* in the past decade. When one compares more recently treated cases with those in the earlier series (treated in the period from 1916 to 1927, Table LI) it is found that the improvement is due largely to an increase in the number of early cases in which the tumor is still confined to the breast, and partially to the increase in the number of cases in which the axillary nodes are involved, but in which the disease has not yet extended beyond the limits of radical mastectomy. If one now adds the further improvement in results obtained in this group (Steinthal II) through post-operative irradiation a maximum apparent improvement of about 10 per cent in five-year survivals has been achieved in certain clinics.

However, such calculations must be looked upon with much skepticism since the increased number of cases in which the disease had not extended beyond the axillary nodes at the time of treatment may be due to a more careful selection of cases and more rigid criteria of operability. Nevertheless, in comparing the cases in our own series treated before and after 1925, the conclusion seems justified that popular education and cancer programs have increased the relative number of early cases in which the disease is confined to the breast and have diminished, also, the relative number of patients with advanced mammary cancers with extensive lymph node and skin involvement who present themselves for treatment.

Hawkins reviewed the results of treatment by various modes of surgery, irradiation, and combinations of both in 1953 cases in nine large hospitals in the East (Table LI, column 4). The five-year survivals for all groups was only 30.0 per cent. His findings suggest that there has been a tendency in certain clinics to place too much reliance on radiation therapy—such as using x-ray or radium only in operable cases; limiting the operation to simple mastectomy in early cases and combining this with post-operative irradiation; postponing operation to administer pre-operative irradiation, etc. When radical surgery is used the completeness of the dissection more often approaches acceptable standards than when radiation

* Some of these patients had in addition, x-ray therapy, but in amounts insufficient to influence the results. In Table LI we have listed only those surgically treated and the computed average survival rate is the same as that for the total number in the series.

therapy is practiced. A number of the cases irradiated in Hawkins' series received a total dose of less than 3,500 r.

It would appear that the best results of treatment can be expected from more widespread use of the standard operation for radical mastectomy, from more reliable standards of operability, and by more widespread use of adequate routine post-operative therapy for cases with lymph node metastases. Since less than one-third of the patients with mammary carcinoma are seen when the disease is still confined to the breast the greatest improvement in therapeutic results which could be expected in the near future would be from a more effective campaign of popular education; one which would bring at least two-thirds of the cases under observation before the disease has extended to the axillary nodes. To achieve such a result Auchincloss, Hawkins and others have advocated that all women over thirty years of age be taught to palpate their own breasts at least six times a year and report immediately to their physicians when a lump is felt.

Such advice has been avoided heretofore because of the assumed undesirability of frightening the patient. But the fact remains, that more women die of mammary cancer annually than could possibly die from or be incapacitated by such forms of fright. It is far more humane and sensible to allow each woman to face the reality of discovering a mass in the breast while it is still curable, regardless of its nature (with or without the induced fear of cancer) than it is to allow her eventually to realize that she has an incurable disease.

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18

Pathology of Mammary Cancer

Generalization in regard to the etiology, diagnosis, and the clinical course of mammary cancer, without reference to the particular variety, is open to criticism because individual forms of carcinoma differ in their mode of onset and clinical behavior. Mammary cancers are of two fundamental pathologic types: (1) the adenocarcinomas, arising from lobular structures and growing either in an infiltrating or circumscribed fashion; and (2) the stratified epithelial cancers, derived from tissues concerned in the development of the nipple and larger ducts.

CLASSIFICATION

The adenocarcinomas or gland-cell cancers comprise 90 per cent of cancers of the breast. The gland-forming tendency of the infiltrat-

ing form (often referred to as scirrhous cancer) is not apparent under the microscope except in the more slowly growing tumors. The less common, circumscribed adenocarcinomas comedo, papillary, gelatinous, which grow more slowly, have more definite glandular arrangements, and this group is usually referred to as adenocarcinoma.

The stratified epithelial cancers are derived from epithelium, resembling that found in the normal epidermis, and include Paget's cancer of the nipple, large cell or pagetoid duct cancer, so-called medullary cancer and cancer cysts.

TABLE LII

CLASSIFICATION OF MAMMARY CANCERS

REGION AFFECTED	I—2,292 GLAND-CELL CANCERS	II—232 STRATIFIED EPITHELIAL CANCERS	III—30 RARE CANCERS
Lobules	A. Infiltrating adenocarcinoma 1,906 cases	A. Medullary cancer Cancer cysts 135 cases	A. Basal-cell cancer 4 cases
Ducts	B. Comedo adenocarcinoma 106 cases	B. Duct cancer 35 cases	B. Sweat-gland cancer 12 cases
Nipple	C. Papillary adenocarcinoma 197 cases	C. Paget's cancer 62 cases	C. Squamous-cell cancer 14 cases
	D. Gelatinous adenocarcinoma 83 cases		

Rare forms of cancer not belonging to these two major groups include squamous-cell cancer, usually complicating benign epidermoid cysts, adenocystic basal-cell cancer, and cancers derived from the sweat glands.

GLAND-CELL CANCERS

Infiltrating Adenocarcinoma

Lobular Cancer, Scirrhous Cancer, Carcinoma Simplex. Most mammary cancers originate in the small tubules or in the acini which form the lobular structures. Since the acini arise by finer ramification of the terminal tubules, there is no definite line of distinction between the two. If studied microscopically when they are 1 cm. or less in diameter, most lobular cancers will show a combination of tubular and acinar arrangements. (Fig. 337.) Later, in rapidly growing lobular cancers, cords or islands of infiltrating epithelium are formed in the surrounding fibrous tissue without definite alveolar or tubular arrangement.

Lobular cancers are infiltrating growths that penetrate into the surrounding fat and connective tissue. They often have an irregular stellate shape, are hard and gritty when cut, and have a shiny, whitish granular surface. It has been stated that the tumor cuts like an unripe pear. Changes in the skin, caused by pressure or adherence of the growth, and invasion of the lymph nodes occur relatively early. Metastases to the axillary nodes are found in 25 per cent of the cases

FIG. 337

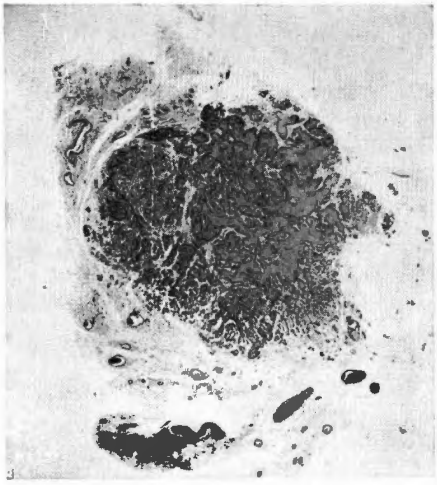


FIG. 338

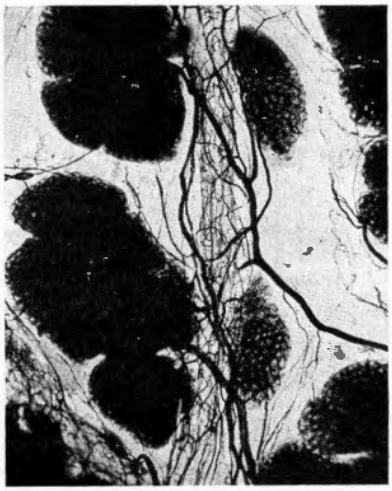


FIG. 337. The structure of lobular cancer. The photomicrograph shows a carcinoma forming solid alveolar structures, replacing a mammary lobule. The tumor measured 8 mm. in diameter.

FIG. 338. Injected specimen of the mammary gland of the monkey. The photograph of the whole mount shows the rich vascular network of the lobular structures in early pregnancy.

in which the diameter of the growth is 1 to 1.5 cm. and in which the average duration of the symptoms is only three months. When these growths have existed for a year or more (as judged from the patient's story) their average size is 5 cm. or more and metastasis to the lymph nodes has occurred in nearly all cases. Invasion of the underlying fascia and metastasis to the internal viscera (as revealed by failure to cure by radical mastectomy) has occurred in approximately 90 per cent of these larger growths. Even when attaining large size, necrosis and degeneration are rare, unless infection has been superimposed following ulceration or fungation.

Most of the generalizations in regard to mammary carcinoma are based on experience with infiltrating lobular cancer, which comprises about 70 per cent of all forms.

Two features concerning the origin of these growths account for their characteristic behavior: First, there is a striking capacity for further growth and development residing in the terminal tubules and lobules from which the cancer arises. Second, in order to provide for the secretory capacity of the functioning gland, there is an unusually rich vascular and lymphatic network surrounding these lobular structures. (Fig. 338.) Cancers arising in this region, therefore (unless the breast has undergone advanced senile changes), have an active focus of contributing cells[1] and a rich vascular and lym-

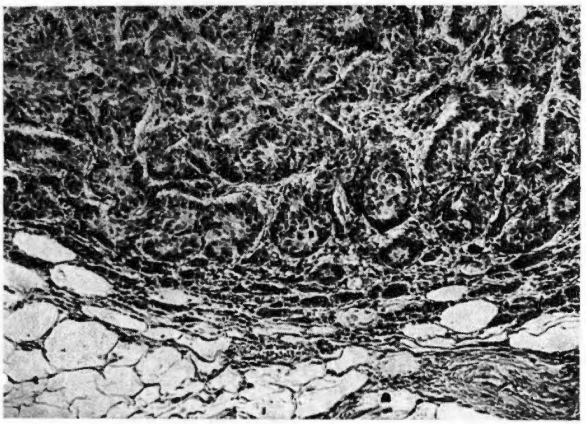


FIG. 339. A slowly growing lobular cancer. The photomicrograph shows a Grade 1 lobular cancer with a distinct alveolar arrangement.

phatic bed. Their rapid growth and spread, therefore, is assured both by adequate nourishment and by easily accessible pathways for extension and invasion.

The rapid invasive growth of these cancers obscures their lobule-forming tendencies. Definite alveolar structures predominate, however, in some which occur in elderly patients or in a localized area of sclerotic fibrous tissue. (Fig. 339.) In most instances, the cells of the cancer are of moderate size. They are slightly larger and have nuclei of varying densities, but in general they resemble those found normally in the acini and terminal tubules. In other instances, the cells resemble the cuboidal epithelium found in the main ducts in spite of their lobular origin. This is not surprising when one considers the amount of undifferentiated epithelium that is carried forward

[1] A number of theories postulate that cancer has its origin in a single cell, and that the entire new growth is formed by the progeny of this single ancestor. This is not the author's opinion. Histologic studies on cancers a few millimeters or less in size indicate that a zone, rather than a single cell, of epithelium undergoes malignant transformation. A group of cells with varying degrees of increased density in their nuclear material mark the onset of the disease. This is also the conclusion reached by Dr. George O. Gey who has traced the malignant transformation of cells in tissue culture.

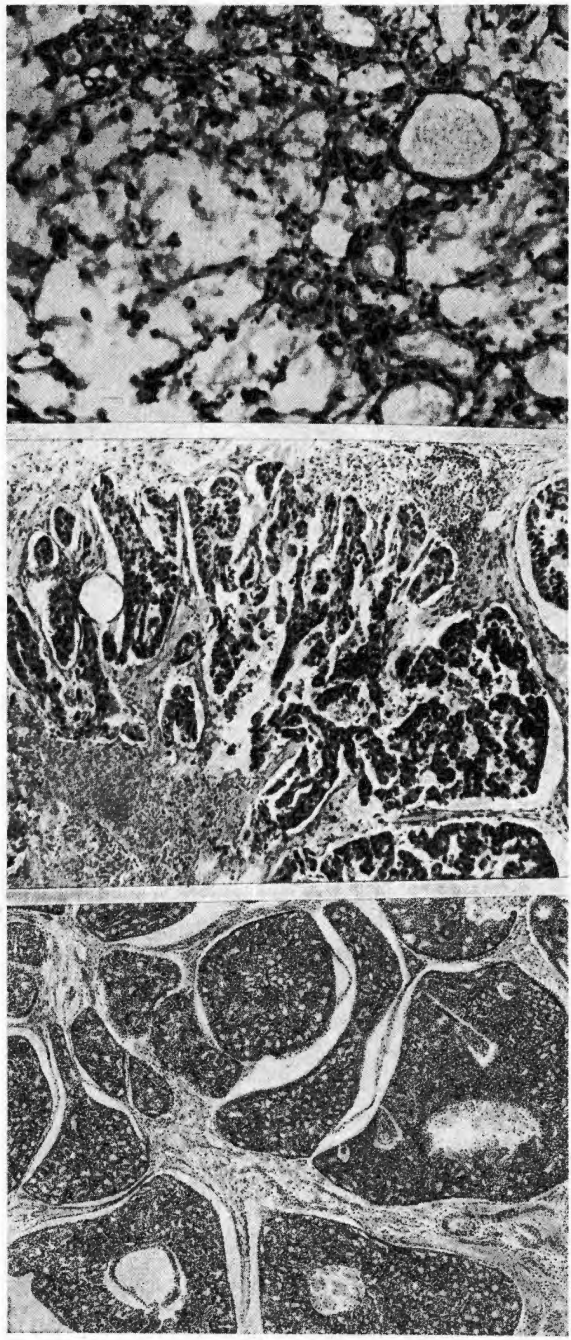
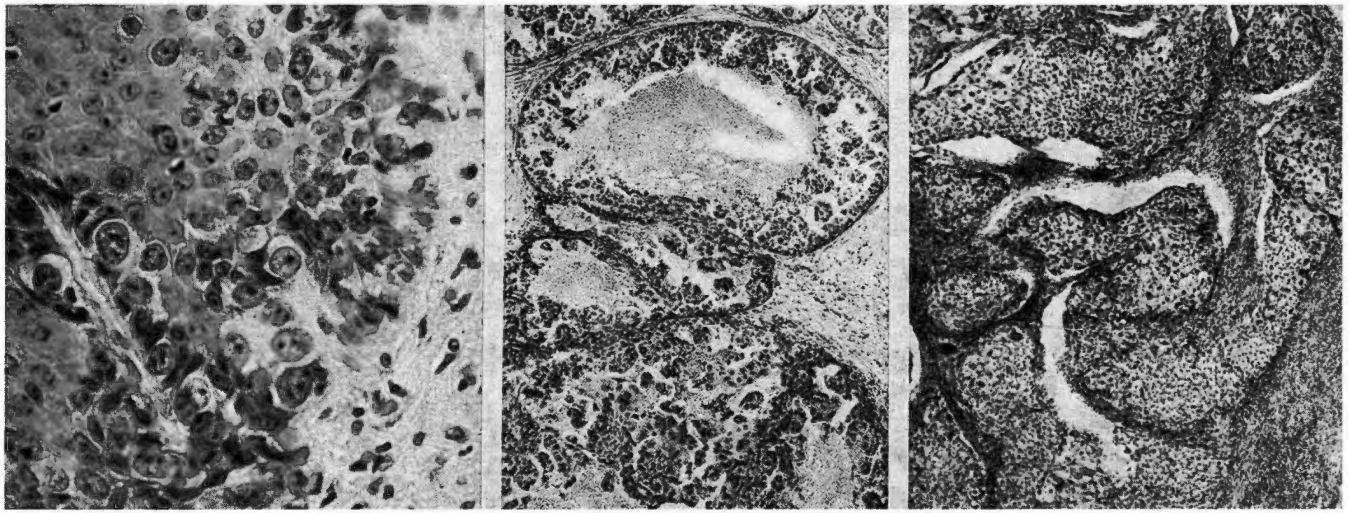


Fig. 340 Fig. 341 Fig. 342

The Histologic Features of Circumscribed Adenocarcinomas.
Fig. 340. Comedo cancer. Fig. 341. Papillary cancer. Fig. 342. Gelatinous cancer.

FIG. 343 FIG. 344 FIG. 345



The Histologic Features of Stratified Epithelial Cancer.
FIG. 343. Paget's Disease. FIG. 344. Duct cancer. FIG. 345. Neo-mammary or medullary cancer.

in the terminal tubules during early development of the mammary gland in order to provide for the further growth of ducts under the stress of pregnancy and lactation.

The Circumscribed Forms of Mammary Cancer. Current discussions about cancer of the breast rarely take into account the less common, circumscribed forms, such as comedo, papillary, and gelatinous adenocarcinoma which differ markedly in their manner of growth and prognosis from the infiltrating form just described. Yet these varieties of adenocarcinoma were accurately described in the literature before the present century. In 1893, Bloodgood observed the first adenocarcinoma with a tubular structure to which he gave the name "comedo." Velpeau described the papillary form in 1856 and Müller reported a gelatinous cancer of the breast in 1834.

Comedo Adenocarcinoma

Some of the slowly growing cancers which arise from the terminal tubules show a tendency to invade the pre-existing ducts and to be confined by the walls of ducts, as well as to form new ducts and tubules. These were described by Bloodgood as comedo cancer and are circumscribed growths which metastasize relatively late and have in general a favorable prognosis. The tumor may be soft and bulge outwardly. The cut surface looks like the cross-section of a freshly sawed plank of wood. On pressure, plugs of tumor cells may be expressed from the ducts, hence the term "comedo." Under the microscope, rings of cancer cells line the pre-existing and newly formed ducts. Small acinar spaces form within the thickened rings of cancer cells. Some of these tumors grow to large size without losing their circumscribed and tubular arrangements (Fig. 340). However, others tend to form the same infiltrating cords and islands found in lobular cancer. Thus transitional forms exist between the circumscribed comedo cancers and the infiltrating lobular forms. This is explained by the close relationship which exists between the epithelium of the terminal tubules and that of the acinar structures.

The transitional microscopic forms which show gradations between infiltrating lobular cancer and circumscribed cancers of the comedo type demonstrate that the epithelium in comedo cancer has the same lobule-forming capacity as that found in the infiltrating forms. The distinction between the two, therefore, must rest upon the structure in which the cancer arises and its decreased vascularity. Apparently the slowly growing or "pure" comedo cancers arise within the terminal tubules which have lost much of their lobule-forming capacities, and in which the vascular supply has undergone corresponding involutional changes.

Papillary Adenocarcinoma

Papillary adenocarcinoma is the most common circumscribed form. These tumors are often of large size when the patient is first seen, hence the term "bulky adenocarcinoma." Many of these growths are soft and vascular. On cross section, friable tufts of tumor tissue may project into a cyst containing bloody fluid, but invasion of the surrounding tissues is found near the point of attachment to the cyst wall. Some of these cancers arise from pre-existing benign intracystic papillomas. The tumor tissue tends to grow in coils and papillary folds and forms acinar structures. (Fig. 341.) It is evident, therefore, that these tumors, like the infiltrating adenocarcinomas, also arise from epithelium destined to form mammary lobules. The lobular tissue from which they arise, however, is not usually of the functioning variety. Instead, it represents remnants of the primary mammary sprouts from which the lobular tissue eventually forms, but which have been left behind in the region of the larger ducts during the course of development. Hence many of the papillary adenocarcinomas have a central location and are found beneath the nipple or areola. Their location within the thick-walled ducts in the nipple zone necessitates a prolonged period of slow growth while the tumor mass is acquiring a sufficient vascular supply. Because of the free borders within the lumen of the duct, they must be nourished in most instances through a single pedicle. It is not until the border of the growth has formed secondary attachments and eroded through the duct wall that additional avenues for lymphatic spread are provided. This usually takes place after the tumor has acquired a well-developed plexus of newly formed blood vessels. Papillary cancer also may arise in the region of the terminal tubules from buds of lobule-forming tissue. In such instances the terminal tubules have undergone cystic dilatation and the proliferating epithelium again projects into the free space of a large cavity.

Gelatinous or Mucoid Adenocarcinoma

Mucoid degeneration occurs in some of the slowly growing papillary adenocarcinomas. Whether this mucoid or gelatinous substance is secreted by the epithelium or is a degenerative change in the connective tissue, or whether both may occur, has been the subject of controversy. An epithelial origin of the gel is most probable. These gelatinous growths have individual peculiarities. They usually grow slowly and metastasize late; some of the largest mammary cancers described have been of this character. Mucoid change may affect any of the glandular forms; it is most often seen, however, as a degenera-

tive change in papillary adenocarcinoma. Mucoid cancers are soft and may have a cystic or fluctuant feeling on palpation. When cut across, a semifluid, tapioca-like material oozes or flows from the incision. Under the microscope the nests of epithelium are widely separated by the pale-staining gelatinous substance. (Fig. 342.) Recurrence due to transplantation of this material into the wound may take place years after operation.

STRATIFIED EPITHELIAL CANCERS

In the development of the breast, the nipple bud, forming from a downgrowth of epidermis, precedes the formation of the mammary sprouts from which the lactiferous ducts, the terminal tubules and the lobular structures are derived. (See Chap. 1.) The invaginating epithelium of the nipple bud undergoes hyperdifferentiation and the central squamous cells are desquamated, forming the hollow of the nipple pouch. Prolongations of the stratified epithelium from this pouch line the openings of the larger mammary ducts. Cancers forming from this epithelium have characteristically large cells with granular, eosin-staining cytoplasm and have been grouped together under the heading of stratified epithelial cancers.

Paget's Cancer

Paget's disease, which comprises 5 per cent of mammary cancers, is characterized by a lesion of the nipple and by the presence of large Paget's cells in the epidermal covering of the nipple and, with few exceptions, in the mouths of the adjoining ducts. In two-thirds of the cases, a cancerous mass is also present in the breast at some distance from the nipple. Some authors have maintained that the large granular Paget's cells are of sweat-gland origin. (Fig. 343.) This resemblance to cells of the apocrine sweat glands is understood when it is recalled that, from an evolutionary standpoint, the breast is a modified sweat gland, and that these epidermoid-like cancers arise from relatively primitive mammary structures derived from the nipple pouch. Paget's cancer, when confined to the nipple and adjoining mouths of the large ducts, can be cured by radical mastectomy in nearly every instance. When the underlying breast is involved, however, less than 10 per cent of the cases survive the five-year period.

Duct Cancer

A small group of cancers originating in the larger ducts are composed of epithelium resembling Paget's cells. For this reason the term "pagetoid duct cancer" was used in a previous report (Geschick-

ter and Lewis). These growths originate in, and for the most part are confined to, the larger ducts. In advanced cases they invade the nipple or the surrounding breast. The cancer cells line the ducts in broad sheets or multiple small papillary-like masses. (Fig. 344.) The cells are large and have an abundant cytoplasm, immense nuclei and show frequent mitoses. Multinucleated giant cells are formed. The involvement of the larger ducts is similar to that found in Paget's disease, except that the nipple is seldom involved.

Medullary Cancer and Cancer Cysts (Neomammary Cancer)

Cancers imbedded deep in the mammary tissue, often in the mid-zone of the breast or the lower hemisphere, may contain epidermoid-like cells such as those seen in Paget's disease and in duct cancer. They form a mass which is usually circumscribed and regular in outline. When cut across, a cystic structure may be found, or a zone of central necrosis. Some of these cancers are solid and are composed of highly malignant cells resembling squamous-cell cancers. Others have been classified as sweat gland in origin. Because of their probable relation to the primitive nipple pouch, the term neomammary cancer has been used for this group (Fig. 345).

RARE MAMMARY CANCERS

The rare mammary cancers include squamous-cell cancer, adenocystic basal-cell cancer and true sweat-gland cancers (Figs. 346-348.)

Squamous-Cell Cancer

Squamous or epidermoid cancer may be found in the breast as a rare complication of other mammary lesions. Squamous-cell cancer may occur in the skin of the areola and invade the breast. In fibroadenomas of long standing, squamous-cell metaplasia may occur in the mammary epithelium (presumably as a result of continued estrogenic stimulation) and undergo malignant change. (Oliver.) More often benign epidermoid cysts are the seat of cancers with keratinizing epidermoid tissue. (See Chap. 15.) The cancers of this group have a distinct histology. They contain epidermoid tissue growing in sheets, often showing the formation of epithelial pearls. Most of these growths, particularly those arising in connection with epidermoid cysts, are of low malignancy.

Adenocystic Basal-Cell Cancer

These are the rarest forms of mammary carcinoma and only four such cases have been studied. They are of a low degree of malignancy

and are encapsulated growths which grow slowly. Metastasis has not been reported. The histology of the tumors is similar to adenocystic basal-cell cancers found in the parotid gland, the skin and the mucous membranes of the nasal passages. Layers of basal cells are grouped about small cystic spaces which contain minute amounts of mucoid secretion. These growths apparently originate from misplaced glandular appendages of the skin (probably the eccrine sweat glands) which are carried into the mammary gland during the process of early development.

Sweat-Gland Cancer

These are papillary or cystic circumscribed tumors usually found either in the axillary prolongation of the breast or submammary fold where the apocrine sweat glands are most numerous. They have a yellowish color in the gross and are not highly malignant growths. They are composed of large pale epithelium which rests on a basement membrane containing smooth-muscle fibers. Bizarre nuclear forms are frequent. In the author's opinion true sweat-gland cancers are rare, but some observers (Lee, Pack and Scharnagel) believe that many forms of mammary cancer may have such an origin.

EXPERIMENTAL DEMONSTRATION OF MAJOR FORMS OF MAMMARY CANCER

The importance and the difficulties in classifying the many forms of mammary cancer have long been recognized. In 1898, Halsted wrote that

"breast cancers are not all alike, every clinician knows; to some the patient succumbs in a year or less, others are borne for twenty years or more.

I know of no very successful attempt at classification of cancers of the breast with reference to their relative malignancy, and yet the importance of such a classification, if it were to any extent possible, is so evident that it is unnecessary to emphasize it. The histories alone, of the operated, as well as the unoperated cases, give one a hint that there must be some basis for such a classification."

More recently Ewing has stated,

"Although no other form of carcinoma absorbs more attention from surgeons and pathologists, the morphology of mammary tumors still requires more searching analysis than it has yet received. So variable and complex are the forms and structure of mammary cancer that the attempt to employ a histogenic classification may be premature."

Factors Determining Pathologic Forms

In the foregoing pages an attempt has been made to enumerate briefly the distinguishing features of the various forms of mammary

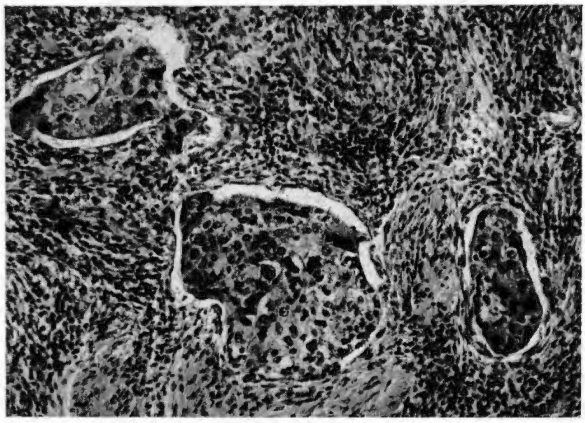


FIG. 346. Histologic features of rarer mammary cancers. Squamous cell cancers.

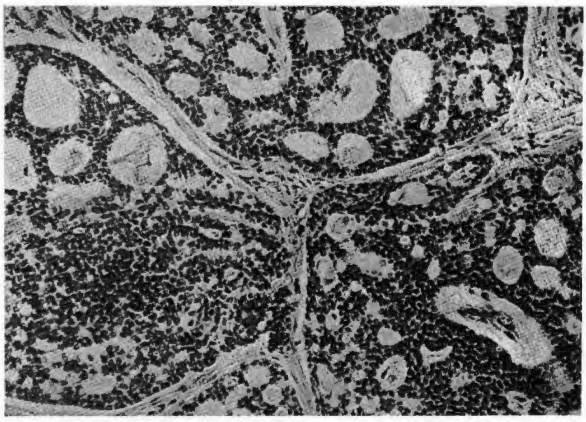


FIG. 347. Adenocystic basal cell cancer.

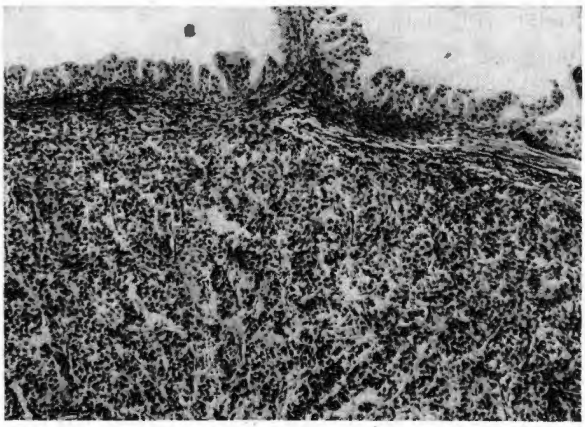


FIG. 348. Sweat-gland cancer.

cancer. There are two fundamental factors which determine the variety of pathologic forms observed. One of these is the pathway of differentiation of the affected tissue, or its histogenesis; the other is the locality which contributes its supporting structures, the so-called tumor bed. It is the pathway of differentiation which distinguishes the adenocarcinomas from the stratified epithelial cancers. Among the adenocarcinomas, the tissue retains its tendency to form lobular structures and among the stratified epithelial cancers there is a tendency to form a lining membrane characteristic of the archaic structures of the nipple pouch.

Within the adenocarcinoma group, the infiltrating lobular cancers and the papillary adenocarcinomas differ in structure because of their sites of origin. Papillary cancers arise from buds of glandular tissue projecting into the lumen of large ducts or into cystic cavities. They grow slowly, producing well-formed coils of tubules or alveolar structures because the free borders of the projecting tissue impose limitations upon the vascular supply. In the lobular cancers, the tumor is more advantageously placed with regard to its nutrient source and its pathways of dissemination; and its more rapid rate of growth and spread is associated with a decreased tendency to produce well-formed lobular structures.

The transitional cancers as a group owe their distinguishing characteristics to a more primitive pathway of differentiation. During development, the mammary gland is preceded by the archaic tubular structures of the nipple pouch, which take part in the formation of the ampulae of the nipple and the proximal ends of the larger ducts. Paget cancer of the nipple, pagetoid cancer of the larger ducts, rare cancers of the sweat-gland type, cancer cysts, and the majority of the so-called medullary cancers (neomammary cancers) show histologic features similar to those of the normal nipple-pouch derivatives. Usually, the cancerous epithelium (found mainly in the nipple zone) forms a lining membrane rather than glandular structures and hence the tendency of these tumors to line pre-existing ducts or cystic cavities and to form sheets or large cylindrical masses. Only rarely when the tumor is growing slowly are secretory features prominent, resembling the structure of the apocrine sweat glands.

Experimental Production

These fundamental distinctions in the forms of mammary cancer are, as will be shown in subsequent chapters, apparent in their clinical behavior and in their response to treatment. They are also apparent among the mammary cancers produced experimentally. That these pathologic types actually represent different pathways

of development in distinct functioning units of the mammary gland is indicated by the experimental studies about to be summarized. These experiments demonstrate that cancer occurs as an end result of regenerative processes. Estrogen promotes the growth of the duct system, its periductal stroma, and, to a lesser degree, lobular development under intense and prolonged dosage. (Chap. 2.) The mammary gland, like other tissues capable of regeneration, contains a number of juvenile or reserve cells remaining from embryonic development which provide for further regeneration in later life. If, under continuous hormonal stimulation, these reserve cells are called upon to mature and replace worn and dead cells their supply can eventually be reduced to a point approaching exhaustion. If these cells are exhausted or eliminated outright by a severe injury, cancer does not result; but if the exhaustion takes place physiologically through long-continued or intensive regeneration, then the reserve cells may avoid extinction by cancerous regeneration. Such an end point can be reached by excessive stimulation with estrogenic hormones.

Estrogen Stimulation. In using estrogen for the experimental production of mammary cancer long continuous action is just as effective as intense interrupted stimulation, and cancer will result from either. Cancer also results when the animal or the organ is previously aged by maintaining the organ at the upper limits of physiologic stimulation for prolonged periods and then supplying intense estrogenic stimulation for a brief period. It is also possible to give intense endocrine stimulation early in the life of the animal and to stop it short of cancer and allow time alone to complete the process of exhaustion, adding a brief period of estrogen stimulation near the end point to bring about the cancer.

Mammary cancer in the rat has been produced experimentally in the author's laboratory in the following ways:[1]

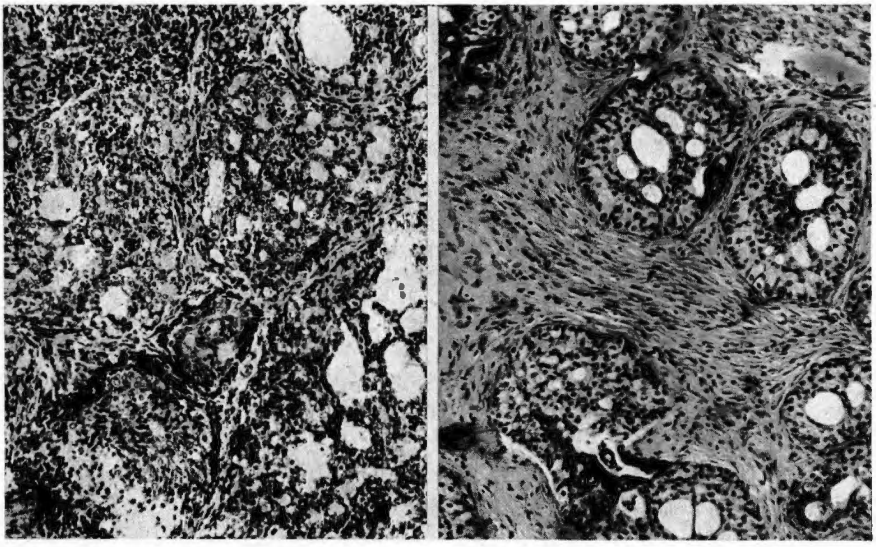
1. Intense interrupted estrogen stimulation. (Repeated daily injections.)
2. Long, continuous but moderate action. (By the implantation of pellets or injections of estrogens with prolonged action.)
3. Aging with physiologic doses of estrogen over long periods plus intense endocrine stimulation near the end-point. (With estrogen or testosterone.)
4. Intense estrogen stimulation short of cancer in young animals, plus time and normal aging. (Estrogen is applied for a short period at the end of two years.)

The two major types of mammary cancer, adenocarcinoma and the

[1] For the details of these experiments, see Chap. 34.

stratified epithelial cancer, appear frequently in the rat's breast in response to estrogenic stimulation. Infiltrating adenocarcinoma is associated with the terminal tubules and lobules. The circumscribed form of comedo adenocarcinoma is found in the ductules. Papillary cancer occurs in the large ducts and in lobular structures that have undergone cystic dilatation. The stratified epithelial cancers nearly always occur in the nipple region in the large ducts. Forms of adeno-

FIG. 349 FIG. 350



Histologic Features of Estrogenic Mammary Cancer in the Rat's Breast.
FIG. 349. Infiltrating lobular cancer.
FIG. 350. Transitional cell cancer in the large ducts beneath the nipple.

carcinoma and of stratified epithelial cancer may develop simultaneously in the same breast in different regions of the gland.

Adenocarcinoma in the Rat's Breast. The changes in the breast associated with infiltrating lobular cancer, differ from those found with circumscribed adenocarcinoma.

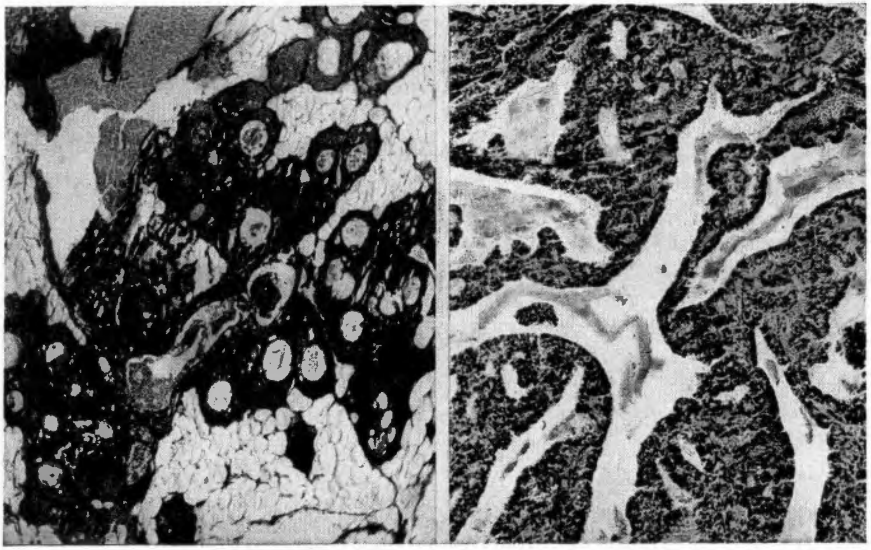
Infiltrating lobular cancer is found in immature rats, where the breast is stimulated to lobule formation by a prolonged action of the estrogenic hormone (through the implantation of pellets or with modified estrogens with a prolonged action), or in noncastrate animals, in which lobule formation is stimulated by luteinization of the ovaries under prolonged estrogenic action.

The cancers do not appear in glands which are normally the seat

of lobule formation in sexually mature animals until involutional changes produced by estrogenic overstimulation have occurred.

When lobule formation with its perilobular lymphatic and vascular bed can be stimulated, lobular cancer results. It begins either at the junction of a terminal tubule and its acini (showing a combination of duct and lobular structure) or it begins within a single or several acini and shows a "pure" lobular structure. The factors, therefore,

FIG. 351 FIG. 352



Histologic Features of Estrogenic Mammary Cancer in the Rat's Breast.
FIG. 351. Comedo cancer in the terminal tubules.
FIG. 352. Papillary adenocarcinoma.

which give the common infiltrating lobular cancer its characteristic pathology are first, its capacity to form and invade lobular structures and, second, its penetration into the rich vascular perilobular bed. As in the human breast, these rapidly invasive cancers in the rat's breast provoke a fibrous reaction. (Fig. 349.)

Circumscribed comedo adenocarcinomas are found in animals that have been castrated and given interrupted daily doses of estrogen. In these animals, lobular development does not occur, and the cancers arise in the involuting lobular buds in the terminal tubules. The ductules which are the seat of such cancers usually have a basement membrane of avascular fibrous tissue. The cancers therefore may remain confined by the duct wall for long periods, and do not provoke the fibrous reaction seen with lobular cancer. (Fig. 351.)

The factors resulting in the characteristic pathology of comedo cancer therefore are: (1) the atrophy and disappearance of the lobular structures in the breast or in the portion of the gland affected; and (2) an associated atrophy of the periductal lymphatic and vascular network in the region of the tubules where the cancer arises.

Papillary adenocarcinoma is relatively rare in the rat's breast but occurs either in the ducts or in cystic acinar structures. (Fig. 352.) The structure of the tumor indicates that papillary cancers have the potentialities to form lobular tissue. When occurring within the lobule, papillary cancer extends along the wall of several dilated or

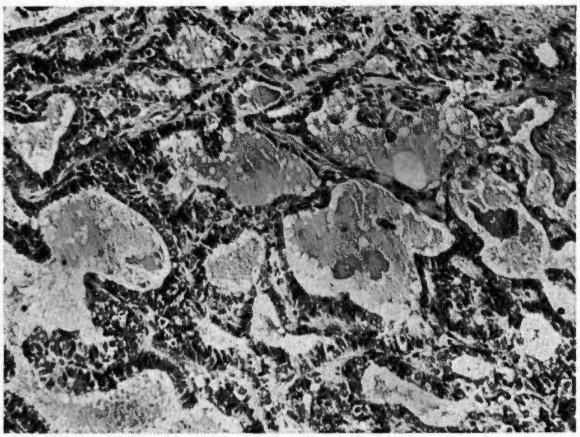


FIG. 353. Beginning gelatinous cancer in the rabbit's breast. The animal received 0.5 mg. of stilbestrol di-methyl ether daily for 20 months. (Compare with Fig. 342.)

cystic acini, the walls of which have ruptured leaving the strands of cancer projecting into the cystic space without attachment except at their base. In this way the characteristic papillary structure arises. When occurring within the larger ducts near the nipple, the cancer apparently arises in the more cellular tissue at the point of bifurcation or infolding so that the cancer at its base extends along the thick wall of the duct, bulging with free margins into the wide lumen. The vascular supply is available only through the portion of the tumor in contact with the duct wall, hence the tumor is usually supplied at only one or several points through a pedicle.

The factors determining the pathology of papillary cancer, therefore, are: (1) the growth of the tumor into a cystic cavity or large duct so that it is in contact with its vessels and supporting stroma at only one margin or at a single point, and (2) the resultant limitation upon the nourishment of the tumor during the early phase of growth.

Gelatinous forms of adenocarcinoma which are a degenerative feature of the lobular, comedo, or papillary forms have not been observed in rats. A probable case of beginning gelatinous cancer has been observed in the rabbit (Fig. 353).

Stratified epithelial cancers are relatively common in the large ducts beneath the nipple in the rat's breast. The tumor begins in the ducts just beneath the nipple and spreads rapidly, infiltrating the neighboring duct or penetrating into the surrounding stroma. The growth is composed of characteristic cells with a large amount of

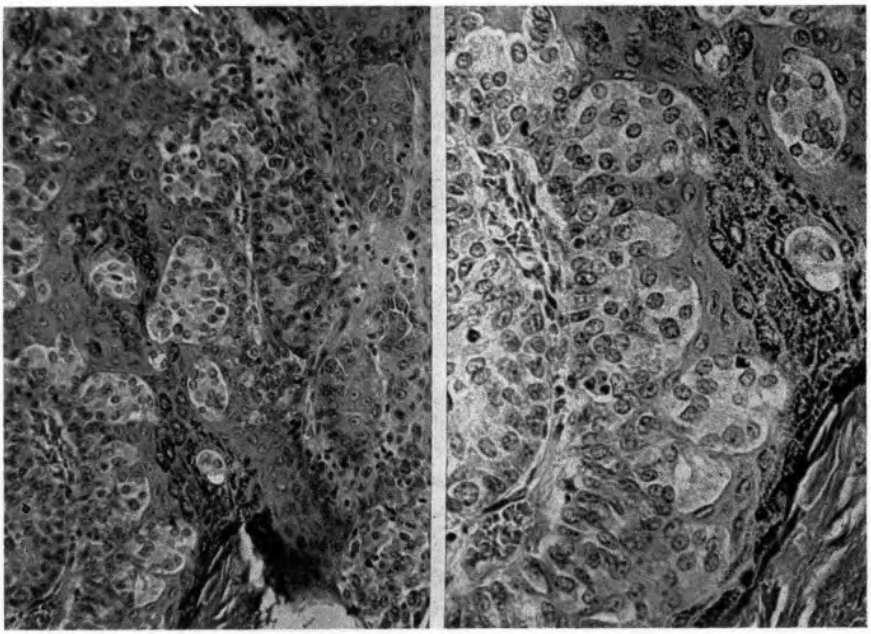


FIG. 354. Paget's disease produced experimentally in the rat. This animal received 5 gamma of estradiol benzoate daily for 14 months. In the photomicrograph on the left the relation of the cancer cells to the epidermis is shown. On the right is a higher magnification.

pale-staining cytoplasm, and nuclei which vary in size, some being exceptionally large. The breasts affected are those in which the estrogenic stimulation has been prolonged and in which atrophic changes in the finer branches of the duct tree have occurred. These cancers begin, as a rule, in the infoldings of the larger ducts and form clusters of new ducts, and cell masses developing small openings which coalesce to form a central lumen. (Fig. 350.) The cancer cells are between the adult lining cells and the basement membrane during the early phase of the growth, and remain for some time within the confines of the duct wall.

Striking changes in the nipple of the rat breast do not occur unless the estrogen (in the form of pellets) is implanted within the mammary gland itself. Under these conditions the nipple elongates, its epithelial covering thickens, and bleeding may occur. Malignant change (such as occurs in Paget's disease) has not been observed. However, cells of the Paget type may occur in mammary cancers in the rat's breast that have undergone squamous-cell metaplasia (Fig. 354).

Neomammary cancers and benign tumors resembling sweat-gland cancers are produced in the mammary gland of the rat if secretory changes are stimulated by administering testosterone in addition to the estrogen. (Fig. 319.)

GROWTH AND SPREAD OF MAMMARY CANCER

Regardless of the pathologic type of the mammary cancer or its rate of growth, the spread of the malignant process can conveniently be divided into three stages:

1. Intramammary extension.
2. Regional invasion.
3. Dissemination and metastasis.

Intramammary Extension

Adenocarcinomas arising in the smaller ducts or in the terminal tubules are confined by the walls of these pre-existing channels during the early stages of growth. Extension along a main duct and its branches, however, soon disperses the cancer through one or more ramifications of the duct tree. Paget's cancer of the nipple or pagetoid and papillary cancer of the large ducts may extend similarly via the milk channels. The extent to which cancer may travel along pre-existing ducts is obscured by the following facts:

1. Cancers arising in the smaller ducts and terminal tubules form additional ducts of tumor origin.
2. Cancers extending along the periductal lymphatics may break through the walls of the ducts and invade these structures from without.
3. The cancer at its inception may be multicentric and involve several branches of the same duct.

From their earliest stages, most of the infiltrating lobular cancers arising in the terminal tubules or acini show disruption of the basement membrane of the epithelial structures involved. The cancer

cells thus gain access to the neighboring lymphatic and tissue spaces and extend into the surrounding stroma. Since the organ affected contributes new blood vessels and a growth of connective tissue to the cancer, the malignant tumor may surround itself with a new and more extensive vascular bed or inclose itself in a dense wall of fibrous tissue. When an extensive vascularity is provoked by the cancer, additional opportunities for its spread are provided. Hence, cancers of the infiltrating type invade the surrounding mammary tissue (1) by dissolving through existing connective tissue membranes; (2) by extending along pre-existing lymphatics and tissue spaces; and (3) by penetrating newly formed vascular spaces which appear in response to their growth.

While the primary cancer tends to expand equally in all directions as a single mass, other portions of the cancer, by extending through the ducts or along the pathways of the lymphatics or through newly formed vascular spaces, establish secondary foci in the breast. Because of the secondary nodules established, it may be impossible after a relatively brief period to determine on pathologic examination which is the primary and which are the secondary colonies of cancer cells, although the primary mass is usually the largest. It is also difficult to decide, even in early cases, the amount or the multiplicity of the tissue which has given rise to cancer.

The extent to which the cancer is dispersed in the mammary gland is influenced by the age of the patient and the physiologic state of the mammary gland. From a study of the specimens of cancer removed from young patients and the cancers affected by pregnancy and lactation, it seems probable that the amount of proliferating material from which the cancer arises is greater and the degree of vascularity in the surrounding tissue more marked in young individuals and during pregnancy or lactation; and that this accounts for the more rapid spread of cancer in these patients. On the other hand the occlusion of vessels and tissue spaces which is found in the involuted mammary tissue of elderly patients apparently accounts for the better prognosis of cancer in these individuals.

The rate, extent and manner in which the cancer is dispersed in the mammary gland determines in a large measure the probability of regional spread and metastases and, hence, is a most important factor in treatment and prognosis. While a great deal has been written concerning regional and distant metastasis, relatively little attention has been given to the factors which govern the local invasiveness of the new growth. The relative importance of the pathologic type of the growth, the character of the tumor bed, and systemic factors in

determining the invasive qualities of the growth are difficult to estimate.

An attempt to discover the manner in which the factors just enumerated alter the growth of the primary tumor remains an important problem for pathologic investigation.

Regional Invasion

The overlying skin and the underlying fascia as well as the regional lymph nodes are commonly involved in mammary cancers. Handley has stressed the importance of the lymphatics as a pathway of invasion to the surrounding structures. He demonstrated the frequency with which, by a process of repeated multiplication, the cancer cells extend in a line along the lymphatics of the fascial planes. Interruptions in this gradual spread or permeation were attributed to a secondary fibrosis of the lymphatics following their permeation by cancer cells. Handley minimized the importance of direct invasion of pre-existing structures and minimized the importance of emboli of tumor cells which gained access to the blood or lymph stream. Nevertheless, the extension of cancer does occur by all three methods: by direct invasion, by lymphatic permeation, and by the transportation of emboli (Batson).

The skin is affected in a variety of ways by mammary cancer. The attachment of Cooper's ligaments (which pass from the mammary stroma to the skin) may be involved so that shortening and pull on the overlying skin (dimpling) occurs. The expansion of the tumor may cause pressure changes in the skin, which becomes thin, shiny, discolored and finally ulcerates. Invasion of the lymphatic plexus which forms a network in the subcutaneous tissue may cause blockage of one or more radicles producing edema and the characteristic "orange peel appearance." When this is widespread, the skin has the erysipeloid appearance seen in inflammatory cancer; or the nests of cells causing the blockage may grow until one or more visible nodules are formed as seen in carcinoma en cuirasse, where the entire chest wall may be studded with such masses. Skin nodules directly over the tumor, or a small zone of lymphedema or discoloration in the same location, does not necessarily indicate that the case is inoperable or incurable. The incurable stage has been reached, however, when the skin involvement is more extensive and appears some distance from the main mass. The removal of a maximum amount of skin in a circular area overlying the tumor, using the center of the tumor as the center for the circular skin incision, is one of the cardinal principles of Halsted's radical mastectomy, and

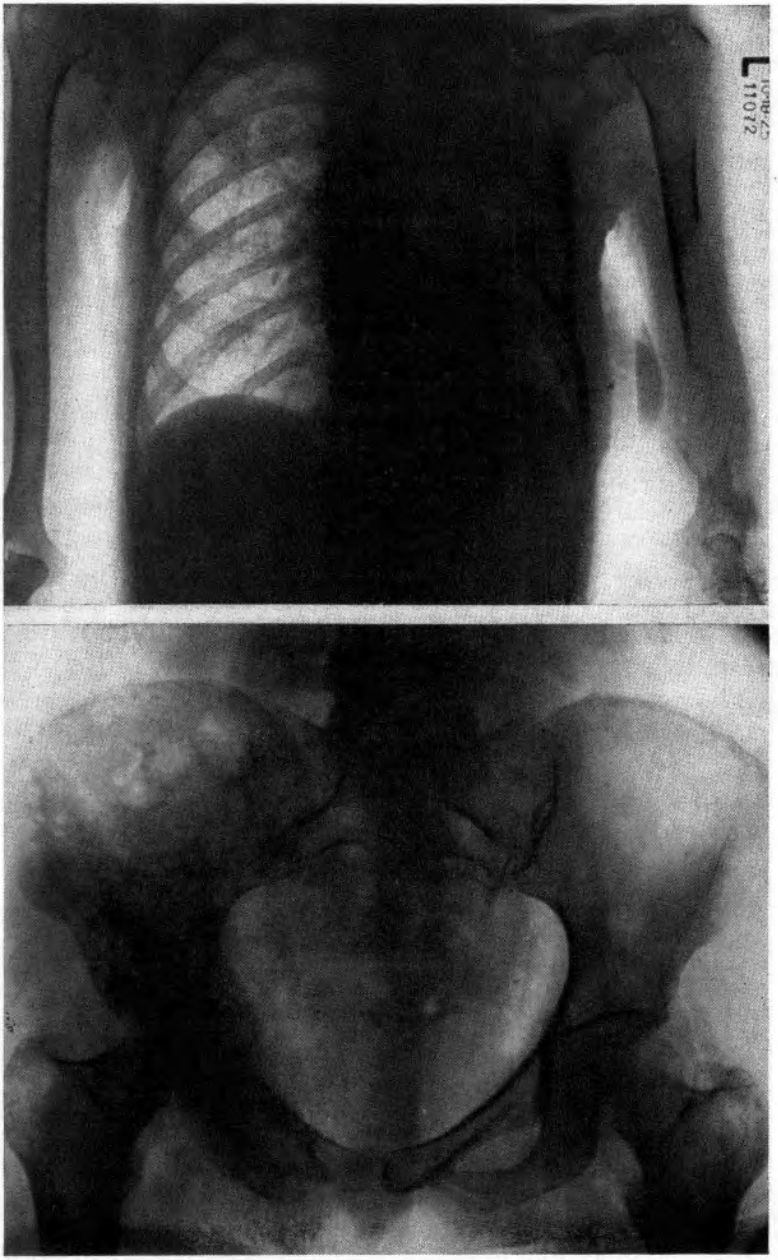


FIG. 355. Roentgenograms of osseous metastasis in mammary cancer. Both bone destruction and new bone formation are seen in the left humerus and right pelvis.

demonstrates the importance he attached to the dangers of skin involvement.

Handley found that mammary cancer travels along the lymphatic vessels of the muscular aponeuroses extending over the pectoralis fascia rather than invading the muscular fibers. Invasion of the muscle itself, however, does occur in rare instances.

Involvement of the regional lymph nodes occurs via lymphatic pathways which have been the subject of numerous painstaking and anatomic and pathologic studies. The lymphatics of the breast have their origin about the ducts and acini, collecting upward toward the nipple to form the subareolar plexus, or toward the periphery to form the deep fascial plexus. (See Fig. 48, Chap. 1.)

Usually two axillary trunks, one from the subareolar plexus and internal portion of the breast and another from the fascial plexus of the outer and upper quadrant and the under surface of the breast, connect with the axillary lymph nodes. Cancer cells transported by these pathways lodge in the axillary lymph nodes, the ones caught in the nearest node forming colonies which may ultimately provide cells for transport to the more distant nodes. From the axillary nodes the lymphatics follow the course of the axillary vein beneath the clavicle, some passing by way of the supraclavicular lymph nodes and others directly to the thoracic duct and then into the superior vena cava. The relatively early extension of cancer cells along these pathways to the regional lymph nodes is the basis for their removal by a careful axillary dissection in performing radical mastectomy.

An intercostal or parasternal lymphatic pathway passes from the medial portion of the breast along the route of the internal mammary artery to the mediastinal lymph nodes. This is one of the reasons for the poorer prognosis of cancers located in the inner mammary quadrants.

An intermuscular trunk drains the lymphatics of the under surface of the breast leading through the pectoralis major to nodes (Rotter's nodes) between the major and minor pectoral muscles. The extension of cancer in this direction emphasizes the importance of removing the pectoral muscles in performing radical mastectomy.

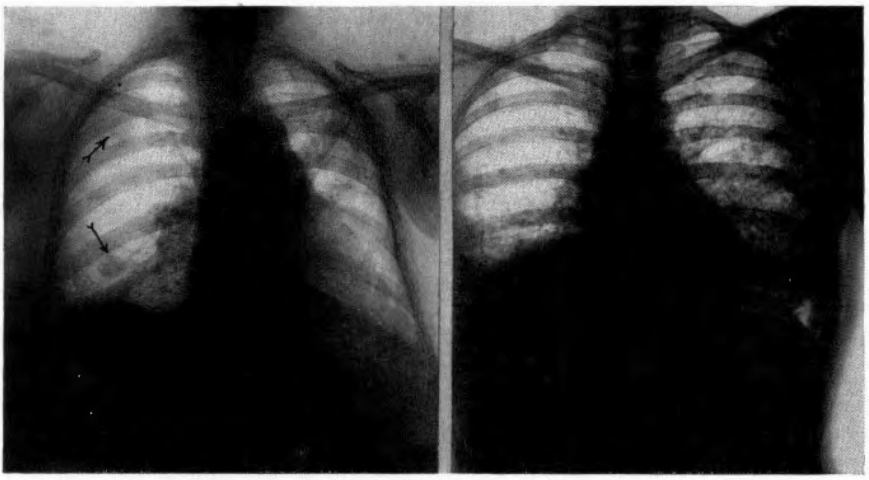
A number of paramammary lymphatic pathways which account for metastasis to the opposite breast or extension of cancer to the diaphragm, liver and peritoneum or along the abdominal wall to the inguinal lymph nodes, have been described in the skin and fascia. (See Chap. 1.) The most important of these are the subcutaneous lymphatic plexus which extends out in all directions from the breast, and the fascial plexus in the region of the xiphoid which passes inwardly to the peritoneum and hepatic ligaments.

Dissemination and Metastasis

Metastasis from mammary carcinoma may affect the lungs and pleura, the liver, the bones and the brain, in the order of frequency given, and may involve any of the internal viscera. Distant metastasis usually occurs after invasion of the regional lymph nodes, but may occur without axillary invasion.

The pleura is invaded (1) via lymphatics from the pectoral fascia, (2) from the mediastinal lymph nodes, (3) from the subclavian nodes,

FIG. 356 FIG. 357



Common and Rare Forms of Pulmonary Metastasis in Mammary Cancer.
FIG. 356. Roentgenogram showing the "cotton-ball" type of pulmonary metastasis.
FIG. 357. Roentgenogram showing a rare type of lymphatic seeding or miliary pulmonary metastasis.

(4) from the lungs or ribs in rare instances, or (5) by retrograde flow along the intercostal veins from the vertebral veins. Fluid, either serous or sanguineous, accumulates in the pleural cavity and diaphragmatic thickening and adhesions occur as the cancer cells settle in the fluid.

The lungs may be invaded (1) from the pleural lymphatics, (2) from the mediastinal nodes, (3) from the subclavian nodes, (4) from venous emboli of tumor cells passing through the heart, or (5) by retrograde flow from the intercostal veins. Usually one or more nodules of appreciable size develop in the mid-lung field, bilaterally or unilaterally, associated with pleurisy or mediastinal involvement. In rare instances, a slowly extending miliary metastasis involves both lungs (Figs. 356, 357).

The liver may be invaded (1) from the fascial lymphatics extending through the suspensory hepatic ligaments from the region of the xiphoid or (2) by venous emboli from retrograde flow through the intervertebral veins or (3) by extension through the diaphragm, which rarely occurs.

The importance of the vertebral veins for skeletal and cerebral metastasis has been recently demonstrated by Batson. According to Batson, the vertebral veins are a valveless plexus which form a separate system or pool for blood forced out of the thoraco-abdominal cavity by any act of coughing, sneezing, lifting or straining. He has demonstrated that material injected into the breast venules enters this vertebral system via the intercostal veins, and "duplicates the pattern of aberrant breast cancer spread; i.e., spread into the spine, the ribs, the shoulder girdle and the skull." Metastasis may, therefore, be distributed anywhere along the vertebral system without involving the portal, the pulmonary or the caval system of veins. According to this concept the system of communicating vertebral veins is "constantly and physiologically the site of frequent reversals of flow. During these reversals a pathway up and down the spine exists which does not 'involve the heart or lungs.' " These veins communicate with the veins of the brain and meninges and have connections with the veins of the body cavities at each intervertebral space.

These findings of Batson's indicate that the venous system is equally as important as the lymphatic system in explaining the dissemination of mammary cancer. Apparently most metastases to the osseous system or to the brain occur via the vertebral venous system described by Batson. In injecting a vein just lateral to the areola, the injection spread to the skin surrounding the injection site and extended past the mid-line. Batson states "the spread of injected material, in the sub-papillary plexus of the skin, indicates that Handley's lymphatic permeation theory even as it concerns the skin, might be restudied with profit." The findings at autopsy in recent studies of metastasis in mammary cancer, such as that of Warren and Witham, and of Turner and Jaffe stress the importance of dissemination via the blood vessels.

The frequency of osseous metastasis at necropsy is more than twice that found on roentgen-ray examination. The bones most frequently involved are those of the spine, pelvis, femur, skull, ribs, and humerus in the order given. Severe rheumatic pain often accompanies the metastasis, so that many clinicians consider this as evidence of bone involvement even when the roentgenograms are negative. The foci are multiple in three-fourths of the cases and solitary in the remainder. The solitary lesions are most common in a vertebra

or femur. Both bone destruction and reactive new bone are commonly seen in the roentgenograms (Geschickter and Copeland).

Farrow and Woodard have discussed the relationships of serum calcium and phosphatase to the sex hormones in cases of skeletal metastasis from mammary cancer. A study of 130 cases of cancer, metastatic to bone, showed numerous disturbances in the serum calcium levels. When osseous metastases were present, large doses of testosterone (400 mg. given over a period of 8 days) or large doses of estrogen (2 to 4 mg.) produced striking increase in the blood calcium levels and a less striking rise in the serum phosphatase. The calcium rise was associated with increased bone destruction and the phosphatase rise with an attempt at bone repair, in the opinion of the authors. They believe that this relationship of the sex hormones to bone destruction by osseous metastasis explains the increased incidence of skeletal metastasis at the time of the menopause in women with mammary cancer and the beneficial effects on osseous metastasis of sterilization with the x-rays.

A study of the author's cases shows that the majority of metastases to the axillary lymph nodes occur between six and nine months after the onset of symptoms, whereas distant metastasis (as measured by bone involvement) becomes manifest between 24 and 36 months after onset. Lymph-node involvement occurred in 64 per cent of infiltrating cancers that had an average duration of eight and one-half

TABLE LIII

PERCENTAGE OF CASES IN WHICH METASTASIS FROM MAMMARY CANCER INVOLVES THE MAJOR ORGANS

	WARREN AND WITHAM	GROSS	TURNER AND JAFFE	SAPHIR AND PARKER
Lymph nodes	71.9%[1]			
Lungs	58%	50%	62%	65%
Pleura	39%	51%		
Liver	59%	48.6%		55%
Bone	43%	20.5%	57.1%	
Brain		9.4%		
Skin	40%			
Other breast	13%	7.8%		
Adrenals	32%			44%
Ovary		8%		16%
Spleen				23%

[1] Warren and Witham found 39 per cent involvement of regional lymph nodes in spite of the fact that 113 of 154 cases had axillary dissection with radical mastectomy and 79 per cent involvement of distant lymph nodes. The figure 71.9 per cent is from the author's cases, based on microscopic study of the axillary nodes removed at operation in all forms of mammary cancer.

months. Bone involvement demonstrated by the roentgenograms was found on an average of 31 months after the onset of symptoms. Warren and Witham report similar findings. Approximately 88 per cent of their cases developed metastasis to distant organs between two and three years after the onset of symptoms (one to two years after treatment). Ten per cent of the metastasis to distant organs became manifest after the fifth year (fourth year after treatment). Warren and Witham found that the opposite breast was involved in 13 per cent of the cases coming to autopsy, and that this usually occurred within two years after treatment. Skin metastasis, which occurred in 40 per cent of the cases, was more consistently late in development than other groups of secondary deposits. Most of these metastases develop more than two years after the onset of symptoms.

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19

Infiltrating Adenocarcinoma

(Lobular Cancer)

CLINICAL GROUPS

Approximately three-fourths of all mammary carcinomas arise from the small tubules or acinar structures of the breast and rapidly invade the stroma. (Figs. 358-360.) The terms, carcinoma simplex, scirrhous cancer, and spheroidal-cell carcinoma are commonly applied to this ordinary form, which is herein referred to as infiltrating adenocarcinoma or lobular cancer. From a clinical standpoint these cancers may be divided into primary, secondary, and fulminant forms. (Table LIV.) This classification is based upon the extent and mode of spread of the disease at the time of clinical examination. It implies no pathologic knowledge other than recognition of the fact that the ordinary hard infiltrating cancer which has a characteristic feeling on palpation has likewise a fairly constant microscopic pathology.

The group of primary infiltrating mammary cancers includes early and advanced cases. Early cancers measure less than 5 cm. in size and have an average duration of symptoms of eight and a half

months. The overlying skin is adherent in 42 per cent of these growths but not invaded, while the axillary lymph nodes are involved in 64 per cent. Advanced lobular cancers are those more than 5 cm. in size with symptoms which average 14 months in duration. Skin adherence and axillary involvement are demonstrable in nearly every case. (Figs. 365, 366.)

In the secondary group are included recurrent cancers following an incomplete or complete operation and widely disseminated cancers with invasion of the chest wall or supraclavicular nodes or internal metastasis at the time of examination.

TABLE LIV

CLINICAL GROUPS IN 1906 INFILTRATING MAMMARY CARCINOMAS

GROUP	CHARACTER OF TUMOR	NO. OF CASES	FIVE-YEAR SURVIVALS
1. Primary Infiltrating Cancer	a. *Small* 1 to 5 cm. in size	1,066	42.8%
	b. *Large* over 5 cm. in size	416	9.3%
2. Secondary Infiltrating Cancer	a. Recurrent cancer	207	7.8%
	b. Carcinosis	74	0%
3. Fulminant Infiltrating Cancer	a. Cancer in pregnancy and lactation	58	19.4%
	b. Cancer in lactation mastitis	38	3.0%
	c. Inflammatory cancer	47	0%

In the group of fulminant cancers are included those occurring in pregnancy and lactation, cases developing in an old lactation mastitis, and acute or inflammatory cancer with erysipeloid involvement of the skin. The breast is diffusely invaded in many of these cases and involvement of the axillary nodes is rapid and extensive (Fig. 361).

The clinical groups shown in the accompanying tabulation differ from the Steinthal classification in two fundamental respects. First, the circumscribed forms, such as papillary, comedo, and gelatinous adenocarcinoma are excluded as well as the pathologic types of Paget's disease, transitional-cell cancers of the ducts, cancer cysts, squamous-cell, and sweat-gland cancers. Thus, the clinical groups all relate to cancers in which the fundamental pathology is uniform. Second, the groups given are without regard to the presence or absence of metastasis in the axillary lymph nodes. Experience has shown that it is difficult to determine clinically whether or not such involvement exists. In one-third of the cases, which are negative to palpation, metastasis to the nodes is demonstrated by subsequent

pathologic examination. Conversely, in about one-third of those cases in which the nodes are enlarged to palpation, pathologic examination fails to reveal involvement.

The present chapter is devoted to the primary forms of infiltrating adenocarcinoma. The recurrent, generalized and fulminant forms are considered in the chapter that follows.

AGE OF ONSET

Approximately 50 per cent of infiltrating mammary cancers occur between the ages of 40 and 55 years, and 75 per cent between the ages of 35 and 60 years. (Fig. 362.) In younger women between the ages of 20 and 30 years, benign fibro-adenoma is the most common lesion; and between the ages of 30 and 40 years, some form of cystic mastitis. While this knowledge is helpful in diagnosis, mammary cancer has been reported at increasingly early ages in the recent literature.

Krauss and Kline were able to find 12 cases of mammary cancer in patients under 20 years in the literature prior to 1926, and added a bilateral case in a girl of 16. Our youngest patient with infiltrating mammary cancer was 15 years old. Nunn reported a similar patient aged 15 and Carnett et al. the history of a girl aged 14 years. In 3 of the cases reported in girls under 20 years, both breasts were ultimately involved.

Although infiltrating mammary cancer (and other forms) are relatively rare under the age of 26 years, the disease may occur any time after the onset of mammary development and has been reported as early as the tenth year (Sears and Schlesinger).

ETIOLOGIC FACTORS

In the present series of cases, approximately 1,400 histories were available in which the patients had been questioned in regard to the various etiologic factors shown in Table LV. In about three-fourths of these cases nothing of significance was elicited. A history of trauma to the region of the breast was reported in approximately 6.5 per cent, and in most instances this served to call attention to a preexisting tumor. Inability to nurse because of insufficient milk, sore or retracted nipples, etc., was recorded in 5.2 per cent[1] and a history of lactation mastitis or abscess in approximately 6 per cent of parous women. The evidence of mammary dysplasia or cystic mastitis was diligently sought, and a record of such a condition, based upon the

[1] Inability to nurse is at least this common in the general population in accordance with the data obtained from our large obstetric clinics.

history, physical examination, or upon the gross specimen, was found in only 55 cases (4 per cent). In 15 cases (1 per cent) there was a history of mammary cancer in several members of the family.

TABLE LV

POSSIBLE ETIOLOGIC FACTORS IN THE HISTORY OF 1,400 CASES OF INFILTRATING MAMMARY CANCER

ETIOLOGIC FACTOR	NO. OF CASES	PER CENT OF TOTAL
History of trauma	91	6.5%
Difficulty in nursing	72	5.2%
Mastitis or abscess	68	5.0%[1]
Mammary dysplasia (Cystic mastitis)	55	4.0%[2]
Discharge from nipple, other than bloody	32	2.3%
Discharge from nipple, bloody	28	2.0%
History of virginal hypertrophy or evidence of same	16	1.0%
Family history of cancer	15	1.0%
History of excision of benign tumors	13	1.0%

[1] Equals 6 per cent of parous women.
[2] Based upon the history, clinical findings and examination of the gross specimen.

In 13 cases, a benign tumor (usually a fibro-adenoma) had been previously excised and 16 cases were reported with virginal hypertrophy or excessive breast development, dating from puberty. Clinical or pathologic evidence of retained mammary secretion was rare. Thirty-two cases had a serous or cloudy discharge from the nipple (in 28 additional cases the discharge was sanguineous). In 29 cases dilated ducts with retained secretion were found at examination or in the gross specimen. Two cases had galactorrhea; and two, a galactocele.

The number of single women (12 per cent) is higher than in the control population and the average number of children among those married (2.3 per cent) is less (see Table XLVII).

When the data obtained from the histories are combined with that recorded in the physical examination, it may be concluded that the origin of infiltrating mammary cancer is related to normal physiologic processes of development and involution, rather than to predisposing pathologic factors. Pregnancy, lactation or lactation mastitis may influence the subsequent growth and spread of cancer as will be indicated later when the fulminant forms of scirrhous cancer are considered. Most of the factors reviewed and listed in Table LV are only rarely of significance, however, in the development of the disease.

SYMPTOMS

The early stages of infiltrating mammary cancer are symptomless. Usually the discovery of a lump which has caused neither pain nor

TABLE LVI

DATA ON 1,482 PRIMARY INFILTRATING CANCERS

I—AGE

20–29	29
30–39	250
40–49	491
50–59	428
60–69	237
70	47
Total	1,482

(Average age—50.1 yrs.)

II—MARITAL

Single	125
Married	916
Married, childless	192
Married, miscarriages	34
Married, one child	192
Married, two or more children	498
No data	441
Total	1,482

(Average number children in parous women—2.3)

III—DURATION OF SYMPTOMS

6 months or less	548
7 to 12 months	219
1 to 2 years	257
2 or more years	120
No data	338
Total	1,482

(Average duration—11.5 mos.)

IV—SIZE

1 to 1.5 cm.	90
2 to 3 cm.	450
4 cm.	127
5 cm.	76
Over 6 cm.	294
No data	445
Total	1,482

V—LOCATION

Unilateral	1,465	Lower, outer quadrant	15.2%
Bilateral (at examination)	17	Upper, inner quadrant	14.5%
Upper, outer quadrant	44 %	Lower, inner quadrant	3.7%
Central	22 %		

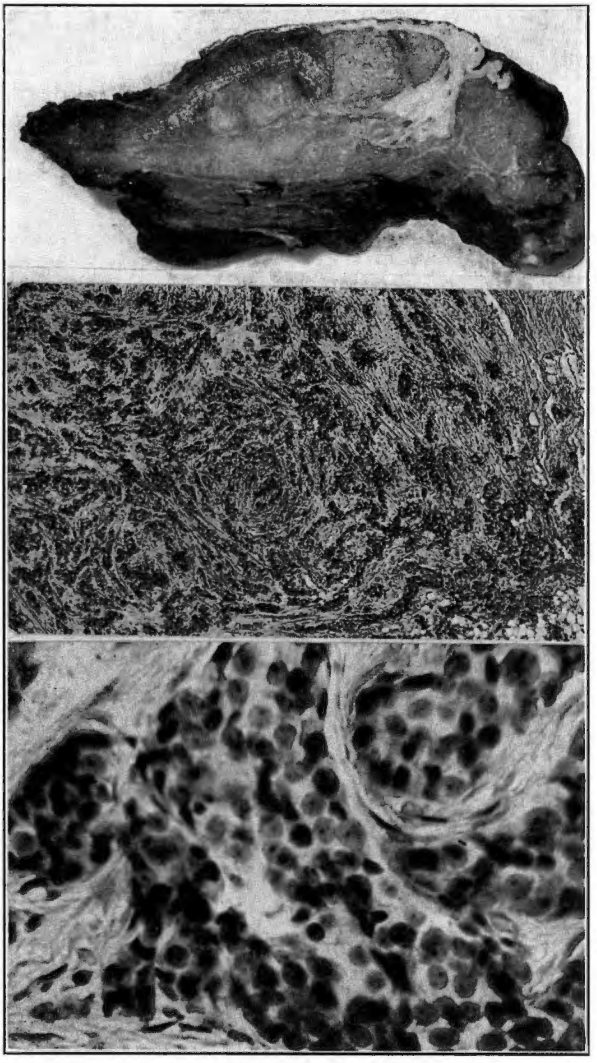
VI—SYMPTOMS

Small Infiltrating Cancers		Large Infiltrating Cancer	
Lump	83 %	Rapid growth of lump	54%
Pain or tenderness	45 %	Pain or tenderness	77%
Skin changes	3 %	Skin changes	23%
Nipple retracted	2 %	Nipple retracted	4%
Nipple discharge (Bloody)	1.7%	Nipple discharge (Blood or pus)	3%

VII—RESULTS OF TREATMENT

Small Infiltrating Cancers		Large Infiltrating Cancer	
Well—less than 5 yrs. or lost	328	Well—less than 5 yrs. or lost	99
Dead—in less than 5 yrs.	422	Dead—less than 5 yrs.	286
Well—5 yrs.+	316	Well—5 yrs.+	31
Followed	738	Followed	317
Five-year survivals	42.8%	Five-year survivals	9.7%

Average Five-Year Survivals—32.8%



FIGS. 358, 359, 360. Gross specimen, low and high-power photomicrographs of infiltrating (scirrhous) lobular cancer. This is the most common form of mammary cancer.

discomfort calls attention to the disease. This occurs accidentally while bathing or dressing, or while holding the arm or some object against the breast. In some the tumor was found by the physician in a routine examination or by the patient after hearing of the importance of prompt recognition of conditions of the breast through friends or relatives or over the radio. In other instances the steady or rapid growth of the mass has alarmed the patient. The symptomless nature of the mass in the breast was emphasized in 2 per cent of the cases by the fact that the initial symptoms related to a metastatic growth, rather than to the primary lesion.

Pain or tenderness was present in approximately 45 per cent of the cases at some time, but was more frequent in the larger growths. It preceded the discovery of the tumor in only 7 per cent of the cases and, in 8 per cent, the pain and the tumor were reported as simultaneous in onset. Pain or tenderness was rarely severe and was often described as an intermittent sticking, stinging or drawing sensation—"burning," "catching," or "pulling" were among the other descriptions given. Unlike the pain of cystic mastitis, there is no exacerbation in the premenstruum.

Changes in the position of the nipple or in the appearance of the skin overlying the tumor, when noted by the patient, are late signs in mammary cancer. They were the reason for seeking medical consultation in approximately one-third of those cases in which the tumor was over 5 cm. in diameter. (Figs. 363, 364.)

Discharge from the nipple is rarely present as a symptom of onset. A sanguineous discharge was noted in 28 cases and in only 7 did it precede the discovery of the tumor. (See Chap. 14.) As noted in Table LV, 32, or 2.3 per cent, of the cases had a serous, cloudy or grumous discharge, but this is coincidental rather than related to the tumor. Among the large infiltrating cancers, pus or blood may collect in the large ducts because of secondary infection, but this is most common where ulceration has occurred.

Duration of Symptoms

The duration of symptoms and the rate of growth of the cancer determine the extent of the disease and the character of the findings on examination. If one separates the infiltrating forms of mammary cancers from other pathologic types, and from the fulminating group associated with pregnancy, lactation, or inflammatory signs, there is a fairly definite correlation between the size of the growth and the duration of symptoms as shown in the accompanying tabulation.

It will be noted that less than 10 per cent of the cases studied were examined when the size of the mass was under 2 cm. in diameter, and

TABLE LVII

CORRELATION OF SIZE WITH DURATION OF SYMPTOMS

(1,042 Cases of Infiltrating Mammary Cancer)

SIZE OF CANCER	DURATION OF SYMPTOMS	NO. OF CASES
1 to 1.5 cm.	3.0 months	95
2 to 3 cm.	8.5 months	450
4 cm.	9.7 months	127
5 cm.	10.8 months	76
over 5 cm.	14.0 months	294

even in this group of early tumors the average duration of the tumor was three months. While some authors (Pack and Gallo) have chosen a period of three months as a reasonable delay in seeking advice and treatment, size rather than duration of symptoms is a more reliable guide to prognosis and treatment. The percentage of cases with involvement of the skin, axillary nodes, and internal metastasis rises sharply when infiltrating cancers become more than 5 cm. in diameter, and the number of five-year survivals shows a corresponding decrease. IT IS FOR THIS REASON THAT A DIAMETER OF 5 CM. HAS BEEN CHOSEN AS THE DIVIDING LINE BETWEEN EARLY AND LATE CASES.

CLINICAL FINDINGS

Early Infiltrating Mammary Cancer

Slightly more than one-half of the cases with infiltrating mammary cancer were in the early group (1,066 of 1,906 cases). The majority of the patients were at or near the menopause (40 to 55 years) and had a painless lump in the breast 2 to 3 cm. in diameter which had been present eight months or less prior to the time of examination. Persistence of the lump, its increasing size, occasional fleeting pain, tenderness, changes in the nipple, or a chance conversation, were the chief reasons to seek advice.

The five major findings on examination of the breast were:

1. The presence of a single lump in a breast otherwise normal to palpation.
2. The hard and irregular feeling of the tumor.
3. The apparent nearness of the tumor to the examining fingers because of atrophy of overlying fat.
4. The restricted mobility of the mass.
5. Flattening or retraction of the skin or nipple on the affected side when the arms or breasts were manipulated.

The malignant mammary tumor is, with few exceptions, a solitary lump and is rarely complicated by the presence of other nodules or

a history of the excision of a previous tumor. The breast affected is usually undergoing involutional changes and much of the glandular tissue and fibrous stroma is replaced by fat. The hardness and the irregular surface of the tumor have been frequently emphasized. Because of the solid nature of the growth, tumors 2 cm. or more in diameter will cast a shadow on transillumination if the light employed is not too intense.

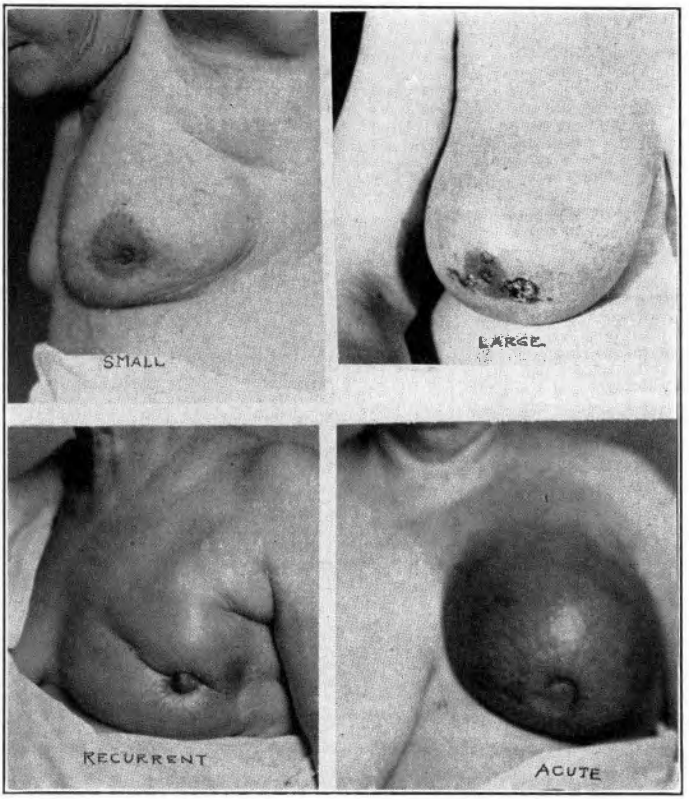


FIG. 361. Photographs of patients with small, large, recurrent, and acute forms of infiltrating lobular cancer (scirrhous cancer).

The restricted mobility of the tumor and the presence of ill-defined margins are impressions frequently gained on palpation. These characteristics of the growth are expressed by the phrase "the mass is of the mastitis type." One of the diagnostic features of this form of mammary cancer is its apparent superficiality. The atrophy of the overlying fat and shortening of the fibrous attachments to the skin (Cooper's ligaments) give this impression on palpation. It is a good clinical rule to classify all superficial nodules in the breast as malignant unless they are obviously epidermal lesions.

Flattening or dimpling of the skin may be a relatively early sign in mammary cancer if the proper procedures are used to demonstrate this. Careful inspection of the breast under oblique lighting, as the arms are slowly raised, may bring out this feature, or gentle compression of the breast between the palms of the two hands may be used to demonstrate it. Flattening or fixation of the nipple or alteration of its position are not early signs unless the tumor is centrally located.

In the 1066 cases grouped as early infiltrating cancer, dimpling or attachment to the skin was found on examination in 43 per cent and retraction or fixation of the nipple in 21 per cent. Discoloration or edema of the skin overlying the tumor was present in only 6 per cent. This does not include the earliest signs of restricted mobility or flattening of the skin apparent on careful manipulation. These findings and other early signs of mammary cancer are best demonstrated by gentle palpation and manipulation. Undue pressure, pulling or squeezing of a mass in the breast should be guarded against at all times because of the danger of provoking metastasis.

Although involvement of the axillary nodes was demonstrated microscopically in 64 per cent of these cases, they were found on clinical examination in only 42 per cent, and noted by the patient in only 1 per cent of the cases.

TABLE LVIII

SYMPTOMS AND FINDINGS IN 1,066 EARLY INFILTRATING CANCERS

FINDING OR SYMPTOM	ON EXAMINATION	SYMPTOM OF ONSET
Mass or tumor	100%	83%
Pain or tenderness	45%	7%
Skin adherence	43%	3%
Palpable axillary nodes	42%	1%
Nipple fixed or retracted	21%	2%
Sanguineous discharge from nipple	1.7%	0.7%

Large Infiltrating Adenocarcinoma

Four hundred and sixteen cases of lobular cancer in which the tumor measured more than 5 cm. in diameter have been grouped separately. These cases belong to the same pathologic group as the smaller infiltrating cancers, but because of their size and extent they require little skill in diagnosis. On the other hand, at the present writing, they offer insurmountable difficulties in treatment. Their hard and irregular outlines are readily recognized on palpation, the skin is adherent to the growth and the nipple retracted. The invading strands of tumor tissue radiate from the main mass

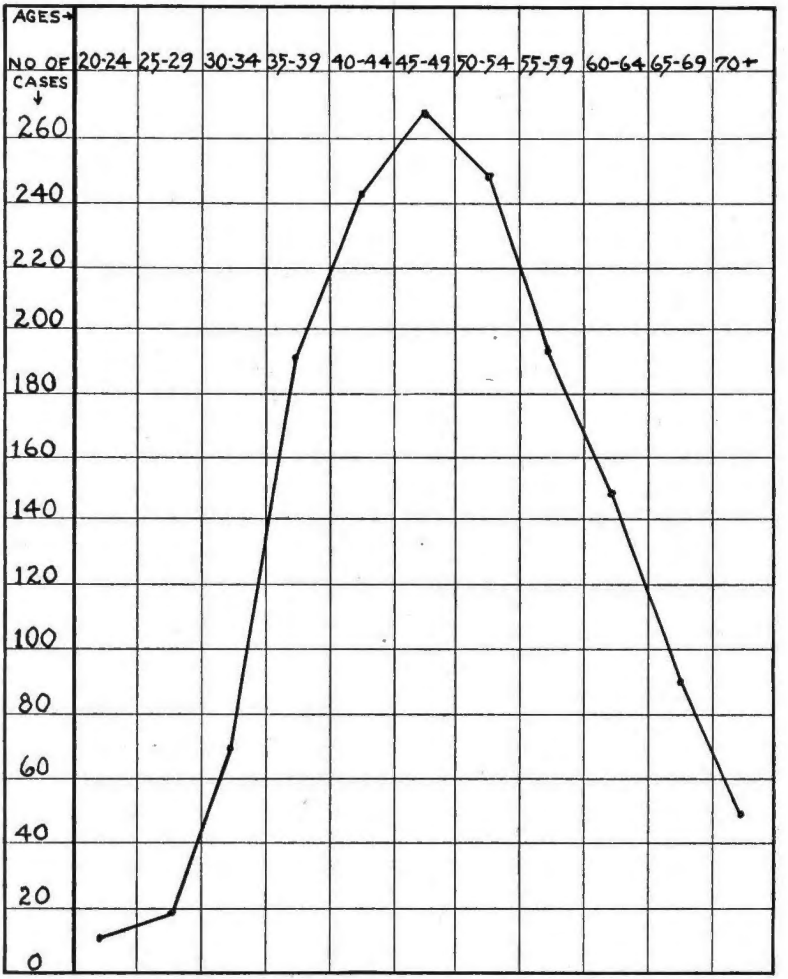


FIG. 362. Chart showing the age distribution of infiltrating mammary cancer.

so that, in many cases, the entire breast seems infiltrated. Regardless of the quadrant or sector of the breast occupied by the cancer, extension to the axillary lymph nodes was ascertained clinically or verified on pathologic study in all but a few cases. In slightly more than one-third of the cases studied, the skin overlying the tumor was edematous, discolored, thin and shiny, ulcerated, or the seat of secondary tumor nodules. (Fig. 361.)

Except for their longer duration and a younger average age,[1] the symptoms of large infiltrating scirrhous carcinoma resemble those found in smaller tumors of the same type. A higher percentage noted pain or tenderness prior to examination and had not sought treatment previously because these symptoms had only recently developed. One-fourth of the cases had noted that the overlying skin had become "angry" or ulcerated and mentioned this as a reason for seeking treatment. (Fig. 366.)

The duration of symptoms, which averaged 14 months, is shown in Table LX.

TABLE LIX

SYMPTOMS AND FINDINGS IN 416 LARGE INFILTRATING CANCERS

FINDING	ON EXAMINATION	AT ONSET
Mass or tumor	100%	54% (Rapid growth noted)
Pain or tenderness	77%	18%
Skin adherence	100%	
Other skin changes (discoloration, ulceration, etc.)	33%	23%
Palpable axillary nodes	92%	0.5%
Retraction of nipple	97%	4%
Blood, pus, etc., from nipple	3%	0.5%

TABLE LX

DURATION OF TUMOR (AS STATED BY PATIENT) IN LARGE LOBULAR CANCERS

Six months or less	96 cases
Seven months to one year	52 cases
One to two years	137 cases
Over two years	61 cases
Not recorded	70 cases
Total	416 cases

When the tumor had been observed for eight or more months prior to examination, the patient usually remarked that enlarge-

[1] In small infiltrating adenocarcinoma 49 per cent of the cases were younger than 50 years of age, and in the large infiltrating cancer 53 per cent were less than 50 years of age.

ment had been gradual at first, and that the mass had grown more rapidly in the past few weeks or months.

This group of cases presents all the classical signs of cancer of the breast emphasized in the older literature. The tumors occupy one or more quadrants of the breast. They are hard and fixed to the overlying skin and sometimes to the fascia of the underlying muscles. Discoloration, edema with "orange peel appearance," secondary nodules in the skin, ulceration, and fungation were among the skin changes noted. Although the affected breast may be drawn closer to the chest wall, its size, because of the extent of the growth, exceeds that of its fellow. Discharge from the nipple was noted in 3 per cent of the cases and was described as bloody, foul, or pus. To this group belong the greatest number of cancers which ultimately involved both breasts. In twelve of the patients both breasts were involved at the time of first admission, the bilateral amputation being done in two on the first admission and in the remaining 10 with an interval of about one month between the removal of the right and left breasts.

DIFFERENTIAL DIAGNOSIS

In infiltrating mammary cancer, the five-year survival rate is as high as 50 per cent only in those cases in which the diameter of the tumors is less than 3 cm. and in which the known duration of the mass averages 8.4 months. In examining the breast it must be continually borne in mind that cancer in this stage usually presents none of the classical diagnostic signs of fixation or extension and is often a symptomless disease. Early cancers simulate many benign mammary lesions. Hence, to determine the presence or absence of malignancy, when the opportunities for cure are greatest, excision and microscopic study of the growth are essential.

The chief lesions to be considered in differential diagnosis are fibro-adenoma, a thick-walled cyst buried in mammary tissue, residual lactation mastitis or plasma-cell mastitis, fat necrosis and indurated tissue in adenosis (Schimmelbusch's disease).

Fibro-adenoma has its onset, as a rule, in young individuals between 20 and 30 years of age; when persisting into the cancer age the tumor often has remained stationary in size over a period of years. Rapid growth may occur in pregnancy or toward the menopause necessitating immediate excision and microscopic diagnosis. These tumors differ from carcinoma in their mobility and freedom from attachment to the skin. They do not have the same degree of hardness. The surface is lobulated rather than irregular and does not give the impression of superficiality on palpation.

A thick-walled cyst is usually seen in women of the cancer age. The tumor is more circular in outline and more freely movable than cancer and is clear on transillumination. If a needle is inserted a cloudy fluid may be withdrawn, confirming the diagnosis.

Residual lactation mastitis may be impossible to differentiate from cancer on clinical examination and may, in fact, be complicated by carcinoma. The history of a lump persisting since a previous lactation mastitis aids in diagnosis, but the same hard infiltrating mass characteristic of cancer may be present. Excision affords an opportunity for microscopic diagnosis and may prevent the occurrence of cancer in mastitis.

Plasma-cell mastitis may simulate cancer. It occurs near the menopause. There is redness of the overlying skin, the nipple may be fixed and the mass is hard and has indefinite borders. The finding of dilated ducts with a grumous discharge of the nipple, the sudden onset of the symptoms and the presence of a low-grade fever suggest the presence of plasma-cell mastitis. Again recourse to biopsy should be had to confirm the diagnosis.

In fat necrosis there may be a history of trauma to an obese breast. The lesion is small, dense and hard and cancer must be ruled out by exploration and microscopic study.

In adenosis there may be a bloody discharge from the nipple. The indurated and tender tissue may be hard and superficial, but there is no attachment to the skin, although there is little overlying fat. Small cysts or intracystic papillomas may occupy a superficial location and be firm to palpation. In spite of the long duration of the symptoms, the multiplicity of the lesions which palpate like a bag of shot and the characteristic saucer-like edge to the breast, one or more areas similar to those just described may feel like cancer. Since the tendency for cancer to arise is definitely greater in these cases than in the normal breast, exploration and microscopic study are indicated.

The larger infiltrating mammary cancers must be differentiated from giant myxoma, mammary sarcoma, or infectious mastitis.

Giant intracanalicular myxomas occur in the cancer age and grow to immense size. Such tumors, however, are lobular and rubbery in consistency with scattered cystic masses. The overlying skin is not fixed or ulcerated and the growth is not adherent to the chest wall. The axillary lymph nodes are not involved.

Mammary sarcoma may be difficult to distinguish from advanced cases of infiltrating cancer. In sarcomas the growth is rapid and yet involvement of the skin or axillary nodes is rare. Biopsy is indicated to establish diagnosis.

TABLE LXI

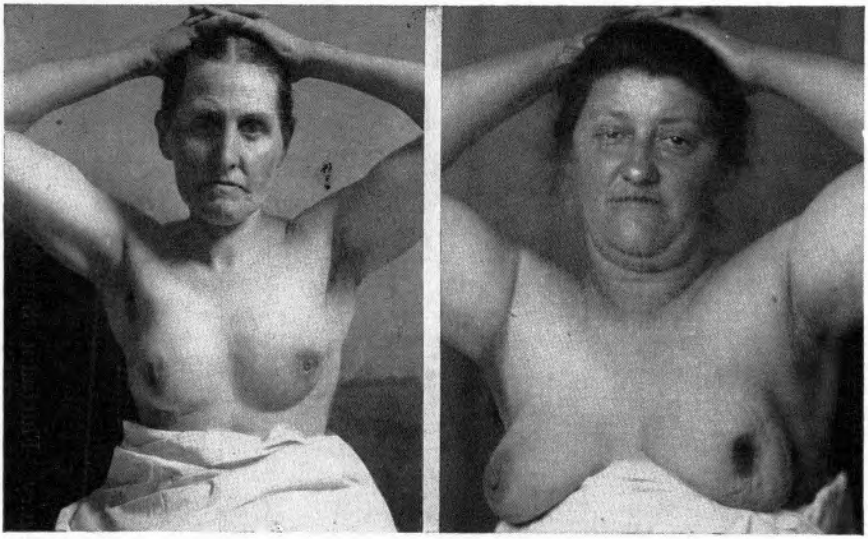
DIFFERENTIAL DIAGNOSIS OF INFILTRATING CANCER

Important Features of Mammary Lesions to Be Considered

LESION	NO. CASES	PREVALENT AGES	AVERAGE DURATION	SINGLE OR MULTIPLE	CONSISTENCY	CONTOUR	MOBILITY	OVERLYING FAT	SKIN CHANGES	COMPLICATED BY CANCER
Infiltrating cancer	1,066	40–55	8.5 mos.	Solitary	Hard	Irregular	Restricted	Atrophied	Adherent	....
Fibro-adenoma	600	20–30	2 yrs.	Solitary	Firm	Lobulated	Movable	Normal	Free	No
Cyst (thick walled)	589	35–50	2.5 mos.	Solitary	Tense	Smooth	Movable	Normal	Free	No
Adenosis	212	35–40	21 mos.	Multiple	Firm	Shotty	Free	Deficient	Free	Yes
Residual mastitis	36	30–50	10 yrs.	Solitary	Hard	Indefinite margins	Restricted	Infiltrated	Adherent	Yes
Plasma-cell mastitis	15	45–55	2 mos.	Solitary	Hard	Indefinite margins	Restricted	Infiltrated	Adherent	No
Fat necrosis	37	40–50	3 yrs.	Solitary	Hard	Irregular small	Free	Involved	Free	No
Giant myxoma	42	40–55	6 yrs.	Solitary	Firm to fluctuant	Lobulated	Movable	Diminished	Free	Sarcoma
Fibro-sarcoma	29	45–55	9 mos.	Solitary	Hard	Nodular	Movable	Diminished	Free	....
Abscess in chronic mastitis	120	20–45	3 yrs.	Solitary	Fluctuant	Smooth	Movable	Normal	Sinus	No

Chronic lactation mastitis, tuberculosis or gumma rarely reach large size without suppuration, caseation, or necrosis. Pus and sinus formation are the rule in advanced cases. In addition there may be the constitutional reactions of fever and leukocytosis. A roentgen-ray of the chest may aid in the diagnosis of tuberculous mastitis; and the Wassermann reaction when a gumma is suspected.

FIG. 363 FIG. 364



FIGS. 363-364. Photographs of patients with infiltrating mammary cancer. Retraction of the nipple and dimpling of the skin indicate fairly large tumors.

PATHOLOGY

The pathologic findings are fairly uniform in infiltrating mammary cancers. On section, the dense, whitish-yellow stellate mass is gritty and its surface retracts when cut. The main growth may extend toward the nipple or toward the periphery of one of the quadrants of the breast in a series of dendritic processes. These radiating tentacles of the tumor may give the impression before operation of a large mass 5 or 6 cm. in diameter although the central mass measures only 2 to 3 cm. across in the gross specimen. Secondary nodules within the breast, separate from the primary nodule, are rare. Tumors reaching a size of 4 to 5 cm. because of the atrophy of the surrounding fat often extend from the skin above to the pectoral fascia beneath but seldom invade the fibers of the muscle. The tumor is found most frequently in the outer and upper or central portion

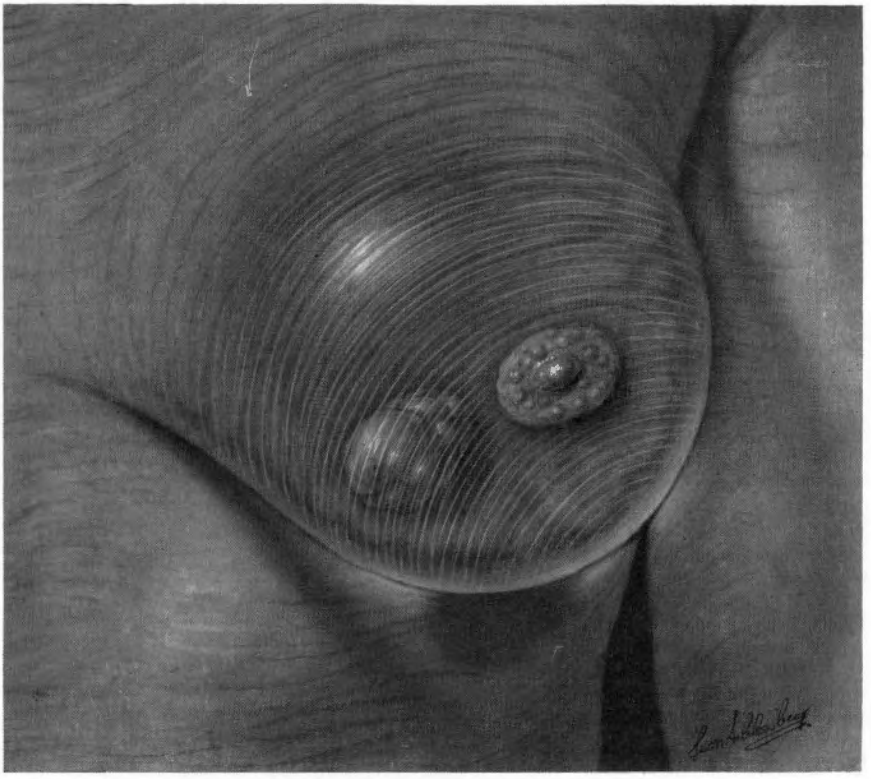


FIG. 365. Drawing to indicate the characteristics of infiltrating carcinoma on palpation. The tumor is hard, irregular, attached, and has the feeling of superficiality because of atrophy of the overlying fat.

of the breast but may occur in any of the various quadrants (see Fig. 335.) These growths remain free from necrosis and softening even when attaining large size, if the overlying skin remains intact. In a few instances infection enters via the nipple and large ducts, causing softening and degeneration.

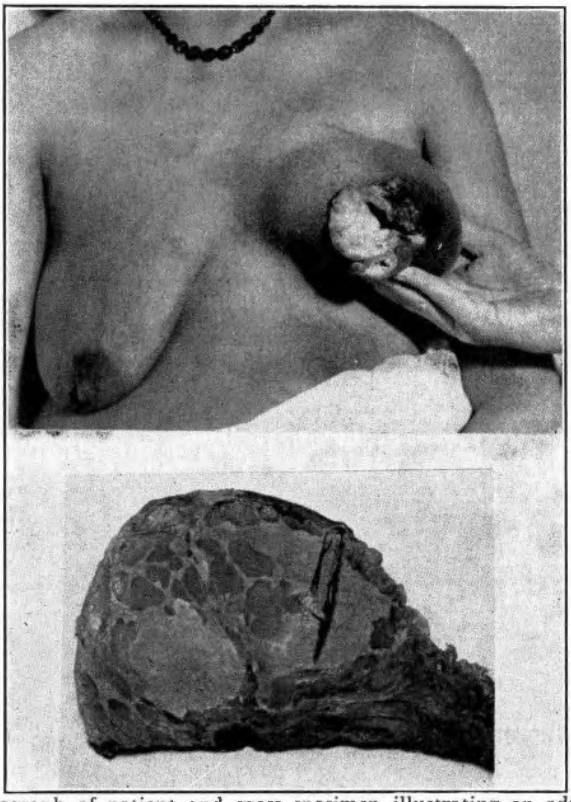


FIG. 366. Photograph of patient and gross specimen illustrating an advanced case of large infiltrating mammary cancer.

The surrounding breast tissue is most often of the senile, fatty type (Figs. 367, 368) with a few dilated ducts extending toward the nipple and thin fibrous bands separating the lobules of fat. In another group of cases the surrounding breast is rich in fibrous tissue, and dilated ducts with numerous branches penetrate the stroma. In only 6 per cent of the cases in this series was there evidence of cystic mastitis in the gross specimens. In an equal number of cases the breast tissue was described as normal with characteristic whitish-pink parenchyma.

Microscopic Examination

On microscopic examination, the tumor cells are of moderate size with moderate amounts of cytoplasm. The vesicular nuclei contain distinct nucleoli and occasional mitotic figures. The cells grow char-

FIG. 367

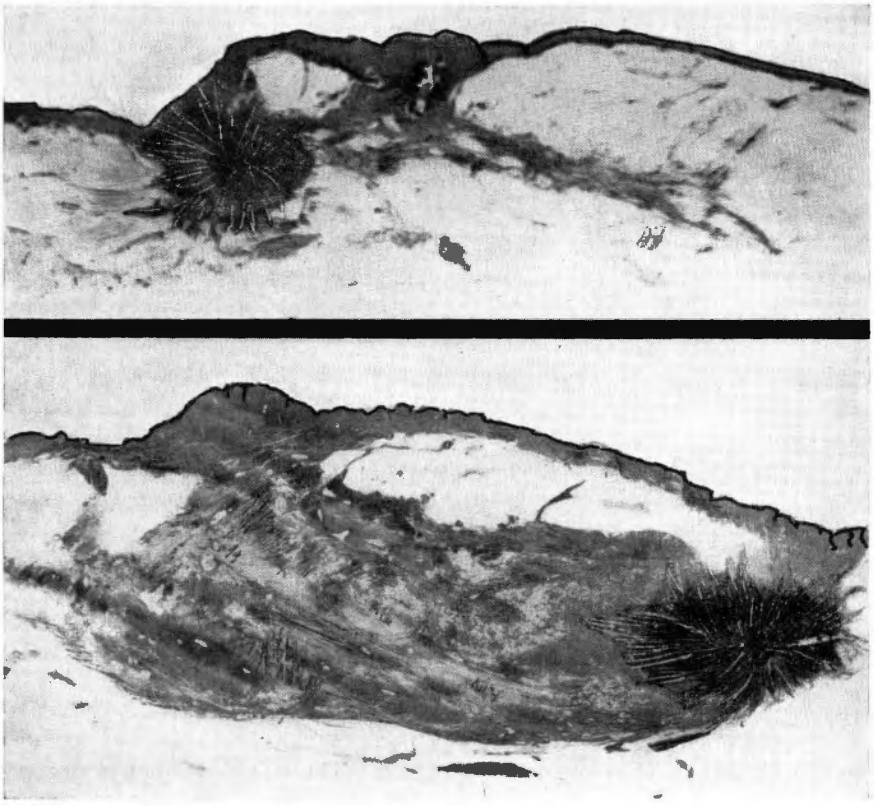


FIG. 368

Whole Sections of the Breast with Infiltrating (Scirrhous) Cancer.
FIG. 367. The cancer has affected a fatty, senile breast. This is the most common picture.
FIG. 368. The cancer has affected a breast with normal amounts of glandular and fibrous tissue.

acteristically in small nests or narrow elongated cords with intervening fibrous tissue and rarely, small amounts of lymphoid infiltration. In the more slowly growing tumors, the cancer cells grow in scattered masses dispersed by large amounts of fibrous tissue or form acinar or tubular structures. In the more highly malignant cancers,

FIG. 369

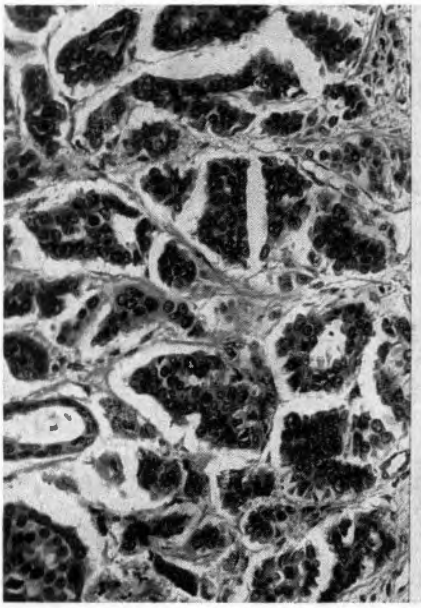
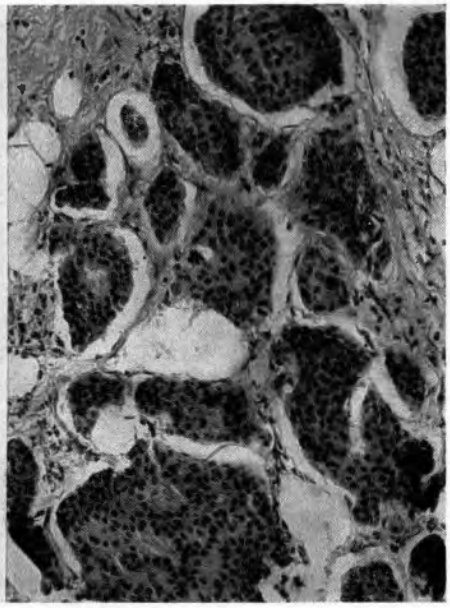


FIG. 370



The Four Microscopic Grades of Infiltrating Mammary Cancer.
FIG. 369. Slowly growing form with acinar arrangement, Grade I.
FIG. 370. Moderately malignant form with solid alveolar arrangement, Grade II.

FIG. 371

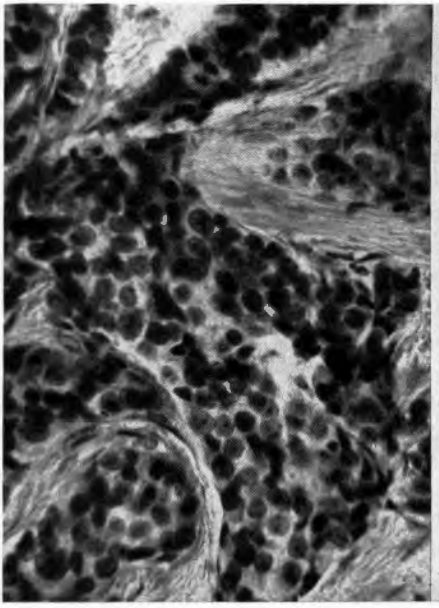


FIG. 372

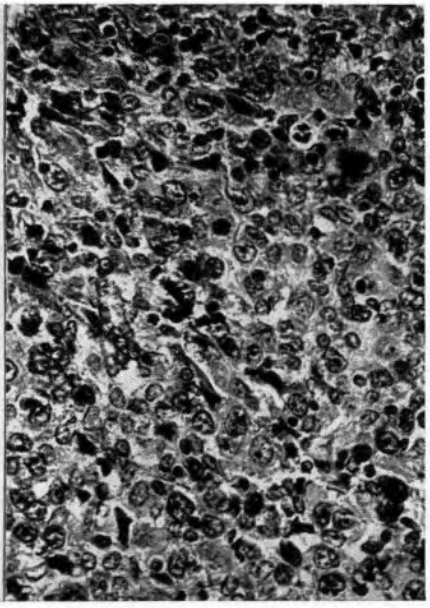


FIG. 371. Rapidly infiltrating form with epithelial cords penetrating fibrous tissue, Grade III.
FIG. 372. Highly malignant form with tightly packed small cells and little stroma. Grade IV.
(See also Figs. 491-494, Chap. 25.)

the size of the cells may be increased and grow in larger sheets; more rarely the cells may be small and compacted, resembling lymphosarcoma.

Microscopic Grading. Attempts to classify mammary cancers, on the basis of their microscopic appearance, into groups which will give more accurate correlation between the pathology of the tumor and its response to surgery or radiation have not been highly successful. One of the chief difficulties has been the failure to classify the cancers into the proper primary groups such as the infiltrating and circumscribed forms of adenocarcinoma and the stratified epithelial forms. If one restricts the grading of the degrees of malignancy to a single pathologic type, such as the infiltrating adenocarcinomas under discussion, more reliable results are obtained. Even under such conditions there are numerous complicating factors such as age, pregnancy, lactation, and duration of the tumor which must be taken into consideration. This was emphasized by Lee who proposed a clinical index of malignancy.

There are, however, certain microscopic features in infiltrating mammary cancers associated with a slower rate of growth. These are discussed in detail in Chap. 25. A distinct acinar arrangement simulating the alveoli found in the normal gland is associated with a low degree of malignancy. This is also true of cases which show moderate-sized masses of cancer cells, ringed about with a zone of connective tissue which gives the appearance of a newly formed basement membrane even though the total amount of connective tissue in the stroma of the tumor is relatively meager. (Figs. 369-370.)

Extreme degrees of malignancy are associated with islands and cords of tumor in which the individual cells show a high degree of anaplasia, that is, relatively large vesicular nuclei and frequent mitotic figures. As previously mentioned, some of the rapidly growing cancers may show a diffuse proliferation of tightly packed cells resembling lymphosarcoma (Fig. 372).

Midway between those cases which show a low degree of malignancy and those with an extreme degree are the largest group of infiltrating adenocarcinomas in which the cancer is broken up into small nests and infiltrating cords by strands of reactive fibrous tissue (Fig. 371).

CLINICAL COURSE AND PROGNOSIS

In infiltrating adenocarcinoma, a delay of 15 months after the onset of symptoms is sufficient for the cancer to pass from optimum to the most unfavorable conditions for treatment. The size of the cancer, involvement of the axillary lymph nodes, and the number of

patients who fail to survive the five-year period, increase in proportion to the duration of symptoms. (Fig. 373.) At approximately the midpoint in this period, when the known duration of the tumor averages 8.4 months, the size of the growth averages 2.7 cm. in diameter, axillary metastases are found in 62 per cent of the cases

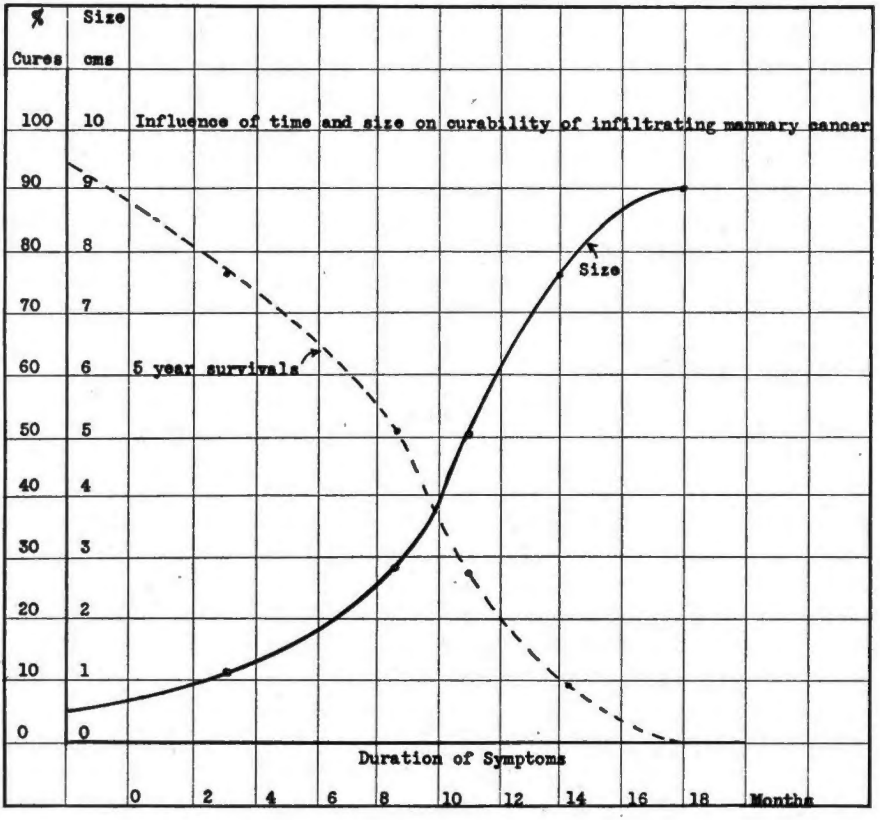


FIG. 373. Chart showing the growth curve of infiltrating mammary cancer. The size of the tumor and the percentage of the five-year survivals has been plotted against the duration of symptoms.

and 51 per cent of the patients survive radical mastectomy for five or more years.

In order to correlate the outcome of treatment with the known duration of symptoms it is necessary to exclude: first, cancers not of the infiltrating form, such as the circumscribed adenocarcinomas and the stratified epithelial cancers; second, cases of fulminant cancer with erysipeloid changes in the skin, cancers in pregnancy or lactation, and cancers complicating lactation mastitis; third, those cases

in which the clinical course is without symptoms until extensive metastases have occurred or those in which a nodule of stationary size, probably of benign nature, had been present for five or more years; fourth, those cases in which the recorded data were inadequate.

After eliminating these cases there remained 1,042 out of 1,906 infiltrating cancers on which the chart shown in Figure 373 was based. In the most favorable group of 95 cases, the tumor measured 1 to 1.5 cm. in diameter, the average duration of symptoms was three months, lymph-node involvement was present in 25 per cent of the cases and the five-year survivals were 73.5 per cent. In the most unfavorable group of 294 cases, the average size of the tumor was 7.8 cm., the duration of symptoms averaged 14 months, axillary metastases were present in 97 per cent and the five-year survivals were 9.3 per cent. Although the unfavorable group is three times as large as the group of the most favorable cases, it must be recalled that these cancers were observed over a period of 50 years. Slightly more than half of the cases (545 of 1,042) were seen when the average duration was 7.5 months and when the lymph-node involvement was 55 per cent and the five-year survivals 55 per cent.

It will be seen that approximately 10 per cent of the most advanced cases (in which a permanent cure is out of the question), survive the five-year period. This survival of five or more years under the most unfavorable conditions of size and axillary involvement must be borne in mind in evaluating any method of therapy, since it is obviously incorrect to credit this to the method of treatment.

That size is more important in prognosis than lymph-node involvement is evident from the consideration of the data tabulated (Table LXII). In extremely large growths of over 5 cm., just under 10 per cent of the patients with axillary involvement survive for a five-year period. With growths between 2 and 4 cm., on the other hand, approximately 25 per cent of the patients with axillary involvement survive this period. For the entire series, the average survivals of patients with axillary involvement is 20 per cent.

As we have indicated, the dividing line between operable and inoperable infiltrating cancers has been placed at a diameter of 5 cm. In point of time, this is the period between 12 and 14 months after the onset of symptoms during which the disease passes from the "curable" to the "incurable" stage. It also represents the period during which the disease passes from objective to subjective symptoms of increasing severity. While metastases to the internal organs have occurred in practically all cases by the end of this period, these do not become clinically manifest (on the average) until another 15 months has elapsed. During this time, however, symptoms of in-

TABLE LXII

FIVE-YEAR SURVIVALS IN INFILTRATING CANCER

NO. OF CASES	PER CENT OF TOTAL	DURATION	SIZE	LYMPH NODE INVOLVEMENT	PER CENT OF 5-YEAR SURVIVALS
95	8.6	3 mos.	1–1.5 cm.	25%	73.5
450	43.3	8.5 mos.	2–3 cm.	62%	51
127	12.2	9.7 mos.	4 cm.	76%	40
76	7.3	10.8 mos.	5 cm.	85%	27
294	28.6	14 mos.	Over 5 cm.	97%	9.3

This table shows that the per cent of five-year survivals in infiltrating cancer (treated by radical mastectomy) decreases as the duration of symptoms, size of the tumor and per cent of axillary metastasis increase.

creasing severity are produced by the local growth or by axillary invasion. Pain is caused by the pressure of the tumor or axillary disease on the neighboring nerves; edema and ulceration of the overlying skin develop, and fungation of the tumor with weeping and foul discharge make their appearance. At the end of 30 months, symptoms referable to internal metastases to the lung, liver, bones, etc., become manifest and death in untreated cases usually occurs at the end of three years. (3.4 years, Nathanson and Welch.)

In estimating the results of treatment, the per cent of five-year survivals is not the sole criterion. Freedom from the local manifestations of the disease must be taken into consideration. A comparison of the life expectancy in treated and untreated fatal cases indicates that although treatment may be instituted too late to prevent the ultimate death of the patient from metastases, nevertheless, the time when such metastases become symptomatic and ultimately fatal is postponed by treatment, which limits the number of the metastases and the rate of their subsequent spread. The difference in the life expectancy between treated and untreated cases averages approximately 15 months.

Although the unfavorable fulminant cancers have been excluded from the cases analyzed in Table LXII and Fig. 373, the prognosis in these tabulated cases is representative of the entire group of infiltrating adenocarcinoma seen in recent decades, if allowance is made for the more advanced stage of the disease which characterized many of those tumors treated between 1893 and 1910. Since radical surgery was performed in the cases listed, it is possible to judge accurately the outcome of treatment in the various stages of the disease.

If tumors over 5 cm. in diameter are taken as the borderline of operability, 42.5 per cent of the cases survive the five-year period fol-

lowing operation. One-fourth of the surviving cases, however, had clinical evidence of disease at the end of the five years; and one-half of this group died of cancer before the end of the 10-year period. Because of this and because of the late recurrences seen 10 or more years after treatment, some observers, such as Lewis and Rienhoff, believe that mammary cancer may be arrested but is practically never completely eradicated or cured.

TREATMENT

The treatment of mammary cancer is discussed in more detail in Chaps. 29-31. Some of the conclusions based upon the foregoing analysis, however, are in order here. Both radical surgery and irradiation are of established value. It is the author's opinion that the two treatments should not be routinely combined, but that in primary cases the best possible choice should be made between surgery and irradiation. No hard and fast rules can be followed.

Radical Surgery

In general, radical surgery is the treatment of choice in infiltrating cancers 5 cm. or less in diameter unless there are already present the classical signs of inoperability such as skin metastases, fixation to the chest wall, extensive metastases high in the axilla, involvement of the supraclavicular nodes, or x-ray evidence of metastases to the lungs or bones.

Roentgen-Ray Therapy

In infiltrating cancers more than 5 cm. in diameter, the disease is too extensive for radical operation and the classical signs of inoperability are usually present. Regardless of whether or not such signs exist, radical operation is contraindicated as a primary procedure according to the above analysis. The presence of the disease should be verified by aspiration biopsy and roentgen-ray therapy given. After a period of eight weeks has elapsed following the usual course of treatment with high voltage irradiation in divided doses, it should be possible to evaluate the sensitivity of the growth. If the response is inadequate to control the disease, simple mastectomy should be performed for palliative reasons and irradiation continued to the regions where extension of the disease is manifest. To date, the benefit derived from routine preoperative irradiation has not been found sufficient to compensate for the added expense, the discomfort to the patient, and the time lost in postponing surgery.

Postoperative Irradiation

Postoperative irradiation should be used when the axillary nodes are involved or whenever the surgeon, after performing the radical operation, is convinced that the extent of the disease has rendered the operation inadequate. Otherwise irradiation should be reserved for the recurrences or metastases which make their appearance months or years following the radical operation. In cases where operation and irradiation have already been used, it may be advantageous to apply radium to localized recurrences. The chief arguments against the routine use of postoperative irradiation are first, the large per cent of cases controlled for five or more years by surgery if proper criteria for operability are used and second, the inefficiency of the irradiation when not directed to definite cancerous involvement.

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20

Recurrent and Metastatic Cancer: Fulminant Forms

The descriptions of recurrent and disseminated mammary cancer found in writings prior to the present century have been largely superseded in current surgical literature, which emphasizes early diagnosis and treatment. Although the majority of cases today are seen when they are operable, only about 40 per cent survive the five-year period, and nearly half of these succumb to the disease before the end of 10 years. Regional recurrences following radical mastectomy occur in about one-fourth of the patients and between 80 and 90 per cent of these ultimately die of metastasis. In our cases regional recurrences were found following radical mastectomy in approximately 28 per cent of all cases. This figure can be broken down into 35 per cent recurrences for infiltrating carcinomas; 14 per cent for circumscribed adenocarcinomas and 15 per cent for carcinomas of the transitional cell type. Haagensen and Stout found local recurrences in 22.8 per cent of their cases within five years of radical mastectomy.

The care of patients with recurrent or metastatic mammary cancer is still a major problem. These are the patients whom the family physician sees, after their sojourn in the larger clinics, with swollen and painful arms produced by recurrent disease in the apex of the axilla and about the brachial plexus; with pains about the chest and ulcerations produced by metastases to the skin and chest wall; with cough and dyspnea resulting from pulmonary invasion; with bone-breaking pains in the spine accompanying secondary deposits in the bones; with ascites, jaundice, and nausea produced by involvement of the liver; and with blindness, persistent headache, or paralysis resulting from cerebral metastasis.

The distinction between recurrent and metastatic cancer is an arbitrary one. Following operation, the appearance of disease in the skin of the chest wall, in the axilla or in the infra- or supraclavicular nodes, or in the opposite breast, is usually spoken of as recurrence. In the author's opinion, however, the inclusion of the supraclavicular nodes or the opposite breast among regions of recurrence seems scarcely justified in many instances. On the other hand, the appearance of the disease in any of the internal organs or in the skin, soft parts, or skeleton beyond the field of operation is classified as metastasis. The primary distinction is between the involvement of those structures that are accessible or feasible for surgical removal and those which are not in this category.

RECURRENT CANCER

Frequency

In 220 cases of infiltrating mammary cancer, radical operation was performed for recurrence after incomplete operation; or dissections were performed for recurrent masses following a previous complete operation. (Figs. 374, 375.) These cases do not represent the total number of recurrences but only that group submitted to additional surgical procedures. In the entire group of lobular cancers, regional recurrence took place in approximately 35 per cent of those treated by radical mastectomy; 82 per cent of the recurrences took place before the end of the second year. (Fig. 376.) The average time for recurrence was 18 months. Many had repeated operations for recurrences. One patient had a radical mastectomy in December, 1921, followed by 20 local operations for recurrences, and finally died in July, 1928. In a similar case the tumor was first excised in 1926; the radical operation was done in 1929; two local operations were done in 1930; and the patient died in 1933. Local recurrence develops as a rule within one year if an incomplete operation is performed.

FIG. 374.

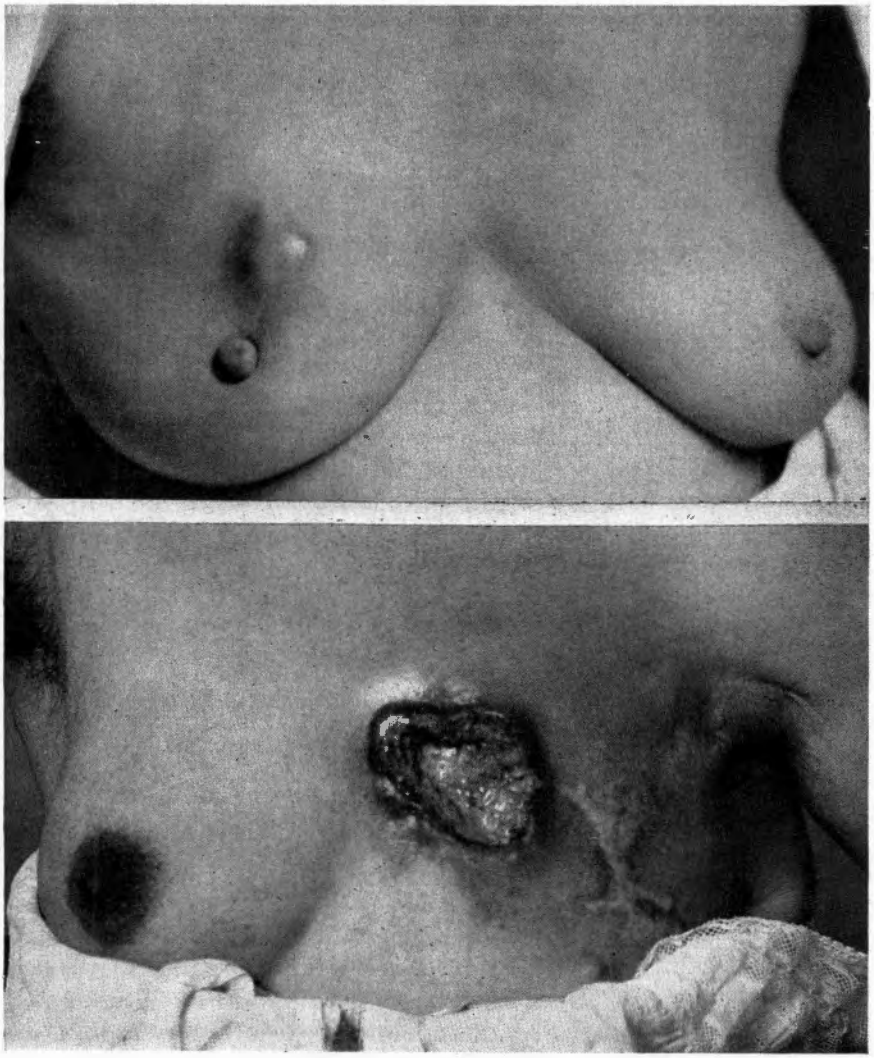

FIG. 375

Recurrent Mammary Cancer.

FIG. 374. Photograph of a patient showing recurrence in the scar following a local excision.

FIG. 375. Photograph of a patient showing recurrence in the scar following radical mastectomy.

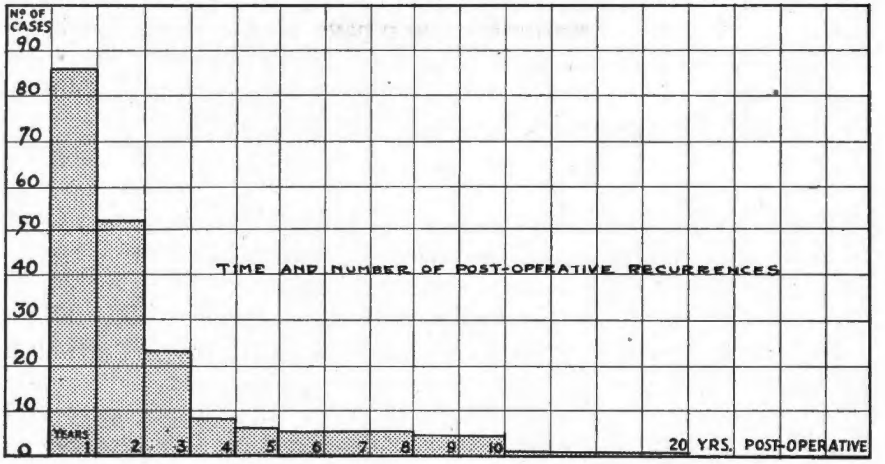

FIG. 376. Chart showing the time and number of post-operative recurrences following radical mastectomy.

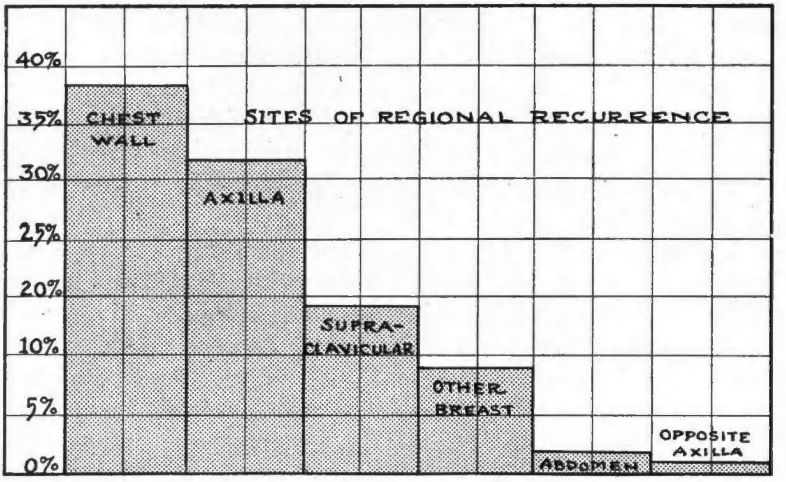

FIG. 377. Chart showing the sites of regional recurrence following radical mastectomy.

There were 14 cases in which the disease reappeared locally five or more years after radical mastectomy; in one case, after 20 years; in another, after 12 years; and in 5 cases, after 10 years. Similar recurrences 10 or more years after operation have been reported by Handley, Kretzler, and others. As pointed out by Lewis and Rienhoff, local recurrence is more common in infiltrating or scirrhous mammary cancer than in other forms.

Site

Recurrence is most frequently seen in the skin and subcutaneous tissues of the chest wall, in the axilla on the affected side, in the supraclavicular nodes on the affected side, and in the opposite breast, in the order of frequency given. (Fig. 377.) Recurrence in the abdominal wall or in the opposite axilla is rare. Lee and Tannebaum found the leading sites of recurrence to be the supraclavicular nodes (26 per cent), the axillary nodes on the same side (20 per cent) and the chest wall (19 per cent).

Recurrence in the chest wall may form in the scar, in the surrounding skin, or in subcutaneous tissues including the ribs. The nodules may be single or multiple. Lewis and Rienhoff found that the large majority of the local recurrences were in the incision, in the skin, and in the subcutaneous tissue, if the wound was closed without a skin defect. Where the amount of skin removed in the radical mastectomy necessitated grafting, some tumors recurred in the skin about the periphery of the grafted area, but the great majority were deep beneath the skin, arising in the chest-wall and later involving the surface. They state, "These probably began either in the lymphatic vessels along the course of the anterior perforating branches of the internal mammary artery or in the slips of origin of the pectoralis major muscle."

Along Incision. When the recurrence is along the incision, the scar may be diffusely thickened or one or more nodules may bulge from it. The affected region is raised and indurated, the visible swelling steadily increases and the tissues become dusky or purplish in color with ulceration eventually developing. Recurrent nodules in the skin are often accompanied by multiple skin metastases and the area over the chest may be extensively involved, giving the picture either of carcinoma en cuirasse or of inflammatory cancer. (These complications are discussed later in connection with the fulminant forms of cancer.)

In Axilla. Recurrence in the axilla may be complicated by edema of the arm on the affected side and painful involvement of the brachial plexus. The entire axillary region may become hard and

tender, and the end of the clavicle or acromion may be invaded. The patient may be unable to raise the arm (which is often swollen to twice its normal size) above the level of the shoulder. In many of these cases the supraclavicular nodes on the same side are involved by the disease.

In Supraclavicular Nodes. In the cases studied, the incidence of recurrence in the supraclavicular nodes was reduced because of the practice of including this region in the dissection in a number of mastectomies performed prior to 1915.

When the opposite breast is involved by cancer, it is difficult to prove whether or not this is extension of the primary tumor or a cancer arising de novo in the remaining breast. Involvement by extension is probable in those cases where the skin and subcutaneous tissue of the chest wall are extensively invaded, and when the second breast is involved at the time that other recurrences are taking place in the surrounding tissues. On the other hand, where the patient has been free of local disease and regional metastasis for several years, the appearance of cancer in the opposite breast suggests a second new growth. Among the cases of recurrent cancer, 10 per cent had involvement of the opposite breast. On the other hand, in patients free of local recurrences for three or more years, the opposite breast was involved in 7 per cent of the cases.

Origin of Recurrence

On the basis of pathologic study, it may be concluded that the secondary nodules in recurrent cases arise from cancer cells which extended beyond the field of operation, or from similar portions of the primary growth which are transplanted in the wound by the handling of the tissues during operation. This is based upon the distribution of the secondary nodules and the fact that they are histologically identical with the primary cancer. Only rarely is the structure altered. When microscopic changes occur, these are usually the result of scarring in the region where the recurrence has taken place, of secondary infection, of proximity to bone or of some other local factor which influences the growth of the tumor.

Malignancy

It is sometimes stated that the recurrences are more malignant than the primary tumor because of their rapid growth or because of the brief duration of life following their appearance.[1] This seems

[1] If the experiments of Casey can be applied clinically, it is probable that when a substantial amount of cancer tissue is present, either as a large primary growth or as numerous secondary deposits, the cancer tissue elaborates a toxic substance which, if present in sufficient concentration, promotes the more rapid growth and spread of cancer.

highly improbable considering the histologic identity of the primary and secondary growths. The more rapid growth of the recurrence is often more apparent than real because of its superficial location. The brief period of survival in many of these cases is associated with the multiplicity of foci both in the region of the former operation and internally. This multiplies the amount of malignant tissue which is contributing to the toxic manifestations of the patient, and also to the daily number of new cells added.

Treatment

Because of the poor prognosis in patients with recurrent cancer the most valuable form of treatment is prevention. The greater the amount of skin and the subcutaneous tissue removed in the radical

TABLE LXIII

(From Lewis and Rienhoff)

FREQUENCY DISTRIBUTION, ACCORDING TO AGE (TEN-YEAR GROUPING) OF 116 CASES OF CARCINOMA OF THE BREAST, WHERE THERE WAS A LOCAL RECURRENCE

AGE IN YEARS	CASES OF CARCINOMA OF BREAST, AGE OF INCIDENCE	LOCAL RECURRENCES, CARCINOMA OF BREAST	PER CENT OF CASES HAVING LOCAL RECURRENCES
20–29	9	6	66.7
30–39	75	31	41.3
40–49	134	30	22.4
50–59	110	26	23.6
60–69	77	19	24.7
70–79	14	3	21.4
Unknown	1	1	..
Totals	420	116	

On the whole the younger the patient is the more susceptible to local recurrences.
The average length of life was reduced from 3.62 years to 2.95 years in recurrent cases.

mastectomy, the fewer the recurrences. Lewis and Rienhoff state that "very large areas of skin should be removed regardless of the size or position of the tumor, whether deep in the breast or superficial, leaving the closure of the defect out of mind until the end of the operation."

In infiltrating cancers over 5 cm. in diameter, the probabilities of local recurrence after operation are greatly increased and irradiation alone or in combination with surgery is the treatment of choice.

The incidence of recurrences can be further decreased if care is taken to change gloves and instruments when cancerous tissue is cut through during the dissection and if postoperative irradiation is given in such cases.

Deep x-ray therapy in divided doses should be given where local recurrence has taken place. The region involved should be treated to the point of tolerance (see Chap. 30). In recurrent disease in the axillary or supraclavicular nodes, some report good results with the implantation of radon seeds. Such treatments have the disadvantage in some cases of provoking a brachial neuritis of several months' duration. It must be remembered that complications such as pulmonitis are more frequent with radiation therapy following radical mastectomy because the chest wall has been denuded of musculature and fat.

METASTATIC MAMMARY CANCER

Sites

The most common sites of metastasis in mammary cancer are the lungs and pleura, the liver, bones, and brain in the order of frequency given. Before subjecting cases of suspected mammary cancer to operation, it is important to rule out if possible the existence of metastasis in these regions. Metastasis to the lungs occurs in between 58 and 62 per cent of fatal cases of mammary cancer and osseous involvement is found in between 43 and 57 per cent according to recent necropsy studies (see Chap 18). Evidence of such metastatic involvement may be apparent any time after the onset of symptoms although in the majority of cases an interval of two to three years has elapsed. Because of the frequency of pulmonary and osseous metastasis, roentgenograms of the chest and skeleton should be made in all cases of suspected mammary cancer in which the radical operation is contemplated. The two most valuable films are those of the chest, including the upper humeri and of the pelvis including the lumbar spine and upper femurs. A satisfactory selection of operable from inoperable cases cannot be made without such studies.

X-Ray Features of Pulmonary Metastasis. The x-ray findings are variable in cases in which the thoracic cavity is invaded by mammary cancer. Involvement of the pleura may be evident by thickening or changes in the contour of the pleural outlines. The sharp angle with the diaphragm may be rounded or the soft tissue shadow may be increased in density particularly in the region toward the base of one or both lungs. Hydrothorax is most common on the affected side and is a frequent complication of either pleural or pulmonary involvement.

Metastatic nodules are most common in the lungs in the region midway between the mediastinum and the periphery. Multiple nodules of increasing density varying from 0.5 to several cm. in diameter

are found in one or both lungs and are more frequent in the lower than in the upper portions of the lung. (Figs. 356, 357.) The nodules are discrete and rounded and have been described as "cotton balls." When both the pleura and lungs are involved, pleural effusion may obscure the lung metastases. Variations from this common bilateral cotton-ball type of metastasis are not uncommon. In one group of cases one to several large dense metastases are seen in the right or left lung. In another and rare group of cases there are miliary metastases in the lower portion of both lungs, which progress slowly and increase in size and density over a period of a year or more. This type of "seeding" is characteristic of the lymphatic spread of cancer in the lungs rather than the more common hematogenous type described above. The mediastinum may be involved with or without invasion of the lungs. Here, one or several large, dense nodules, usually in the mid or upper mediastinum, may be produced by metastasis to the lymph nodes.

Osseous Metastasis. Lesions of metastatic carcinoma of the breast which have localized in the bones are most often multiple, occurring as a single focus in about one fourth of the cases affected. The majority of these solitary metastases are in the vertebrae or femurs. (Fig. 355, p. 433.)

Two types of metastatic lesions are noted in the x-ray films. The more common one is osteolytic or bone-destructive, while the other is a sclerosing or bone-forming process. Often mottling with increased density of bone occurs about the zone of destruction and thickening of the cortex appears above or below the site of metastasis. When such bone formation produces mottling within an area of destruction in the bone, it favors the presence of a metastatic carcinoma as opposed to the more definitely punched-out areas of destruction seen in multiple myeloma.

Multiple involvement of the spine in the lumbar and lower thoracic regions is the most frequent form of involvement. The pelvis, upper femurs, ribs, cranial bones, and upper humeri are next in order of frequency. In advanced stages, the entire skeleton may be riddled by multiple foci although extension to the bones below the elbows or below the knees is rare (Geschickter and Copeland).

Involvement of the vertebrae can be demonstrated more frequently at autopsy than in the x-rays and pain in the lumbar spine of severe and constant nature may indicate the presence of metastasis when the x-ray film fails to confirm the diagnosis.

Metastasis to Liver and Brain. When metastasis to the liver or brain becomes clinically manifest the remaining term of life is usu-

ally a matter of only a few months. The earliest sign of liver involvement is simple enlargement, which is followed by progressive increase in size and nodularity. Ascites, jaundice and emaciation are soon added to the clinical picture. While loss of sleep due to pain and loss of appetite through the use of narcotics are the most common causes of emaciation with metastatic cancer, patients with liver involvement apparently lose weight rapidly because of a fundamental disturbance in metabolism, whether or not nausea is a conspicuous feature.

Symptoms from increased intracranial pressure such as severe headaches, nausea and vomiting may be due to brain metastasis or to intracranial extension from secondary deposits in the cranial bones. Metastasis to the brain itself produces localizing signs which vary with the site of involvement. Aphasia, blindness, paralysis or convulsions are usually not seen until shortly before death.

Brachial Neuritis. Metastasis or extension of the disease to the region of the brachial plexus is one of the most distressing complications in mammary cancer. The outstanding feature is severe and intractable pain which fails to respond to opiates and results in sleepless nights. The arm, shoulder and hand are stiff and held close to the body. There is progressive paralysis of the hand muscles and those of the forearm. The hand has a dusky discoloration. External irradiation by radium pack, or high or low voltage roentgen rays is ineffective, and interstitial irradiation cannot be used. Cordotomy is the only hope for relief. The operative risk is high because the pain tracts must be severed in the upper cervical region of the cord and respiratory paralysis may result. The operation must be performed with great care, but is the only recourse in these desperate cases. Grant has described the procedure and the indications for its use.

Carcinosis. In 74 cases, the mammary cancer was hopelessly advanced when the patient came under observation. Since no operation was performed, microscopic confirmation of the type of cancer was not obtained; nevertheless these cases have been classed with the infiltrating lobular cancers because of the findings on palpation and their clinical course. The chief cause for inoperability in these cases was delay. This was indicated by the duration of symptoms which averaged 18 months, by the size of the cancer which usually involved the entire breast and by extensive swelling or induration in the axillary or supraclavicular lymph nodes. In this group of late and hopeless cancer the tumor was between 8 cm. and 10 cm. in diameter in 89 per cent of the cases, the axilla was extensively involved in all but five cases and the cervical or supraclavicular nodes were involved

in more than 50 per cent. The skin was ulcerated or there were metastatic skin nodules in 40 per cent with a clinical picture of carcinoma en cuirasse in 5 cases. (Table LXIII A, Figs. 378, 381.) Evi-

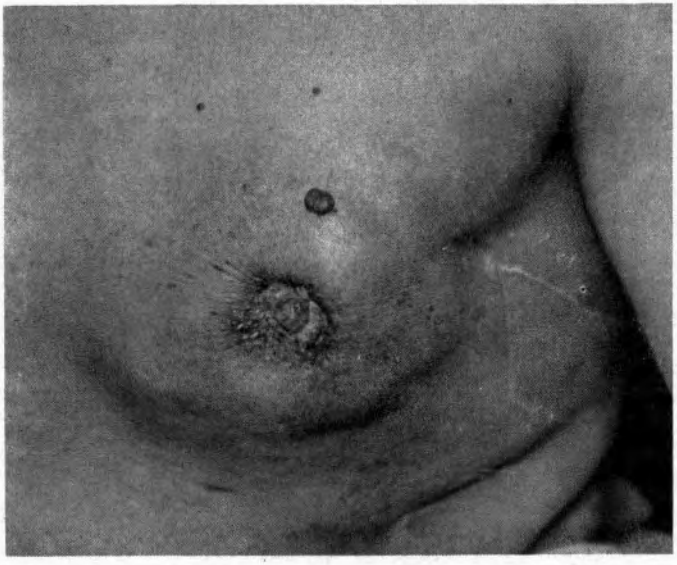

FIG. 378. Photograph of a patient with mammary carcinosis. This patient has, in addition to the secondary skin nodules shown, involvement of the lungs and skeleton.

dence of bone metastasis was present in nine cases, and in seven patients both breasts were involved by the disease. In five instances, the liver was enlarged and nodular, in four the arm on the affected

TABLE LXIII A

FINDINGS IN LATE INOPERABLE MAMMARY CANCER

Number of Cases		74
Average Age		53 yrs.
Average Duration of Symptoms		18 mos.
Number of Fatal Cases		74
Average Duration of Life		30 mos.
Large size 8 to 10 cm.	66 cases	89 %
Extensive axillary metastases	69 cases	93 %
Supraclavicular involvement	37 cases	50 %
Skin ulceration or metastases	30 cases	40 %
Bone metastases	9 cases	12 %
Both breasts involved	7 cases	9.5%
Enlarged nodular liver	5 cases	6.8%
Swollen arm	4 cases	5.4%
Lung metastases	4 cases	5.4%
Primary symptoms referable to metastases	8 cases	10.8%

side was swollen, and pulmonary metastases, indicated by persistent cough, dyspnea and pleural effusion, were found in four cases.

Age

The average age of the patient in this group was 53 years. None of these cases survived the five-year period. The average duration of life after examination was just under one year. This, together with the average duration of symptoms of 18 months, gives a total life expectancy of only 30 months for this group. This is 10.8 months less than that of the untreated cases studied by Nathanson and Welch who report a life expectancy of 40.8 months for untreated cases. Apparently, because of the intense interest in the radical operation in Halsted's Clinics, these untreated cases represent a more hopeless group. In any event, the stated duration of symptoms is of dubious accuracy in a group of patients who were obviously so ignorant or careless about their person as to tolerate the advanced changes found.

Extent of Primary Growth

However, there were eight patients in this group in whom the inoperable state of the disease could not be attributed to the neglect of symptoms. In these patients it was the metastasis rather than the extent of the local disease which precluded treatment. In one case, the patient had been on the medical wards because of numerous nodules of the skin extending over the trunk and the extremities as far as the elbows and the knees. There was no complaint referable to the breast although when questioned the patient stated that the breasts had become small and masculine in the past year. Biopsy of the skin nodules disclosed metastatic mammary cancer and re-examination of the breasts showed that they had become flattened, indurated and adherent to the chest wall.

In two cases, the complaint was pain in the spine and small breast tumors were discovered only after the x-rays revealed extensive metastatic carcinoma of the spine.

In two other cases tumors between 2 and 3 cm. were found in the breast, the axilla was negative to palpation, but the liver was large and nodular. In a similar case a lump 2 cm. in diameter had been present four months, but the chest on the same side was filled with fluid. In one case, a tumor 4 cm. in diameter had been present for seven months in the lower inner quadrant. A small nodule was found in the opposite breast and large indurated lymph nodes in both axillae and in the neck on both sides. In another patient a mass 3 cm. in diameter had been present for 1 year. The patient was not

concerned until the arm began to swell. On examination the axilla was found to be extensively infiltrated.

TABLE LXIV

THE LIFE EXPECTANCY IN INFILTRATING MAMMARY CANCER

DATA	UNTREATED CASES	TREATED CASES SURVIVING LESS THAN FIVE YEARS		TREATED CASES SURVIVING FIVE OR MORE YEARS
		REGIONAL RECURRENCE	METASTASIS	
Per cent of total	4.3%	34%	29.2%	32.5%
Duration of symptoms	18 mos.	11.2 mos.	12 mos.	8.1 mos.
Recurrent symptoms	..	18.0 mos.	19 mos.	..
Subsequent life	12 mos.	18.0 mos.	15 mos.	76 mos.
Total duration of life	30.0 mos.	47.2 mos.	46.0 mos.	84.1 mos.

The average length of life in all cases is 58.2 months.

ACUTE OR INFLAMMATORY CARCINOMA
(Erysipeloid Cancer—Carcinomatous Mastitis)

Site

The appearance of a rapidly widening area of inflammation and redness in the skin overlying mammary carcinoma is a grave prognostic sign. This complication may appear early in the disease and precede the recognition of the underlying tumor or may occur relatively late when the mass has reached large size, or involve the skin surrounding the scar of a mastectomy performed for cancer. When such skin changes occur, the disease has been variously termed acute or inflammatory mammary cancer, erysipeloid cancer or carcinomatous mastitis. The frequency with which this form of the disease may occur during pregnancy or lactation has suggested the term lactation cancer. (Fig. 379.)

Taylor and Meltzer have divided inflammatory cancer into primary and secondary forms. In the primary form the inflammatory signs apparently arise simultaneously with the cancer in a previously normal breast. In the secondary form, the inflammatory signs appear in the same or opposite breast after the tumor has reached large size or occur in the region of the scar following mastectomy. In all cases whether primary or secondary, the skin changes are caused by extensive invasion of the subepidermal lymphatics, and the duration of life following the appearance of the skin changes is about one year.

Age of Onset

In the present study there were 20 primary inflammatory cancers, nine of which appeared during pregnancy or lactation. There were 27 secondary inflammatory cancers, two of which occurred during

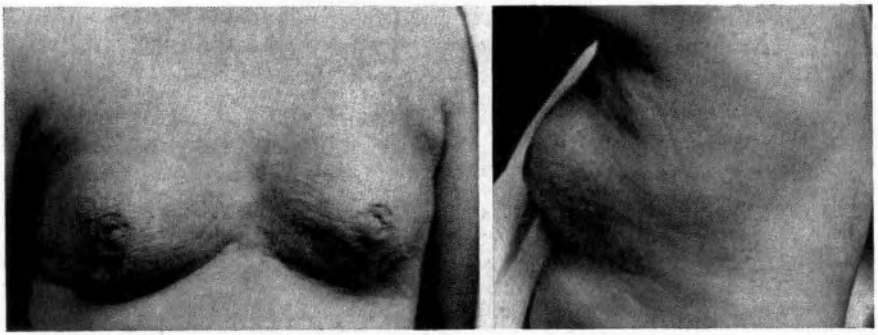

FIG. 379. Photographs of a patient with inflammatory or acute carcinoma. The lateral view shows the extent of the involvement of the skin of the chest wall.

lactation and seven of which occurred in the region of the scar following a previous mastectomy. (Table LXV.)

TABLE LXV

DATA IN 47 CASES OF INFLAMMATORY MAMMARY CARCINOMA

FORM	NO. OF CASES	AGES	AVER.[2] AGE	AVER. DURATION OF SYMPTOMS	PUERPERAL	BILATERAL	AVER. LIFE AFTER APPEARANCE OF INFLAMMATORY SIGNS
Primary	20	9—(Under 40) 11—(Over 40)	41 yrs.	4.5 mos.	9 cases	7	12.1 mos.
Secondary	27[1]	6—(Under 40) 21—(Over 40)	47 yrs.	15.6 mos.	2 cases	4	11.5 mos.

[1] Includes 7 cases with the scar of a previous radical mastectomy for cancer.
[2] Aver. = average.

Acute or inflammatory mammary cancer shows a tendency to occur in younger women, women with obese pendulous breasts, and during pregnancy or lactation. Among our cases, the average age was 44.5 years compared to 52.4 years for mammary cancer in general. There were five cases in which a note in the history gave the weight as more than 200 pounds, and 11 cases occurred during pregnancy or lactation. The inflammatory signs may mask the malignant nature of the disease. Poultices, hot applications, lamp treatments, etc., were the initial therapeutic procedures in five of our cases and in one pa-

tient, whose history is given below, the impression of acute mastitis was recorded prior to operation.

A white female, 37 years old, six weeks ago noted redness over the breast and pain in the left axilla and, in feeling this region, discovered a small lump. In the dispensary she was advised to wear a bandage and use hot applications. Three weeks later when she returned the breast was tremendously enlarged, the overlying skin red with increased temperature, the veins over the upper portion of the breast and left axilla dilated, and the left arm red and swollen. The entire left breast was indurated to palpation. The overlying skin was edematous and pitted on pressure. There was practically no tenderness.

The breast was explored in November, 1923, under the impression of acute inflammation. Incision into the indurated breast showed a soft, creamy white mass which on section was composed entirely of carcinomatous tissue. The radical operation was performed, cancer being found in the pectoral fascia and in the axillary lymph nodes. The patient died subsequently but an accurate note on the time and cause of death was not obtained.

Symptoms

In the majority of the cases the patient had noted a small tumor in the breast or in the axilla before the appearance of the inflammatory signs. These appeared within a few weeks in the primary cases and within a period of months in the secondary cases. The changes in the skin are characterized by a reddish or purplish discoloration which spreads rapidly over the entire breast and may extend up the neck and down the arm on the affected side or across to the opposite breast and shoulder. The opposite breast is involved often (11 of 47 cases) and usually soon after the first. A prolonged low grade fever, the result of some complication, occurred in 6 of 38 cases in the series of Taylor and Meltzer. The white cell count may be elevated to 14,000. The regional lymph nodes are enlarged, usually in one or both axillae or in the supraclavicular region. In one of our cases, occurring in a woman of forty years in mid-pregnancy, the skin over the entire right upper half of the body was a dusky red color, in back as well as in front, and the lymph nodes in the groin as well as the axillae were palpable. Similar cases with extensive skin involvement have been recorded in the literature and are responsible for the term erysipeloid cancer.

The duration of symptoms prior to observation is brief in these cases, averaging 4.5 months in the primary group and 15.6 months in the secondary group. In this secondary group, however, the inflammatory signs were of recent origin occurring suddenly in breasts where a cancer of increasing size had been known to be present for months or years.

The rapid spread of acute cancer through the lymphatics of the

skin cannot always be correlated with the degree of malignancy of the primary tumor. In the cases reported by Taylor and Meltzer, inflammatory signs appeared in six cases following a radical mastectomy and in one after simple mastectomy, the time interval being eight months to four years after operation and from eleven months to five years after the onset of the primary cancer. Among the seven cases in our series which had had previous radical mastectomies for cancer, the interval following operation was four to 26 months in six instances, but in the seventh, which had received postoperative irradiation, the interval was nine years.

Pathology

The inflammatory signs seen in acute or erysipeloid cancer are produced by invasion of the superficial lymphatics and blood ves-

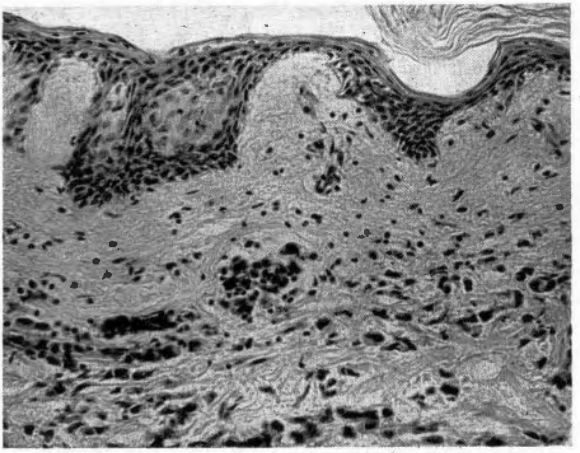

FIG. 380. The pathology of inflammatory carcinoma. The photomicrograph shows cancer cells permeating the lymphatics of the skin.

sels rather than by a true inflammation. There is no special irritant or toxin developed by the cancer in these cases but a retrograde spread of malignant cells toward the skin. In cases of primary inflammatory cancer, the superficial spread of the cancer may be due to blockage of the deep lymphatics with cancer cells. In discussing the pathology of inflammatory carcinoma and cancer en cuirasse, Schreus stresses the frequency with which these complications follow an unsuccessful radical mastectomy. In such cases Schreus believes that, because of the removal of the ordinary drainage channels in the region of the axilla, the lymphatic currents are forced to take an entirely different direction and that the flow of cells takes place from the deeper tissues to the surface. When the skin is reached,

the meshwork of skin lymphatics is then filled with cancer cells which have no other means of distribution. (Fig. 380.)

The duration of life following the appearance of the inflammatory signs is brief. In the secondary cases, where the onset of skin manifestations were more accurately determined, the average duration of life was 11.5 months and in the primary cases it was 12.1 months from the appearance of the first symptom until death. In most of these cases, however, inflammatory signs were noted one to several months after the appearance of the tumor. Visceral and skeletal metastases were widespread in this group and involvement of the lungs, liver or bones was manifest at the time of the initial examination in about one-third of the cases.

There is no sharp dividing line between the inflammatory change in the skin observed in acute carcinoma and the more common pigskin or lenticular dermatitis observed late in the disease in cases of large infiltrating mammary cancer. Discoloration and edema of the skin is found in practically one-third of all infiltrating mammary cancers over 5 cm. in diameter at the time of observation. Multiple discrete skin metastases are less common and occur in between 5 and 10 per cent of late and recurrent cancers. The orange-peel changes in late cancer differ from the changes of acute cancer only in extent and rate of spread. The discrete skin nodules seen with lenticular carcinoma are also found in cases of acute carcinoma, and all degrees of variation are found between a tendency to discrete nodule formation and the inflammatory signs found in the dermatitis of acute cancer.

Diagnosis

Inflammatory mammary cancer may be difficult to distinguish from acute mastitis. This is particularly true when the carcinomatous mastitis occurs during pregnancy or lactation. Lactation mastitis, however, is more frequently accompanied by the systematic signs of fever, leukocytosis, and malaise, is more tender on palpation and the skin manifestations are more limited in extent. An area of abscess formation with fluctuation and thinning of the overlying skin occurs within a few days after onset. Lactation mastitis usually runs a brief course and is most commonly seen before the fifth month of lactation. In any case of supposed mastitis persisting for more than two weeks, however, biopsy is indicated to rule out inflammatory cancer. This is the rule of DaCosta cited by Taylor and Meltzer.

The differential diagnosis between erysipelas and inflammatory carcinoma may be difficult. Again the constitutional manifestations are more pronounced in the true infection, and the response to sulfanilamide therapy aids in making the distinction.

Radiation dermatitis may also simulate inflammatory carcinoma of the breast. The history of irradiation and the restriction of the dermatitis to the field irradiated are diagnostic.

Large ulcerating mammary cancers may become secondarily infected. Here the area of necrosis and the toxic manifestations as well as the finding of pus are important differential points.

Treatment

In our cases all varieties of therapy were equally unsuccessful. The majority were treated by radical surgery which by modern

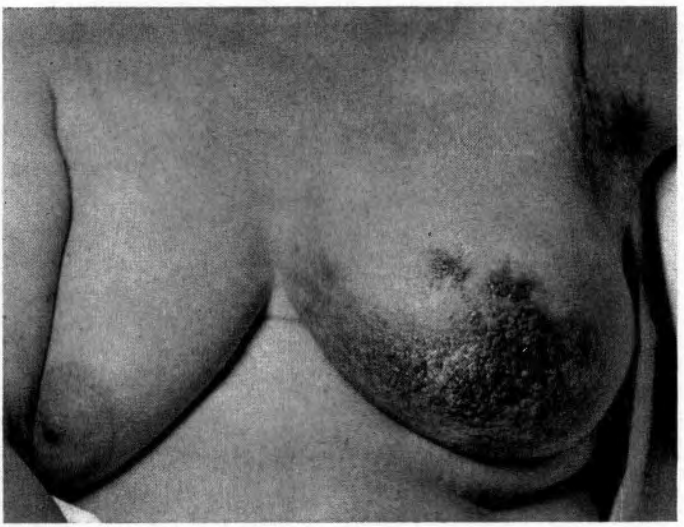

FIG. 381. Photograph of a patient with carcinoma en cuirasse. There is extensive involvement of the skin with discrete and confluent cancer nodules.

standards is contraindicated. This apparently shortened the life of the patient if we compare the duration of life in our series, which averaged about one year, with that of 21 months reported by Taylor and Meltzer. In their cases the majority were treated by irradiation. Operation with the cautery or soldering iron had no advantage over the knife. Apparently the response to irradiation is insufficient to offset the rapid spread of the disease. The induction of artificial menopause as reported by Taylor and Meltzer is without benefit.

Carcinoma en Cuirasse or Lenticular Carcinoma

Lenticular cancer, like inflammatory cancer, is a metastatic involvement of the skin of the chest wall. It spreads through the superficial lymphatics localizing in the form of nodules. The extension is slow and discontinuous in contrast to the rapid and diffuse involve-

ment seen in inflammatory cancer and it is not accompanied by edema of the skin. The skin invaded forms a sclerotic thickened mass rather than the red, edematous involvement seen in acute cancer. (Fig. 381.) Because of the slow and progressive course, ulceration is more commonly found. There is no sharp dividing line between the two conditions, however, and typical lenticular nodules are often seen in inflammatory carcinoma.

Treatment. Schreus has recommended soft radiation with 3 mm. aluminum filtration for the treatment of carcinoma en cuirasse and inflammatory cancer. A field 15 × 15 cm. is used and 300 r of unfiltered radiation is given daily to each field using 80 kv. A total dose in the neighborhood of 3,600 r is given. This method has the advantage of avoiding severe reactions.

CANCER IN PREGNANCY AND LACTATION

Mammary cancer occurring in pregnancy or lactation has an unfavorable course. Almost without exception these tumors are of the infiltrating type and arise in connection with the lobular develop-

TABLE LXVI

MAMMARY CANCER IN PREGNANCY

P.N.	MOS. OF PREG.	NO. CHILD.	AGE	DURATION	EXTENT	RESULT
51224[1]	2	1	38	1 mo.		Lost
34456	Misc.	2 3 misc.	41	6 mos.		Well, 7 yrs.
32403	2	1	33	9 mos.	2½ cm.	Dead, 9 mos.
2755[1]	2	5	26	4 mos.	7 cm.	Dead, 18 mos.
46546[1]	4½	1	29	1 yr.	3 cm.	Dead, 32 mos.
17560[2]	4½	3	40	4 mos.	Entire	Dead, 7 mos.
39832[1]	5	2	37	8 mos.	4 cm.	Dead, 19 mos.
30585[1]	5	1	38	8 mos.	6 cm.	Dead, 6 mos.
13429[1]	5	1	32	1 yr.	6 cm.	Dead, 6+ mos.
24925	7	2+	42	2 yrs.	4 cm.	Dead, 1 mo.
3	7	1	39	9 mos.	6 cm.	Dead, 8 mos.
3199	7	1	32	9 mos.	Entire	Dead, 2 mos.
47048	8	4	42	4 mos.	3 cm.	Dead, 23 mos.
10632	8	6	34	3 mos.	6 cm.	Dead, 33 mos.
2460[2]	9	1	38	5 mos.	Entire	Dead, 4 mos.
59814	8	1	26	4 mos.	4 cm.	Well, 22 mos.
9598	After misc.	1	36	1 yr.		Well, 6 yrs.
7397	After misc.	1	44	3 yrs.	½ Entire	Dead, 1 yr.
13419[2]	After misc.	6	40	4 yrs.	10 cm. bilateral	Dead, 19 mos.

[1]Operated on during pregnancy (2755—Amputation only) All other cases had radical mastectomy (46546—Excision only) after childbirth.

[2]Acute Cancer. Misc. = miscarriage.

ment which is at its height in women of the childbearing age. There are a number of reasons for the less hopeful outlook in this period: First, the women affected are in the younger age groups. Second, the increase in the size and fulness of the breast tends to mask the presence of the tumor so that the growths are usually of large size when treated. Third, the increased vascularity at this time results in some instances in rapid invasion of the neighboring tissues, so that extensive involvement of the skin with erysipeloid changes occur. These acute or inflammatory cancers are relatively common in pregnancy or lactation. Fourth, the rate of growth of the cancer is increased, particularly in the early months of pregnancy, apparently because of the increased estrogen output. (In late pregnancy this estrogenic influence is apparently offset by the increase in luteal hormones; estrogen is not a factor in cancer arising during lactation.)

TABLE LXVII

MAMMARY CANCER IN LACTATION

P.N.	MO. OF LACT.	AGE	NO. OF CHILD.	DURATION	EXTENT	TREATMENT	RESULTS
10703[1]	1 mo.	46	4	12 mos.	Entire breast, skin involved	Simple mastectomy	Dead, 7 mos.
11826	1 mo.	32	4	12 mos.	8 cm.	C C	Dead, 5 mos.
9740	2 mos.	44	1	10 mos.	10 cm., skin involved	C C	Dead, 11 mos
9700	3 mos.	34	1	7 mos.	7 cm., skin involved	C C	Dead, 7 mos.
2498	3 mos.	40	1	7 mos.	6 cm.	C C	Dead, 3 yrs.
36202[1]	4 mos.	41	3	9 mos.	6 cm., recurred opp. breast	C C bilat.	Dead, 9 yrs.
1441	5 mos.	38	9	8 mos.	7 cm., skin involved	C C	Dead, 4 mos.
13605	5 mos.	43	2+	5 mos.	quadrant	C C	
12308	5 mos.	33	1	5 mos.	7 cm.	C C	Well, 13 yrs.
49626	6 mos.	21	1	6 mos.	quadrant	C C	
23238	6 mos.	34	4	2 yrs.	4 cm., nipple ulceration	C C	Dead, 12 mos.
573	6 mos.	29	1	4 mos.	8 cm., skin ulceration	C C	Dead, 6 mos.
4853	7 mos.	37	4	6 mos.	entire breast	C C	Dead, 2 mos.
8204	8 mos.	31	5	3 mos.	5 cm., skin involved	C C	Dead, 1 yr.
5550	8 mos.	29	1	3 mos.	3 cm.	C C	Dead, 7 mos.
4480	8 mos.	45	1	4 mos.	9 cm., skin adherent	C C	Well, 5 yrs.
9242	9 mos.	46	6	6 mos.	7 cm., skin involved	C C	Dead, 3 yrs.
4749	9 mos.	45	10	9 mos.	4 cm.	C C	Dead, 2½ yrs.
1590	9 mos.	34	1	4 mos.	4 cm.	C C	Well, 20 yrs.
36508[1]	11 mos.	23	3	3 mos.	diffuse, acute	C C	Dead, 9 mos
7292[1]	11 mos.	33	1	9 mos.	diffuse, acute	Simple mastectomy	Dead, 3 mos.
26496	12 mos.	39	4	12 mos.	10 cm., skin	C C	Well, 6 yrs

[1] Acute cancer.
C C = Complete operation for cancer.

In the present study there were 15 cancers diagnosed during pregnancy, four instances in which the tumor was noticed shortly after miscarriage, and 39 cases observed during or shortly after lactation, a total of 58 cases. (Tables LXVI-LXVIII.)

TABLE LXVIII

CANCER AT THE END OF LACTATION

P.N.	AGE	NO. OF CHILD.	DURATION	EXTENT	TREATMENT	RESULT
31135[1]	36	1	7 mos.	Diffuse, acute	C C	Dead, 8 mos.
18550[1]	36	2	4 mos.	3 cm.	Amp. only	Dead, 7 mos.
36428	40	5	2 yrs.	3 cm.	C C	Well, 5 yrs.
1070	38	1	1 yr.	4 cm.	C C	Well, 8 yrs.
33092	30	2+	10 mos.	9 cm. skin, gl.+	C C	Lost
32458	33	3	6 mos.	7 cm.	C C	Dead, 3 yrs.
37288	33	4	1 mo.	1½ cm.	C C	Dead, 3 yrs.
40538	30	3	3 mos.	6 cm., gl.+	C C	Dead, 3 yrs.
17047	40	2	15 mos.	2 cm., gl.+	C C	Well, 5 yrs.
7780[1]	46	11	3 mos.	Entire	C C	Dead, 6 mos.
6334	37	1	18 mos.	5 cm., skin+	C C	Dead, 6 mos.
1057	50	7	3 yrs.	4 cm., skin+	C C	Dead, 2 yrs.
1560	42	1	18 mos.	5½ cm., skin+	C C	Dead, 1 yr.
1128	38	1	12 mos.	4 cm.	C C	Dead, 2 yrs.
35960[1]	44	3	2 mos.	6 cm.	None	Dead, 5 mos.

[1] Acute Cancer.
C C=Complete operation for cancer. gl + = nodes involved.

Cancer During Pregnancy

A cancerous lump discovered during pregnancy usually has been present for several months prior to gestation. In our series the duration of symptoms exceeded the duration of the pregnancy in all but two cases, which were discovered during the eighth and ninth months. The rapid growth of the tumor which may produce hardening of the entire breast, causes the patient to seek advice for a lump formerly disregarded. Nine of the 15 cases were primigravidae, and all were past the age of 25 years when the tumor was discovered. In five cases the cancer was discovered during the first half of pregnancy, and in 10 during the latter half.

The average size of these cancers was 5 cm. and the average duration of symptoms was six months for those in the first half of gestation, and 8.6 months for those in the latter half. Since cancers of similar size in the nonpregnant breast have an average duration of 10.8 months, it is evident that pregnancy increases the rate of growth.

Cancer in pregnancy involves the overlying skin and metastasizes earlier than in ordinary cases. The lymph nodes in the axilla were involved in every case studied. In addition to the rapidly enlarging mass, pain and changes of the skin were the chief symptoms. In one case occurring in the fourth month and in one case in the last month of pregnancy, there was a diffuse reddening of the skin of the entire breast, giving the clinical picture of inflammatory carcinoma. In both of these cases the tumor had been noted less than six months and the postoperative duration of life was less than eight months. the entire clinical course of the disease lasting about one year.

While the brief duration of symptoms in cancers in the first half of pregnancy (as compared to the second half) indicates more rapid growth at that time, the outcome was equally unfavorable in both groups. This coincides with the experience of Lee. Any distinction between the two halves of pregnancy is difficult to establish since cancers discovered late in pregnancy have usually existed throughout the course of gestation.

In the cases studied, therapeutic abortion was not performed although it was recommended in the more recent cases. Approximately an equal number of cases received radical mastectomy during pregnancy or at term. In two cases, biopsy or local excision was followed by irradiation during pregnancy and the radical mastectomy was performed after childbirth.

Since cancers discovered following spontaneous abortion have a better prognosis than those in which pregnancy is uninterrupted, therapeutic abortion is indicated in the first two-thirds of pregnancy if the disease is not hopelessly extensive at the time. Since the disease is obviously hopeless, irradiation rather than surgery is indicated. When the disease is well advanced, the family's wishes for a viable child should be taken into consideration in planning treatment. There are no advantages to abortion in the last third of pregnancy. In the cases of acute or inflammatory cancer arising during pregnancy, irradiation is entirely palliative and massive dosage is contra-indicated. (See: Treatment in Carcinoma en Cuirasse or Lenticular Cancer, pp. 482, 684.)

Cancer During Lactation

Thirty-nine cancers were operated upon during or shortly after lactation. Judging from the duration of the symptoms and their size (average 6.8 cm.) the majority of cases operated upon at this time had their origin during the latter part of pregnancy. (Table LXVII.) During lactation the early growth of the cancer is masked by the

fulness of the breast or may be interpreted as engorgement. For this reason these tumors are not discovered until late and in only one instance was the diameter less than 4 cm. Cancers developing during lactation may first become evident after weaning because of the rapid involution of the gland. Smaller and more recent growths also may be apparent at this time for the same reason. Seven cancers, 4 cm. or less in size, were operated upon in postlactation. With two

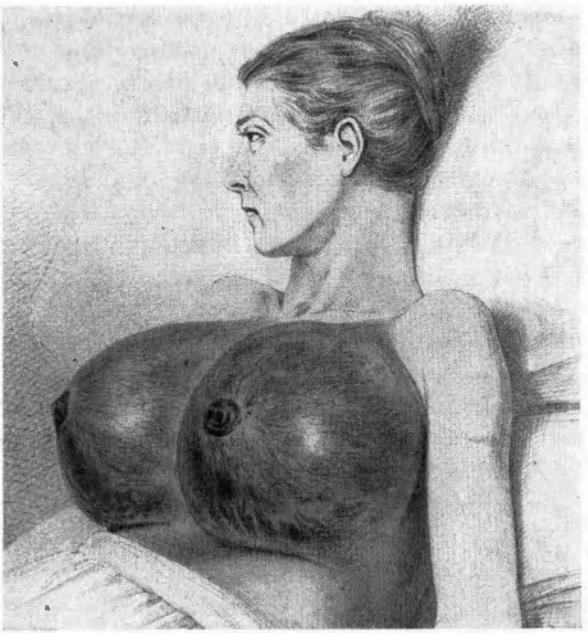

FIG. 382. Acute cancer in lactating breasts. The photograph taken from Billroth shows the extensive involvement of the breasts with cancer during pregnancy. The old term for this was mastitis carcinomatosis.

exceptions these were the cases which survived five or more years after treatment.

Except for the difficulty in recognizing the presence of the cancer, lactation does not appear to influence the growth of the tumor unfavorably. The average size of the tumors was 5 cm. and the average duration of symptoms was 11.4 months. This is the average rate of growth for these tumors in the nonlactating breast. There was a 25 per cent of five-year survivals of cancers operated on in lactation or in the postlactation period. This was also the average for tumors of this size in ordinary infiltrating mammary cancers.

In spite of the increased vascularity of the lactating breast, it is apparent that cancers developing during this period have a prognosis

in keeping with their size. The increased vascularity of the breast is apparently responsible, however, for the cases of inflammatory cancer with erysipeloid involvement of the skin seen at this period. (Fig. 382.) There were four cases of acute cancer arising during lactation in this series. The treatment of cancers in lactation is the same as for nonlactating breasts. Radical mastectomy is the treat-

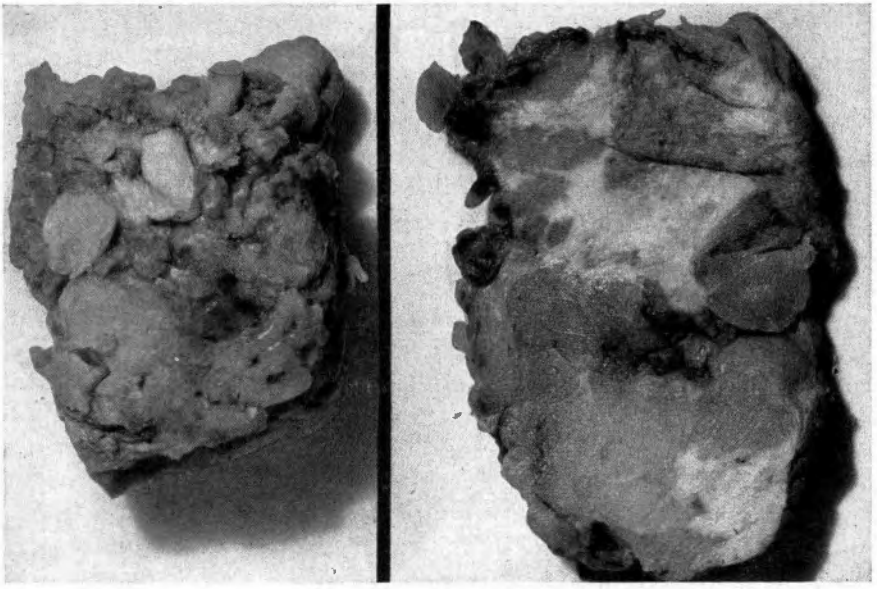

FIG. 383. Gross specimen of cancer in the lactating breast.

ment of choice except in the larger hopeless tumors, or in those with the skin changes of inflammatory cancer in which radiation should be employed.

The better prognosis of cancers in lactation as compared with those in early pregnancy suggests that the more rapid rate of growth in pregnancy is the result of increased estrogen stimulation, since in both pregnancy and lactation the mammary gland is equally vascular and there is no essential difference between the ages of the two groups.

Cancer in Lactation Mastitis

The incidence of puerperal mastitis, both suppurative and nonsuppurative, is about 2 per cent in the larger obstetric services at the present time. Among 1,260 cases of infiltrating mammary cancer occurring in parous women 78 (or 6 per cent) gave a history of lactation mastitis with or without abscess formation. This percentage

is not remarkable when one considers that the cancer records studied extend over a period of 50 years and include the decades when lactation mastitis was far more prevalent. In only 38 of these 78 cases, moreover, was the cancer related definitely to the scar or the residual lump of a former abscess or area of inflammation. This reduces to 3 per cent the true incidence of cancer following mastitis in parous women.

The following observations on cancer in lactation mastitis are based upon 38 cases, in which the cancer arose beneath the scar of a former abscess or within a persistent lump of residual mastitis. The time elapsing between the acute phase of mastitis and the appearance of the mammary cancer averaged 21.5 years in this series. The ages of the patients at the time cancer developed was between 39 and 67 years. The onset of the malignant growth was related to rapid enlargement of a pre-existing lump, to the development of a mass beneath the scar, to the appearance of pain and tenderness in the quiescent lesion, or to changes in the overlying skin. The symptoms referable to the malignancy were usually of several months' duration only, and the cancerous growth progressed rapidly. The majority of the tumors were 5 cm. or more in diameter at the time of operation. Fixation or ulceration of the overlying skin occurred in approximately one-half of the cases and the axillary lymph nodes were involved at operation in all but two cases. The patients in the present series were treated by radical mastectomy with one exception. This patient was treated palliatively by simple mastectomy. None of the cases was known to have been cured. Three were not traced, one was living four years after a radical mastectomy and two years after excision of cervical lymph nodes involved by metastasis, and another died with metastasis eight years after radical mastectomy. The remainder died of the disease within several months to four years after the radical operation.

This study indicates that cancer arising in lactation mastitis is often a fulminant disease. Among our cases the prognosis is worse than in those cases of cancer arising in pregnancy or lactation. The following cases are illustrative:

Case 1. A woman, 39 years old, had two children. A breast abscess was lanced while nursing her first child seven years ago. Six months ago a lump developed under the scar of the abscess. The tumor measured 4 cm. in diameter and the axillary lymph nodes were approximately the same size. A radical mastectomy was performed. The patient developed metastasis to the spine 15 months later and died with wide-spread metastasis 29 months after the onset of the symptoms.

Case 2. A woman, 46 years old, had three children. She had had nonsuppurative mastitis 18 years ago, while nursing her second child.

This subsided without incision or drainage, leaving a lump about 1 cm. in diameter. This was not affected with the third lactation and remained quiescent for 14 years. Four years ago the lump began to grow and became painful in the past 10 months. At the time of examination the nipple was retracted and the skin was adherent to the lump which occupied one-half of the breast. Radical operation was performed. Two years later a lump appeared in the opposite breast. This involved the entire breast and the axilla; the liver was enlarged. The patient was referred for radium treatments but died three months later.

Case 3. A patient, 52 years old, had eight children. During lactation twenty-six years ago an abscess was incised. Eleven months ago a lump which gradually enlarged appeared beneath the scar, and became adherent to it. The mass when examined was four centimeters in diameter and the overlying skin was reddened. No enlarged nodes were palpated in the axilla. A radical mastectomy was performed in January, 1914, but the growth recurred in the scar in August, 1915. The number of recurrent nodules in the skin about the chest wall rapidly increased and the patient died in April, 1917.

Case 4. A woman, 56 years old, with four children, had pain in the right breast and an axillary lump which developed two months ago. The pain was in the region where a lactation abscess had been incised 33 years previously while she was nursing the first child. A mass was found beneath the scar which was 2 cm. in diameter The lesion was explored. A diagnosis of cancer was made on the gross appearance of the tumor and a radical operation was performed. The axillary nodes were involved. The patient died of metastasis eight years later.

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21

Circumscribed or Adenoid Forms of Mammary Carcinoma: Comedo Carcinoma

CIRCUMSCRIBED FORMS

In the recent literature on the clinical course and treatment of cancer of the breast, little importance is attached to the particular pathologic variety. Statistics dealing with the prognosis in relation to size, duration, age and axillary involvement are based, as a rule, on all forms of mammary cancer as a group. This disregard of the pathologic subdivisions of mammary carcinoma is in contrast with the views of the older authors such as Velpeau, who was convinced that certain types of cancer, then known as encephaloid, differed markedly from the scirrhous form.

Velpeau in 1856 stated:

> We do not see, no one, perhaps, has ever seen, a ligneous scirrhus, well marked, become an encephaloid tumour, or not continue ligneous from the commencement to its complete destruction, to the death, in fact, of the patient. Moreover, I have never seen the encephaloid cancer, perfectly established, assume the evident characteristic of scirrhus, at any period whatever of its evolution.
>
> The encephaloid tumours have the air of being encysted; they are movable, rolling as it were, in the midst of the organs, whether in the concrete state, or when they are softened. Nevertheless, these exudations (of the tumor) are far from always leaving the neighboring tissues untouched . . . In a total of 250 cancers of the bosom of which I have

taken note, there were only sixty encephaloids against one hundred and ninety cases of scirrhus.

As stated in Chap. 18 on the pathology of mammary cancer, approximately one-fifth of the cases differ clinically and pathologically from the more common variety of scirrhous or infiltrating cancer. These circumscribed forms of cancer include comedo cancer, papillary adenocarcinoma and gelatinous cancer. (Fig. 384.)

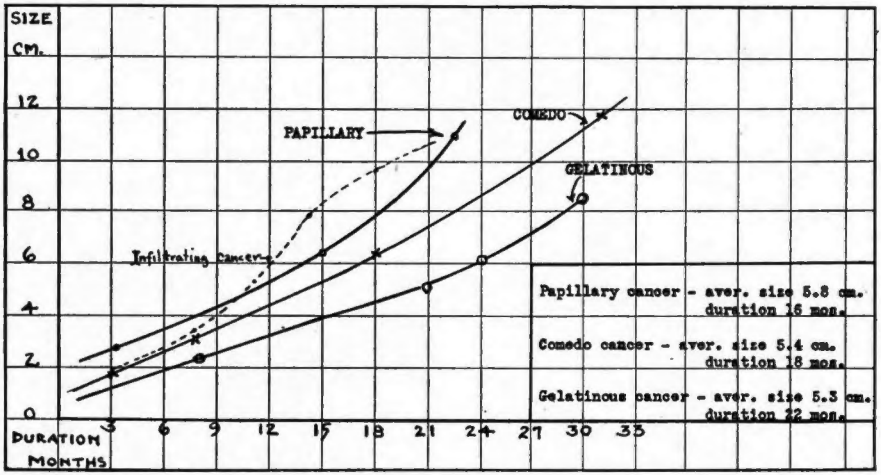

FIG. 384. Chart showing the growth curves of circumscribed mammary adenocarcinomas. The size of the tumor has been plotted against the duration of the symptoms.

These, as a group, are slowly growing tumors which are often 5 cm. or more in diameter and of more than a year's duration at the time of examination. The tumor remains for a long period circumscribed, bulging, and movable on deeper structures. The majority of these patients survive the five-year period.

In previous chapters the importance of doing aspiration biopsies on all cystic tumors of the breast and all clinically malignant tumors 5 cm. or more in diameter has been stressed. This rule applies particularly to the circumscribed adenocarcinomas under discussion which are often of large size or cystic in character. If the aspiration biopsy reveals gelatinous carcinoma, preoperative irradiation is contraindicated since such growths are radioresistant. Preoperative irradiation is indicated if, in a large tumor, the aspiration biopsy reveals papillary adenocarcinoma, or if in such a large tumor in the absence of ulceration there is an associated bleeding from the nipple. Comedo cancer and papillary adenocarcinoma are more often

associated with a sanguineous discharge than other forms of mammary cancer and are radiosensitive neoplasms. Preoperative irradiation in large tumors facilitates radical mastectomy and increases the percentage of permanent cures.

DEFINITION OF COMEDO CARCINOMA

The term "comedo" is applied to a circumscribed form of adenocarcinoma originating in the mammary tubules, for when the tumor is cut, plugs of cancer cells may be expressed from the ducts, in the same way that a plug or comedo is expressed from an ordinary blackhead. (Figs. 385, 386.) The term has nothing to do with any changes noted in the skin during the clinical course of the disease. Bloodgood was the first to give the name "comedo" to this type of growth. In an article in the American Journal of Cancer in 1934 he wrote:

> In 1893, forty-one years ago, I assisted Dr. Halsted in exploring a benign tumor of the breast. The patient was sixty-seven years of age and had observed a small tumor for about eleven months. It was our custom then to cut into the tumor and decide on its pathological nature from the naked-eye appearance of the tissue. This tumor was not encapsulated and not cystic, but distinctly circumscribed and buried in a senile breast. The moment we cut into and pressed on it, there exuded from its surface many grayish-white, granular cylinders, which I called at that time comedos. From the gross appearance the tumor was diagnosed as malignant, and the radical operation was performed. The nodes were not involved, the breast was senile, and there was no gross or microscopic evidence of chronic cystic mastitis. The patient lived nineteen years after operation, dying at the age of eighty-six.
>
> Since then I have been recording such cases and have divided them into two groups—pure comedo-adenocarcinoma and comedo-adenocarcinoma with areas of fully developed cancer of the breast. Examples of the latter group, in which areas of pure comedo are present in an otherwise fully developed cancer of the breast, are the more frequent, and for this reason the operator must always bear in mind the possibility of cancer when comedos are present in a tumor. Hence, if the tumor is too large to exclude the presence of malignant areas by frozen section, a radical mastectomy should be done.

CLASSIFICATION

Aside from the peculiar histologic appearance (Fig. 387) which distinguishes this form of duct cancer from the more malignant varieties (which have epidermoid-like cells) in the larger ducts beneath the nipple (with or without the complication of Paget's disease), there are other important considerations which entitle this group of neoplasms to a separate and distinct place in the classifica-

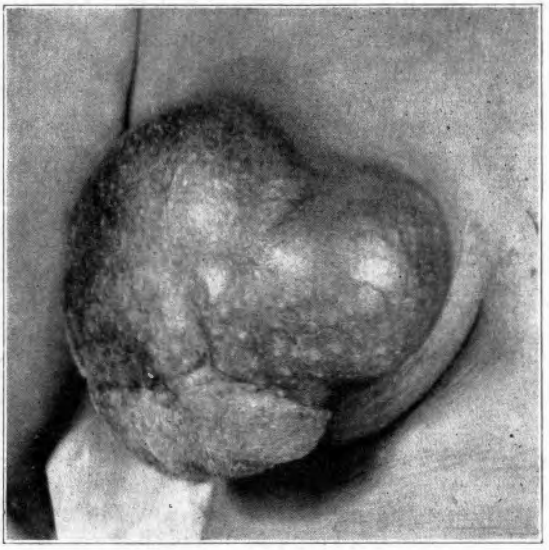

FIG. 385. Photograph of a diffuse comedo carcinoma. The tumor had been noted for seven years. The elevations seen in the skin are caused by the comedos in the ducts.

FIG. 386. Cross section of the breast shown in Figure 385. The surface of the tumor resembles in appearance wood which has been sawed across. The comedos may be seen projecting from the surface of the tumor.

tion of mammary cancers. One of these considerations is their relatively slow growth. A number of years may elapse before the tumor attains large size, ulcerates through the skin or involves the axillary nodes. Another is their more favorable prognosis. The majority of patients with this form of mammary cancer survive the five-year period. Finally, their dissociation from the more common forms of

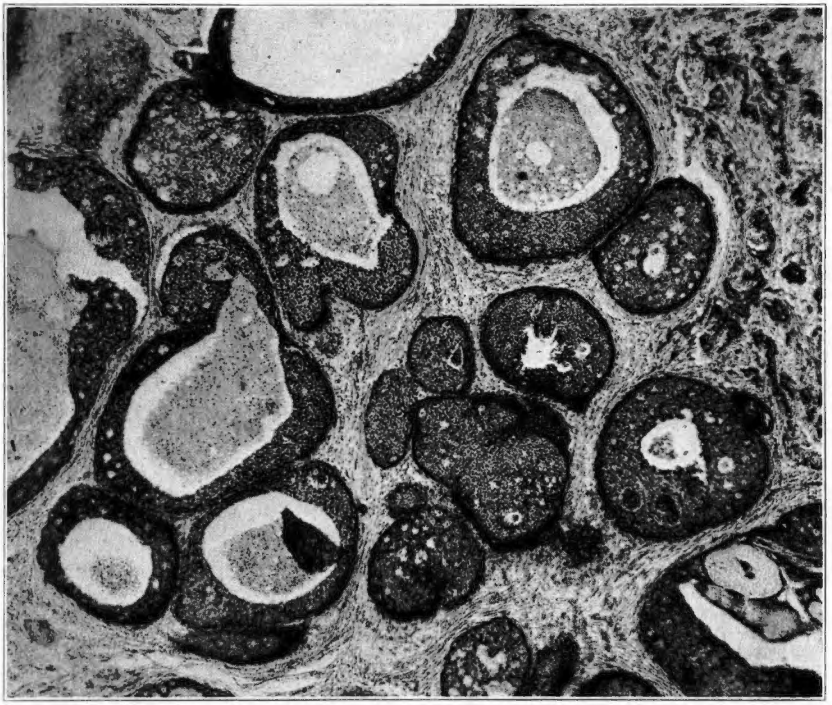

FIG. 387. The histologic structure of comedo carcinoma. The photomicrograph shows rings of tumor cells lining the ducts and plugging newly formed tubules.

lobular cancer has been experimentally demonstrated. This form of cancer is seen in female rats castrated a period of several months before the onset of the new growth. In these animals, comedo carcinoma arises in the mammary tubules in which the capacity for lobule formation has been lost or inhibited.

It is significant therefore that no case of adenocarcinoma of the comedo type has been described in connection with pregnancy. Comedo cancer is seen in women past the menopause, or in younger women with a history of surgical castration, sterility, or of chronic cystic mastitis. There are eight cases in this series that arose shortly after the end of lactation (ten months to three years afterward),

TABLE LXIX

DATA ON 106 CASES OF COMEDO CANCER

AGES		DURATION		SIZE		LOCATION	
25–29	7	1–5 mos.	37	1–2 cm.	14	U.O.Q.	15
30–34	2	6–12 mos.	17	3 cm.	26	U.I.Q.	10
35–39	20	1–4 yrs.	25	4–5 cm.	18	L.O.Q.	7
40–44	22	5 yrs.+	9	6–7 cm.	24	L.I.Q.	4
45–49	15	Unknown	14	8–9 cm.	9	Diffuse	15
50–54	19			10+ cm.	9	Central	42
55–59	8			Unknown	6	Unrecorded	13
60–64	9						106
65–+	5					Bilateral	3
Not stated	9						
	106		106		106		

MARITAL STATUS

Married women	64—71.2%	Married—2 children	14
(*No. children not stated 8*)		Married—3 or more children	24
Single	26—28.8%	Average children per family	2.4
Married—no children	10		
Married—1 child	8		

CLINICAL DATA		FOLLOW-UPS	
Serosanguineous discharge from nipple	27	Not followed	26
Evidence of chronic cystic mastitis		Followed	80
Clinically and microscopically	12	Dead within 5 years	19
Microscopically only	15	Living 5 years+	61
Axillary Nodes involved	15	Over 10 years	31
		Per cent of 5 year survivals	76.2%

when the lobular tissue is undergoing rapid involution. The loss of lobular elements, and the lymphatic and vascular bed associated with these structures, as well as the origin and growth of the tumor within the tubules, gives this form of cancer its characteristic histology. Comedo cancer, however, may show transitional forms, with infiltrating cancer in the surrounding glandular tissues. Such penetration (with a transition to the infiltrating forms of mammary cancer) is a late manifestation of true comedo cancer and is most common in those cases where recurrence takes place after a complete or incomplete operation. In the present study there were 68 cases of comedo carcinoma, referred to by Bloodgood as pure comedo, and 38 cases showing a transition toward infiltrating mammary cancer. In the latter group were included only those cancers in which the greater part of the tumor was confined to or produced mammary tubules, and in which the component cells of the new growth were small or moderate in size as in the "pure" comedo cancers.

CLINICAL FEATURES

The age distribution of patients with comedo carcinoma shows two peaks, one between 40 and 45 years and one between the ages of 50 and 54. (Fig. 388.) The average for the group is 51 years. In

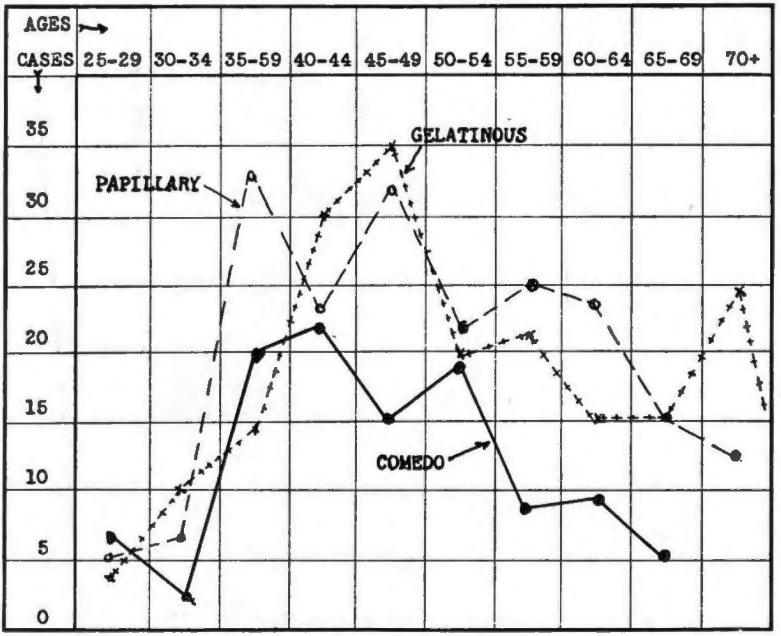

FIG. 388. Chart showing the age distribution of the three individual forms of circumscribed adenocarcinoma. The heavy line shows comedo cancer.

about 25 per cent of the cases the tumor was of more than two years' duration, and in nine the mass had been noted for five years or more The average duration of symptoms was 18.2 months. The number of single women with this form of cancer (28.8 per cent) is striking and is explained by the percentage of the cases in which evidence of a pre-existing mammary dysplasia is found (11 per cent).

The three distinctive features of comedo carcinoma are the slow and gradual growth of the mass, the number of cases with symptoms referable to the nipple and the frequency with which this form of cancer is found in women with chronic cystic mastitis of the "adenosis" type.

The patient usually complains of a slowly increasing swelling in the breast which is either painless or which occasions only a mild degree of discomfort. Tenderness, however, is frequently noted. A

serous or sanguineous discharge from the nipple was present in 36 per cent of the cases. Sometimes the patient stated that the discharge had been clear or creamy and had only recently become yellow or orange in color. In other instances, the patient was unaware of the secretion, but a small amount of clear fluid was expressed from the nipple on examination. In eight cases the discharge was the symptom of onset and preceded the discovery of the tumor by a year or more.

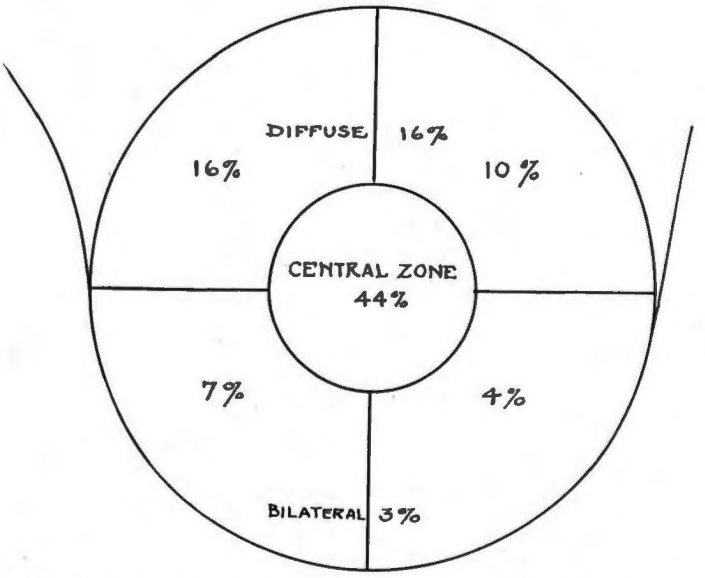

FIG. 389. Chart showing the location of comedo cancers in the breast.

In four cases the sanguineous discharge and a dense shadow on transillumination were the only clinical findings. In six cases the patients' attention was attracted to the nipple by burning, itching, or redness.

Small comedo cancers may be found in women with adenosis, in whose breasts multiple bilateral shot-like masses may be palpated. If the cancer has attained large size, the evidence of mammary dysplasia may be found in the opposite breast or on microscopic study only.

The frequency with which the patient notices symptoms referable to the nipple is due to the extension of the growth along the ducts, and to its frequent location in the larger ducts of the central zone. In 93 cases where the location had been recorded accurately, the tumor was found in the region of the areola or a few centimeters from the nipple in 42. In six additional cases the central zone of the breast was diffusely involved, and in nine cases the upper half of the

entire breast was affected. In 36 cases the tumor was found in a quadrant of the breast toward the periphery (Fig. 389).

The average size of the tumor in the cases studied was 5.2 cm.

The findings on palpation in comedo cancer are variable and often fail to yield a clue as to the benign or malignant nature of the tumor. In most cases the mass has neither the hardness nor the definition of ordinary mammary cancer. Often the breast is diffusely involved in one or more zones and an isolated tumor cannot be palpated in the enlargement. There is a zone of increasing swelling, denseness, or tenderness which may ultimately involve the entire breast; or as mentioned above, the affected zone palpates like the surrounding breast, but casts a dense shadow on transillumination. Usually the tissue is firm and definitely tender, and may resemble the caked area in mastitis. Dimpling over the affected region and atrophy of the overlying fat may be difficult to demonstrate. Even when it has attained a large size the mass remains movable, and often there are no palpable lymph nodes in the axilla.

The larger growths which may occupy the entire breast give the clinical picture of the diffuse comedo carcinoma. The following cases are examples:

Case 1. L. S., a white woman, 53 years old, had had three children. The menopause occurred at the age of 42 years. One month before the present examination she felt a burning sensation in her left breast. She touched the area and found a tumor. On examination, a mass about 7 cm. in diameter and without definite margins was found to the outside of the left nipple. The overlying skin was slightly dimpled. There were no palpable lymph nodes in the axilla.

The complete operation for cancer was done on Nov. 14, 1932. Plugs of solid material could be expressed from dilated ducts in the gross specimen. The microscopic diagnosis was comedo carcinoma. Examination of the lymph nodes for cancer gave negative results. The patient was seen on Dec. 5, 1935, at which time the roentgenograms of the spine and lungs did not show evidence of metastases.

Case 2. B., a white woman, 48 years old, had had seven children, whom she nursed. Since nursing her last child, three and one-half years before the present examination, she had noted a hardness of the right breast with crusting of the nipple, apparently due to a chronic discharge. On examination a hard mass was felt which involved the entire upper half of the breast and dimpling of the overlying skin was noted. A few drops of serosanguineous discharge was expressed from the right nipple. No enlarged lymph nodes could be palpated in either axilla.

A radical operation was performed on Aug. 31, 1927. The gross specimen had the typical appearance of a comedo carcinoma. Plugs were expressed from the ducts and the diagnosis was confirmed microscopically. Metastases were found in the mid axillary nodes but not in the nodes at the apex or base of the axilla. The patient died with metastasis five years after operation.

Case 3. M. F., a white woman, 34 years old, was examined for a lump in her breast following lactation. This breast had not produced milk. The patient's mother and her mother's mother both died of carcinoma of the breast. The tumor had been noted for four and a half years, more than three years before pregnancy. Four months ago it became painful. The nipple discharged fluid, became retracted, and the tumor increased rapidly in size. Both breasts were large, but the left was nearly twice the size of the right. The tumor was the size of a grapefruit, and was firm, lobulated and adherent to the skin. There were no palpable axillary nodes. A radical operation was performed on March 4, 1917. Many dilated spaces were found on gross examination, and from these was discharged a fluid which resembled condensed milk. The patient was well and free from recurrences in 1936, nearly twenty years after the operation.

In the localized form the tumor is small, measuring from 1 to 3 cm. in diameter. It is usually situated at the margin of the areola just beneath the skin and is freely movable. The axillary nodes, as a rule, are not involved, and a yellowish or watery discharge from the nipple may be noted. The affected breast is slightly larger than the uninvolved breast. The mass may feel like a thick-walled cyst or may be flat and disk-shaped. A firm tumor in the location just described and associated with atrophy of the overlying fat and a yellowish discharge suggests a comedo carcinoma.

In the case described in the following report a tumor appeared in each breast.

O. N., an unmarried woman, 44 years old, for five years had noticed a swelling of the left breast, which was diagnosed as chronic cystic mastitis. Recently the tumor grew rapidly, but no pain and no discharge from the nipple was noticed. On examination a firm mass, 2 cm. in diameter, was palpated just beneath the left areola.

A radical operation was performed on June 27, 1933. On gross examination the tumor was white and firm and the ducts contained plugs of carcinoma cells. The microscopic diagnosis was comedo carcinoma. In October, 1933, a small tumor appeared in the opposite breast and in April, 1934, the right breast was amputated. Pathologic examination revealed a cancer similar to the previous one. The patient was well in 1940.

In typical comedo cancer without infiltration of the fat and connective tissues, axillary metastases are rare but were found in two patients, one of whom ultimately died with brain metastasis at the end of seven years. In six comedo carcinomas, in which excision was the primary treatment and in which recurrence ultimately developed, the axillary lymph nodes were involved. Metastasis to these glands was also found in seven cases in which the tumor had been classed as infiltrating on microscopic study. In all, there were 15 cases with involvement of the axillary nodes (about 14 per cent).

Comedo carcinoma is associated with mammary dysplasia or cystic

mastitis more frequently than other forms of cancer of the breast. In 12 cases (11 per cent) multiple shot-like nodules or small cysts such as are found in adenosis or Schimmelbusch's disease were noted in the clinical examination or described in the gross specimen. It is

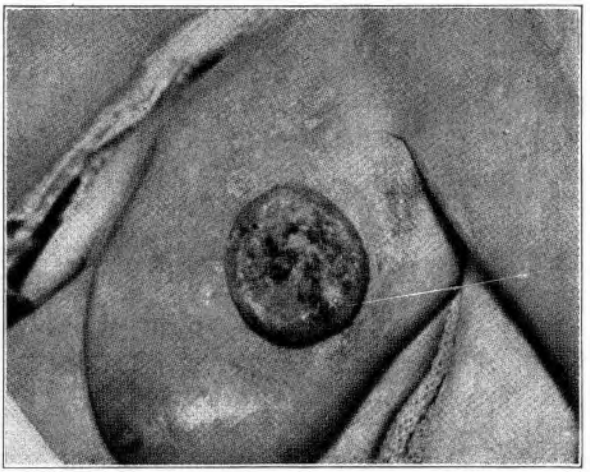

FIG. 390. A case of fungating comedo carcinoma.

particularly in cases of adenosis with a sanguineous discharge from the nipple that the possibility of comedo cancer must be excluded.

DIAGNOSIS

Comedo carcinoma is characterized by the following clinical features:

1. The long duration of the symptoms. The average duration was 18.2 months.
2. The relatively large size of the mass. In more than a third of the cases a quadrant or more of the breast was involved. The average size was 5.2 cm.
3. The central portion of the breast is involved most often. The smaller growths are frequently located near the margin of the areola. The larger growths are often in the central zone below or above the nipple.
4. The frequency of a discharge from the nipple. In 36 per cent of the cases the patient had noted either serous or sanguineous secretion; or fluid could be expressed from the nipple at the time of examination.
5. In the majority of cases the tumor had neither the hardness

nor the definition of ordinary mammary cancer. The growth retains its mobility even when of large size. In the diffuse form, swelling, induration, tenderness, or only a dark shadow on transillumination is found, instead of a hard definite mass. In the localized form, the tumor is freely movable, small, well circumscribed, and frequently described as palpating like a thick-walled cyst.

6. Dimpling of the skin over the tumor or retraction of the nipple is infrequent even in the larger growths.
7. Enlarged axillary nodes are rarely found on examination.

Differential Diagnosis

Comedo cancer is differentiated from cystic disease by the dark shadow on transillumination and by its failure to yield a cloudy fluid on aspiration. It resembles benign intracystic papilloma because of its frequent location near the nipple and the sanguineous discharge. Comedo carcinoma, however, is usually firmer and larger. Exploration and microscopic study may be necessary, however, to differentiate the two. In adenosis or Schimmelbusch's disease the presence of a sanguineous discharge and a mass 1 cm. or more in diameter that is dense, tender, and ill defined on palpation may indicate the presence of comedo carcinoma. The diagnosis must be made by exploration and with the microscope. The large diffuse comedo carcinoma that occupies the entire breast may palpate like a giant myxoma. It has the same degree of firmness and mobility; and enlargement of the axillary nodes is absent. The nodular and cystic masses palpated in large myxomas, however, are absent. The two conditions are easily differentiated under the microscope.

PATHOLOGIC FEATURES

Comedo cancer forms a mass which is circumscribed or infiltrating but not encapsulated. On section, the tumor tissue is firm and grayish in appearance, with softer and whiter material in the lumen of the distended ducts. These plugs in the ducts exude on pressure. The cut surface resembles consolidated pulmonary tissue with multiple foci of caseation seen in miliary tuberculosis. The surrounding breast tissue is fatty and senile or has the dense pinkish-white appearance seen in adenosis or Schimmelbusch's disease.

Comedo carcinoma arises from small oval cells with dense nuclei and scanty cytoplasm. These resemble the basal cells of the epidermis. There are numerous intermediate cell forms with increasing amounts of cytoplasm showing a differentiation into duct epithelium

with an irregular secretory border. These cells form a thick lining of many layers in the ducts. The larger secretory epithelium surrounds the central lumen which contains secretory debris; the smaller basal cells rest upon a membrane which sharply demarcates the duct epithelium from the periductal fibrous tissue (Fig. 391). The nuclei of the tumor cells are small, dense, and in general show no conspicuously malignant features. All of the duct channels throughout one or

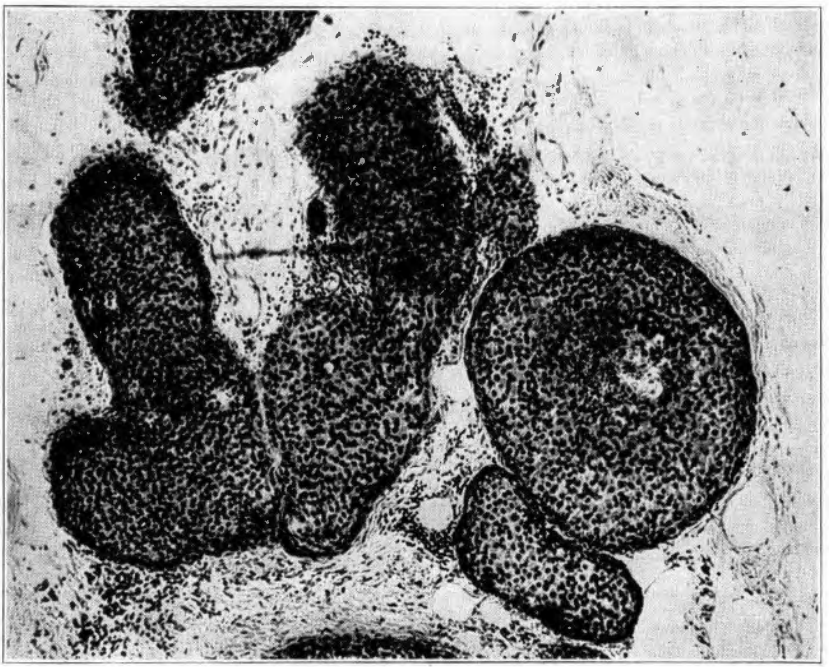

FIG. 391. Photomicrograph of comedo cancer showing the small basal cells from which the tumor develops.

more quadrants of the breast may show this characteristic reduplicated lining (Figs. 392, 393). The tumor cells not only line pre-existing ducts but also form new secretory channels; so that small secondary openings appear in the cross-section of the lining epithelium of the larger ducts. The tumor grows slowly and metastasizes to the axillary lymph nodes late. In cases where metastases occur, the epithelium in the lymph nodes may form characteristic thick-walled ducts lined by secretory epithelium with numerous transitions toward basal cells. Such formations in metastatic foci (Fig. 394) indicate clearly that the tumor cells are capable of forming new ducts and are not simply invading pre-existing ducts.

In typical comedo carcinoma the tumor cells are confined by a

basement membrane and form solid or thick-walled epithelial channels; invasion of fat or fibrous tissue is inconspicuous or absent. The transition between basal cells and secretory epithelium occurs gradually with the persistence of numerous basal-cell forms. This group of cases described by Bloodgood as "pure comedo" has a highly favorable prognosis but it must be distinguished microscopically from duct cancer related to Paget's carcinoma and from adenocarcinoma with duct invasion in which comedo-like areas are combined with areas of typical scirrhous or lobular carcinoma.

In duct carcinoma showing a histologic relation to Paget's cancer, the tumor cells approach squamous epithelium in type. The cells have abundant cytoplasm and large dense or vesicular nuclei with numerous mitoses. Multinucleated tumor giant cells are common.

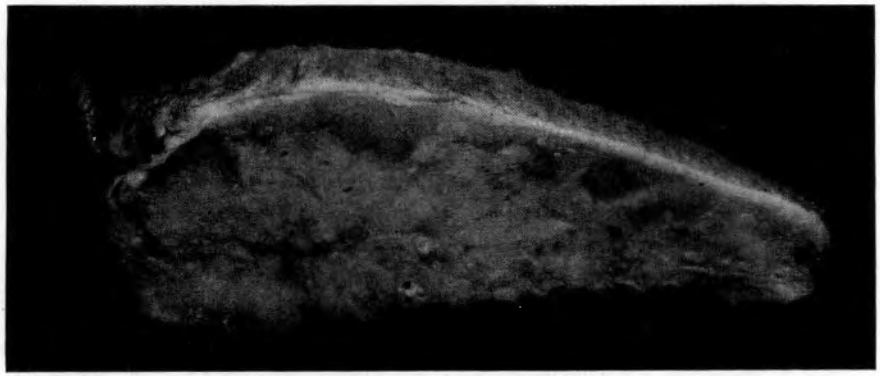

FIG. 392. Cross section of a breast showing diffuse involvement of the smaller ducts with comedo cancer.

Areas of central necrosis are seen within duct channels lined by such highly malignant epithelium. The tumor invades the large ducts, and ulceration of the nipple may occur giving the classical clinical picture of Paget's carcinoma. The growth of the tumor is rapid and the prognosis is poor. This group of cases of duct cancer is more closely allied in its behavior to Paget's cancer of the nipple than to comedo carcinoma.

In typical scirrhous cancer (infiltrating adenocarcinoma) areas of duct invasion resembling comedo carcinoma may be found occasionally in the smaller ducts. These cases should not be confused microscopically with true comedo cancer. In carcinoma arising in the smaller ducts and terminal tubules, invasion of fat and fibrous tissue by islands of scirrhous carcinoma is a prominent feature which allows these cases to be differentiated microscopically from comedo cancer.

Many of the cases described in the literature as duct cancer are

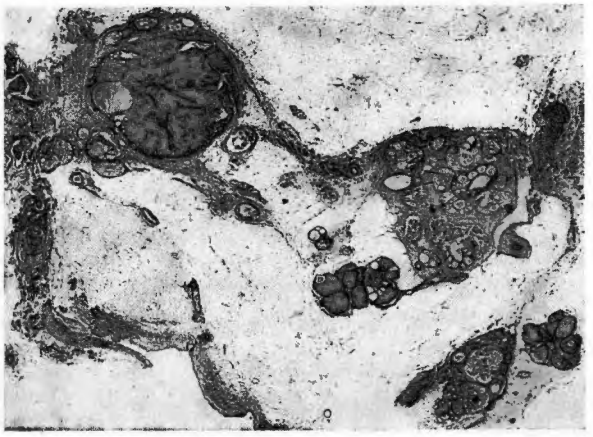

FIG. 393. Photomicrograph of comedo cancer. The circumscribed nodules are invading a senile, fatty breast.

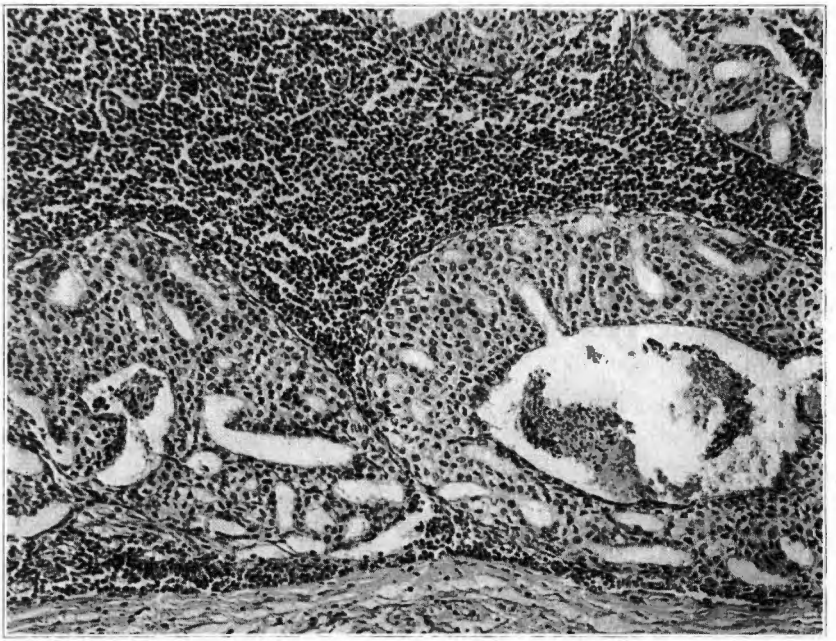

FIG. 394. Photomicrograph showing metastasis from comedo carcinoma in an axillary lymph node. The brushlike border of secreting epithelium can be seen surrounding the lumen. The histologic picture indicates that the tumor cells are capable of forming new ducts.

examples of slowly growing adenocarcinoma developing in intraductal papilloma. Although arising within the confines of the ducts, the epithelium giving rise to these tumors has acinar-forming potentialities and the resulting papillary adenocarcinoma grows in tufts and coils quite distinct from the tubular arrangement of comedo carcinoma.

TREATMENT AND PROGNOSIS

Of all the forms of carcinoma of the breast, comedo cancers offer the most favorable prognosis. There are 76.2 per cent of five-year

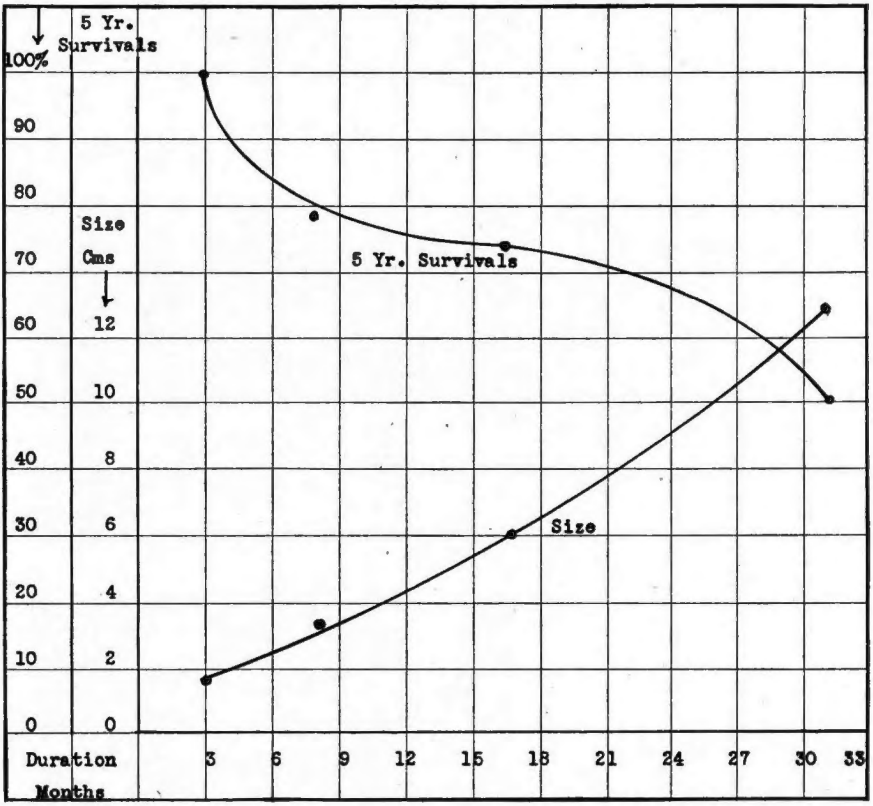

FIG. 395. The prognosis of comedo carcinoma in relation to size and duration of symptoms. The size of the tumor and the percentage of the five-year survivals have been plotted against the duration of symptoms.

survivals in this group. The majority of the patients living more than five years after operation have remained well for 10 or more years.

Three patients have remained well more than 20 years, and a fourth patient has remained well for 36 years. These favorable results are only exceeded by cases of gelantinous cancer in which no evidence of a pre-existing scirrhous cancer can be found on microscopic examination (Fig. 395).

There were 8 cases of comedo carcinoma in which the initial treatment consisted of local excision. In 6 of these the growth recurred locally—in one to four years. In these cases, radical operation was performed later, and metastases to the axillary nodes were found at the second operation. In the two additional cases treated by local excision, one of the patients has remained well for 11 years, and another for seven years. One patient was treated with irradiation followed by amputation of the breast without axillary dissection. This operation was performed in May, 1934, and the patient died with metastases to bone and to the skin over the wall of the chest in 1937.

When biopsy of the breast reveals early comedo carcinoma arising in chronic cystic mastitis, particularly in women who have not reached the menopause, there may be a temptation to restrict surgical measures in favor of excision, or simple mastectomy combined with postoperative irradiation. A study of the 61 cases of comedo cancer followed in the present series shows that such conservative measures are not justified. One hundred per cent of the patients with comedo cancers of 3 cm. or less in diameter survived the five-year period with radical mastectomy. In such cases there is no need for postoperative irradiation. With more conservative measures there were six recurrences among 8 patients.[1]

INFILTRATING COMEDO CARCINOMA

The pure form of comedo carcinoma just discussed grows slowly and remains confined to the ducts over a period of years and metastasizes very late to the axillary nodes. In the group about to be described, there were 77 cases of infiltrating comedo carcinoma which resembled histologically those previously described but which showed, in addition, cancer cells infiltrating beyond the basement membrane of the ducts and invading fat and fibrous tissue. (Figs. 396-398.) That this group represents a more rapidly growing form of comedo carcinoma rather than late cases of the pure form is indicated by the age distribution which parallels that of pure comedo

[1] Recently, the ninth case has been referred to the author. The local excision was performed one year ago for a small "cystic" tumor associated with a sanguineous discharge from the nipple, under the impression of benign papilloma. One year later (Sept., 1941) the patient had recurrence with involvement of the axillary nodes.

cancer, by the shorter duration of symptoms, and by the comparatively small size of the tumor. The average age of infiltrating comedo

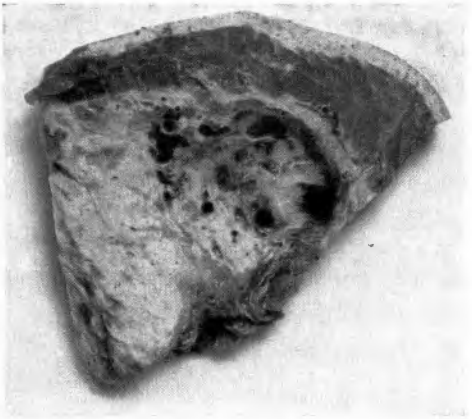

FIG. 396. The pathologic features of infiltrating comedo carcinoma. Gross specimen showing a circumscribed tumor with infiltrating cancer along one margin.

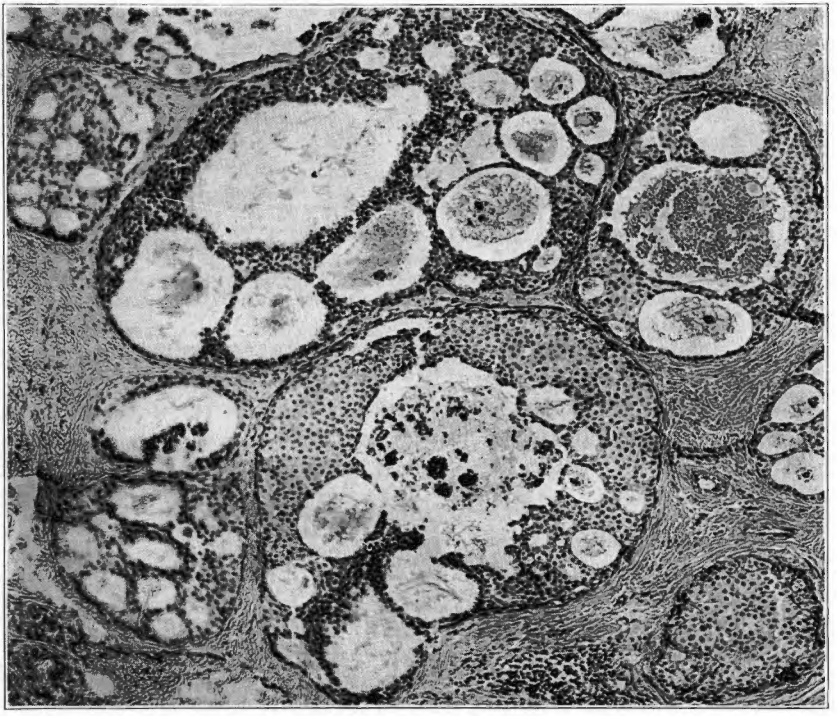

FIG. 397. Photomicrograph showing a portion of the tumor confined to the ducts.

carcinoma was 46 years, the same as for the noninfiltrating or circumscribed form. The average duration of symptoms in the 28

patients with infiltrating comedo cancer who had noted a tumor for more than a year was three and a half years and the average duration for 49 patients who had noted a tumor for less than a year was 3.6 months. The average size for all the tumors in the group was 4.8 cm.

The clinical characteristics of these tumors resemble those of the noninfiltrating form of comedo cancer rather than scirrhous cancer in that they are frequently freely movable and are often associated

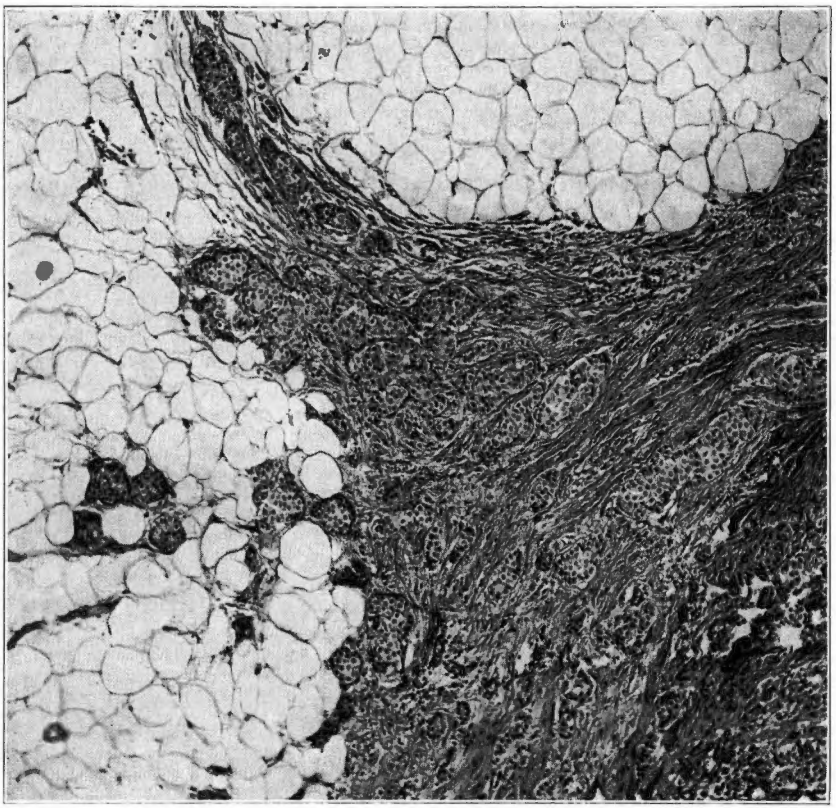

FIG. 398. Photomicrograph showing infiltration of the fat in another part of the tumor.

with the larger ducts near the nipple. In this group there were six patients treated by local excision in the first instance. One of the recent cases had no further operation. Three had the complete operation within a month following local excision and two of these died within a year, the third not being traced. In the two remaining cases the excision preceded the complete operation by more than one year. Both, however, have remained well for 14 years following the complete operation.

At the time of writing, 22 cases have not been traced for a period sufficient to learn the results of treatment and 55 have been followed. Twenty-seven of the followed cases are known to be dead, and 28 have survived the five-year period. All the cured cases except the two just mentioned were treated by radical surgery. None of the cured cases received preoperative irradiation. There are 51 per cent of five-year survivals.

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22

Circumscribed Forms of Mammary Cancer: Papillary Adenocarcinoma

The largest group of circumscribed mammary cancers shows a papillary or adenocystic structure in the gross or under the microscope. They are often of large size and of slow growth. The central portion of the breast near or beneath the nipple is often affected and a sanguineous discharge from the nipple occurs in approximately one-tenth of the cases. These growths differ from infiltrating lobular cancer, being softer to palpation and remaining in many instances freely movable, despite large size (Figs. 399-402). Distant metastases occur late and local recurrence or involvement of the other breast often precedes metastasis to the internal organs.

Judging from the description given by Velpeaux, the fungoid type of encephaloid cancer described by him is identical with the papillary cancers under discussion. Bryant in his book on "Diseases of the Breast," published in 1887, described instances of papillary cancer under the caption of carcinomatous intracystic growths.

Selling described a malignant tumor 7 cm. in its greatest dimension. Its papillary structure was demonstrated when water was allowed to flow over its cut surface. The tissue spaces contained nests of tumor cells, and the blood and lymph vessels were involved. The nature of the tumor is expressed in the title published in 1898, "Carcinoma Intracanaliculare Proliferans Mammae." Despite numerous contributions, the classification of papillary or bulky cystadenocarcinoma of the breast has remained ill-defined. There are two

chief reasons. One is the practice on the part of some pathologists to include benign intracystic papillomas in this group of malignant tumors. The other is the change in the use of the term "medullary"

FIG. 399 FIG. 400

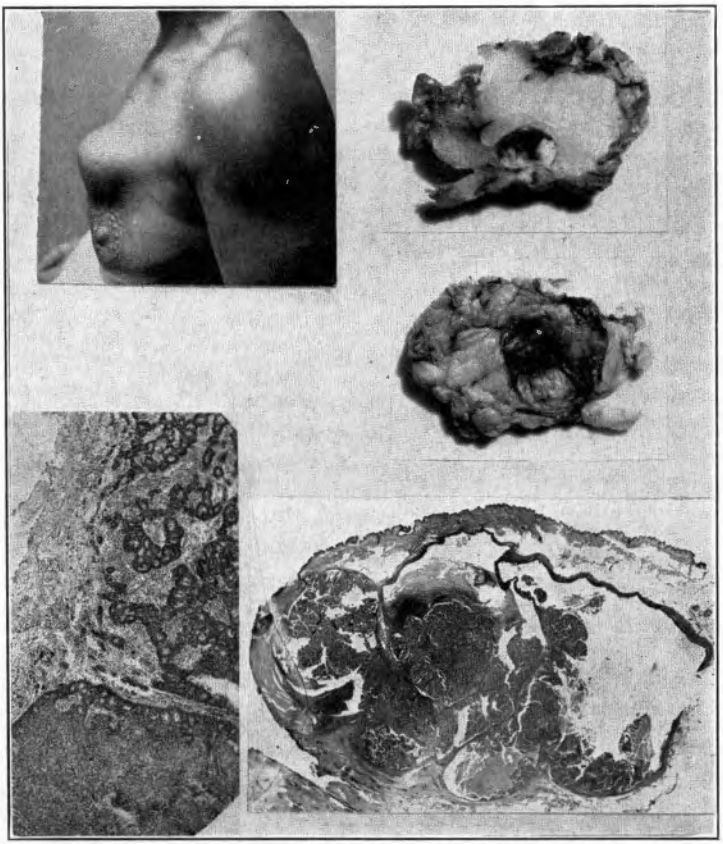

FIG. 401 FIG. 402

FIGS. 399, 400, 401, 402. Photographs of the patient, two views of the gross specimen, and photomicrographs of papillary adenocarcinoma. The bulging and the sharply circumscribed character of the tumor are shown.

first used to describe the gross appearance of soft cystic forms of circumscribed cancer and now applied as a microscopic description to highly cellular or malignant tumors of the breast. The softer, circumscribed forms of mammary cancer, as first pointed out by Lebert, contain relatively more epithelial and less fibrous tissue than scirrhous cancer, but as will be shown subsequently they pursue a less malignant course.

CLINICAL FEATURES

Age of Onset. Malignant papillary or intraductal carcinoma may occur at any age after puberty as a primary malignant growth, or through secondary malignant change in a pre-existing benign papilloma. For this reason, this form of cancer has an unusually wide age distribution, practically equal numbers occurring in each decade

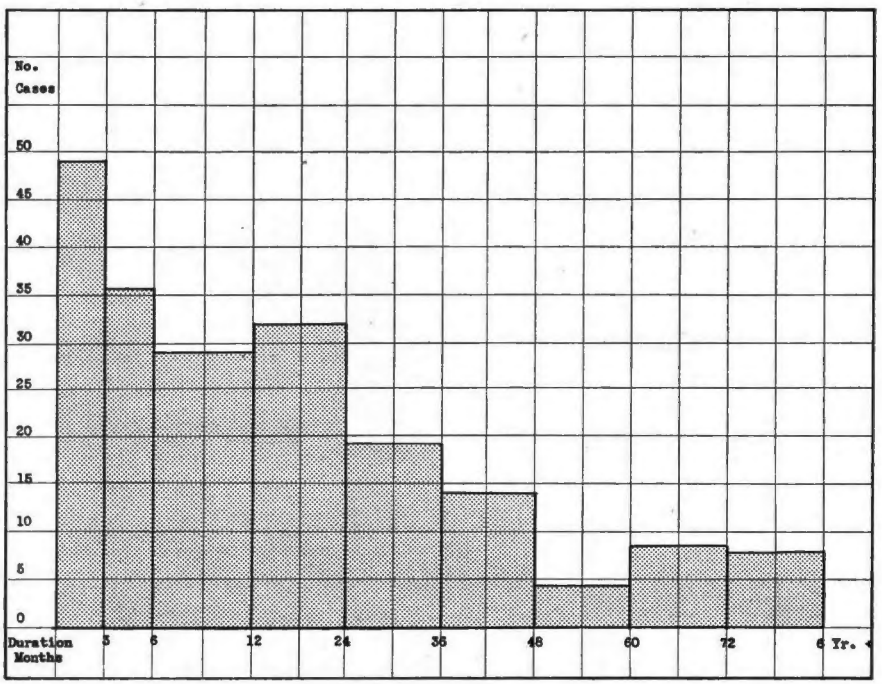

FIG. 403. Chart showing the duration of symptoms in cases of papillary adenocarcinoma.

between thirty and seventy years. Women between the ages of 35 and 40 were affected as frequently as those between the ages of 45 to 50 years, which is the peak of incidence for the infiltrating forms of mammary cancer. (Fig. 388.) The discovery of a lump in the breast rather than pain was the leading symptom of onset, although one-third of the patients did not report for examination until changes in the overlying skin were noted. A sanguineous or serous discharge from the nipple was noted in 14 per cent of the cases.

The average duration of symptoms is 16 months. In 40 cases the disease had been present for two or more years, 28 patients had noted the tumor more than one year but less than two years, and 107 had

noted the growth for a period less than 12 months. (Fig. 403.) The average size of the tumor at the first examination was just under 6 cm. (5.8 cm.). In 15 cases, the tumor was 10 cm. or more in diameter the largest being 30 cm. in its greatest dimension. All portions of the breast were affected (Fig. 404). The outer upper quadrant was in-

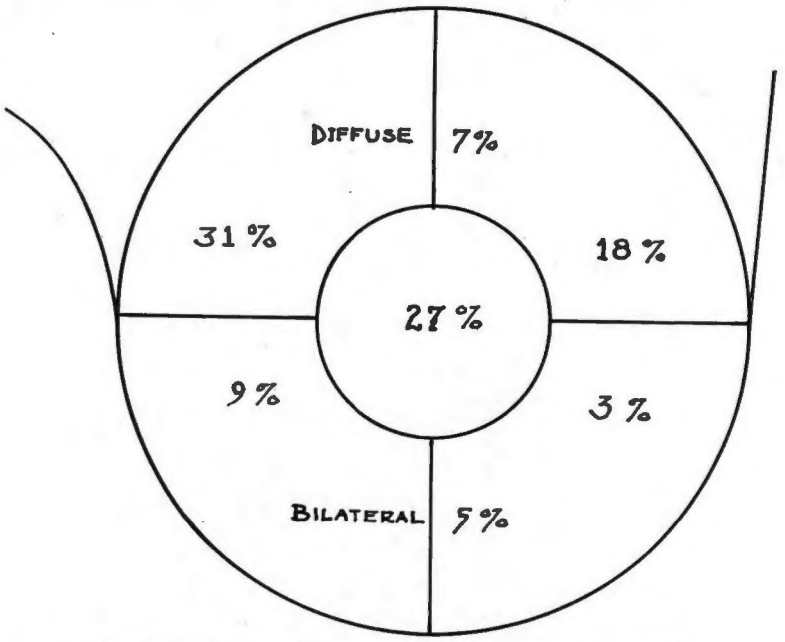

FIG. 404. Chart showing the distribution of papillary adenocarcinoma.

volved most frequently (in 26 per cent of the cases) and the central or nipple zone in 23 per cent. The upper inner quadrant was the next in order of frequency. Less than 20 per cent of the tumors were found in the lower hemisphere.

On palpation these carcinomas are often smooth and rounded, are definitely outlined and movable. Even when the tumor is large and fixed in the breast, the breast remains freely movable. Soft, cystic or fluctuating areas are frequently found. The skin over the tumor undergoes fixation, thinning and discoloration in the larger growths, the tumors having a tendency to protrude and to fungate. (Fig. 405.) Secondary nodules or bosses appear on the surface of the larger growths and may be palpated immediately beneath the skin. The rounded nature of the growth, its relatively smooth surface and its mobility in spite of its size, and its tendency to undergo softening, favor the diagnosis of papillary adenocarcinoma. In some cases multiple small lumps formed preceding the appearance of a large con-

TABLE LXX

DATA ON 197 CASES OF PAPILLARY ADENOCARCINOMA

AGES		DURATION		SIZE		LOCATION	
25–29	5	1–3 mos.	48	2 cm.	15	U.O.Q.	51
30–34	7	4–6 mos.	36	3 cm.	32	U.I.Q.	30
35–39	33	7–9 mos.	21	4 cm.	23	Central Zone	45
40–44	23	10–12 mos.	7	5 cm.	32	L.O.Q.	17
45–49	32	1–2 yrs.	33	6 cm.	24	L.I.Q.	6
50–54	21	2–3 yrs.	19	7 cm.	5	Entire Breast	12
55–59	25	3–4 yrs.	14	8 cm.	15	Unrecorded	36
60–64	24	4–5 yrs.	4	10 cm.	10		
65–69	15	5–6 yrs.	8	10+	12		197
70+	12	7 yrs.+	7	Unrecorded	23	Bilateral	8
	197		197		197		

DATA		FOLLOW-UPS	
Sanguineous discharge from nipple	19	Not followed	43 cases
Serous discharge from nipple	4	Followed	154 cases
Lymph Nodes		Living five years+	84 cases
Involved	130	Well 5 yrs.+	40
Not involved	67	Well 10 yrs.+	22
Skin Involvement		Well 15 yrs.+	9
Ulcerated	22	Well 20 yrs.+	13
Adherent	122	Dead under five years	70 cases
Negative	53	Per cent of 5-year survivals	55%
		Local recurrences	36 cases

fluent mass. In other cases, two lumps instead of one were present from the time of examination. The tendency to multinodularity which appears either early or late in the course of the growth is exceedingly unusual in other forms of mammary cancer. While the operative findings subsequently disclosed axillary involvement in two-thirds of the carcinomas studied, enlarged nodes were palpated in only 50 per cent of the cases.

Skin changes were noted in slightly more than one-third of the cases and in 12 ulceration had occurred. The changes noted included discoloration, edema, increased tension with thinness, and ulceration (Fig. 405). Skin metastases were not noted. A surprising number of cases with skin changes and palpable nodes survived the five-year period. Hence such findings do not contraindicate radical surgery in these cases.

DIAGNOSIS

The diagnosis of papillary adenocarcinoma is aided by the following findings:

1. A circumscribed bulging tumor exceeding 5 centimeters in

size and of more than one year's duration which is adherent to the overlying skin but movable on the deeper structures. The major portion of the tumor is solid or firm but may contain softer or fluctuant areas.

2. A sangineous or sero-sanguineous discharge from the nipple.
3. A central location.

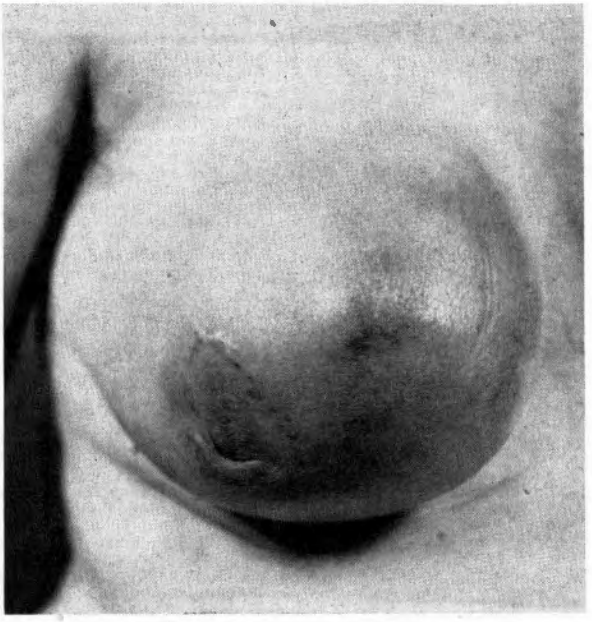

FIG. 405. Photograph of a patient showing a characteristic bulky adenocarcinoma of the papillary type with beginning ulceration of the skin.

4. The presence of one or more smaller nodules adjoining the main mass.
5. The absence of metastasis in the overlying skin, in large tumors of more than a year's duration.

Papillary adenocarcinoma must be differentiated from benign intracystic papilloma, giant mammary myxoma and thick-walled, blue-domed cysts. Papillary cancers are larger, more often adherent to the overlying skin and firmer on palpation than benign intracystic papilloma. The occurrence of one or more fluctuant areas in a large papillary cancer may simulate giant intracanalicular myxoma. The differentiating features of papillary cancer are adherence to the skin, the occurrence of palpable axillary nodes, and the presence of a sanguineous discharge in one-tenth of the cases. Biopsy may be necessary. In thick-walled, blue-domed cysts, the tumor transilluminates

clearly and aspiration, which yields a cloudy fluid, establishes diagnosis.

PATHOLOGY

The adenocarcinomas under discussion are circumscribed in the gross, and often encapsulated except at one or two points. The cut surface is friable, contains hemorrhagic areas, and the tumor appears

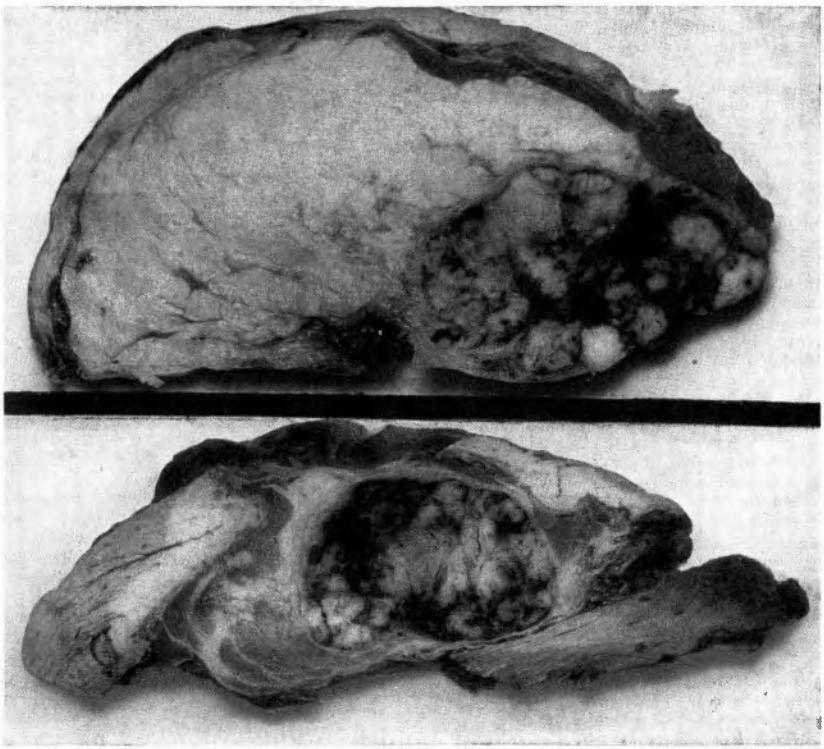

FIG. 406. The pathologic features of papillary cancer. The gross specimen shows the friable surface of the cut tumor.

to be made up of masses with varying degrees of consistency (Figs. 406, 407). The papillary or cystic structure is often definite. A stringy, branching mass of fibers enmeshes soft, hemorrhagic tissue which distends the tumor capsule. In the cystic tumors, solid tissue lines one or more locules within the main cavity, other compartments contain necrotic tissue or hemorrhagic fluid (Figs. 408, 409).

Ewing has described this form of adenocarcinoma as arising in cysts or in papillary growths. He states:

This is the most characteristic type of mammary cancer. It arises in cysts, in the walls or in papillary growths within cysts, or it arises from

an isolated segment of breast tissue. The architecture of the blood system in these tumors is dendritic, so that they grow expansively, displacing rather than infiltrating the breast tissue, and tending to produce a single multilobed compact mass. In any case, the growth is encapsulated or circumscribed, and infiltration occurs only in the later stages.

These tumors will grow to large dimensions, often rapidly. They protrude and often fungate through the skin, with ulceration, bleeding, and

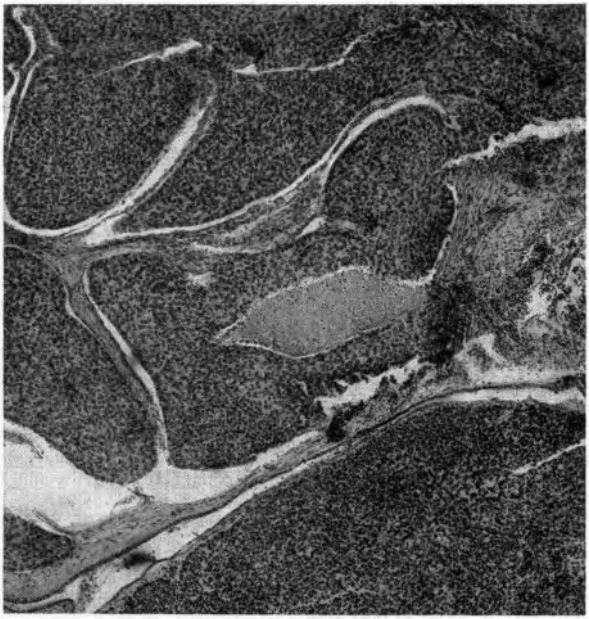

FIG. 407. The photomicrograph shows the growth of the epithelial tissue in coils.

sloughing. The invasion of lymph nodes is delayed, but only in accordance with the grade of malignancy. Many of them long spare the nodes, so that the prognosis is generally better than the extent of the local disease suggests.

The relation of papillary adenocarcinoma to a preceding benign papilloma is indicated in many specimens not only by the papillary and cystic character of the gross specimen but also by microscopic study. In some instances multiple benign papillomas are found in the surrounding breast, and the encapsulated carcinoma is composed of a large papillary growth which has undergone malignant change. (Fig. 410.) Such structure was found in 23 cases in the present series. In other instances the papillary growth is of immense size, but the benign structure persists in one of the smaller adjoining cavities or ducts adjacent to the larger malignant mass. At times the entire growth has a papillary structure with histologic features closely resembling benign papilloma, but metastases of a similar histology are

FIG. 408

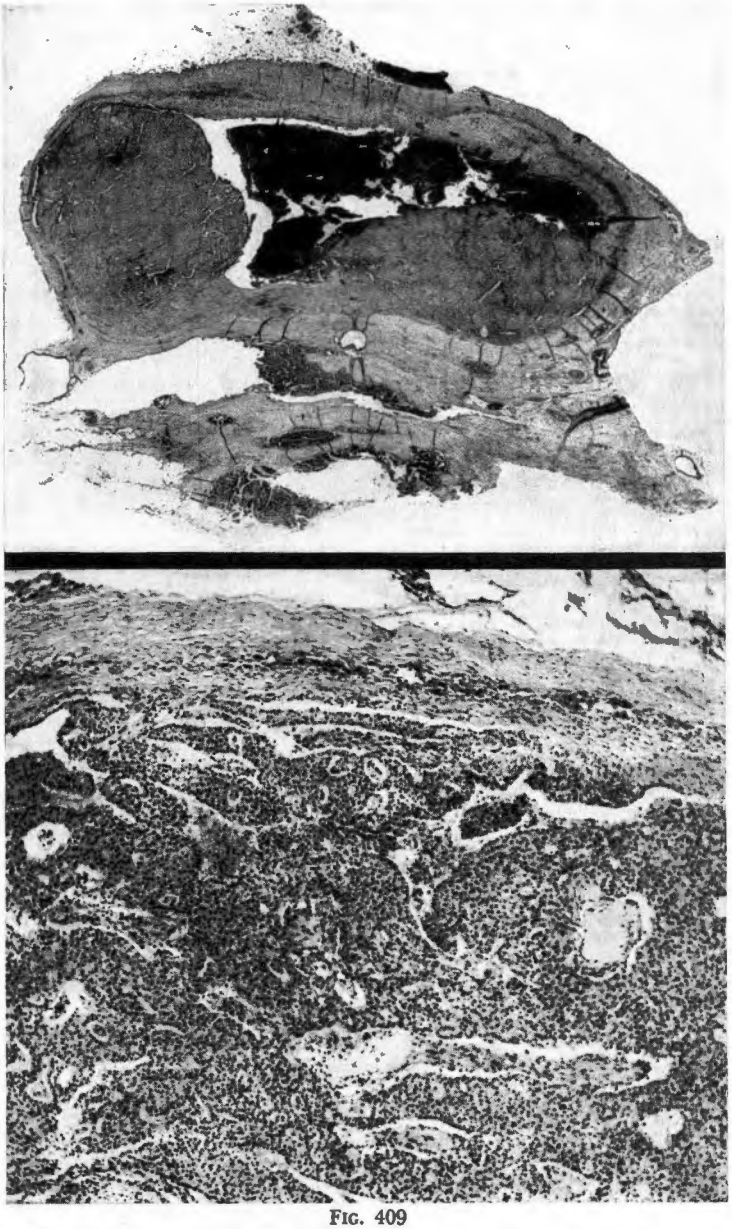

FIG. 409

Papillary Adenocarcinoma Forming an Encapsulated Hemorrhagic Growth.
FIG. 408. Cross section of the tumor showing the enclosed hemorrhagic cavity.
FIG. 409. Photomicrograph showing the sharply demarcated margins of the tumor.

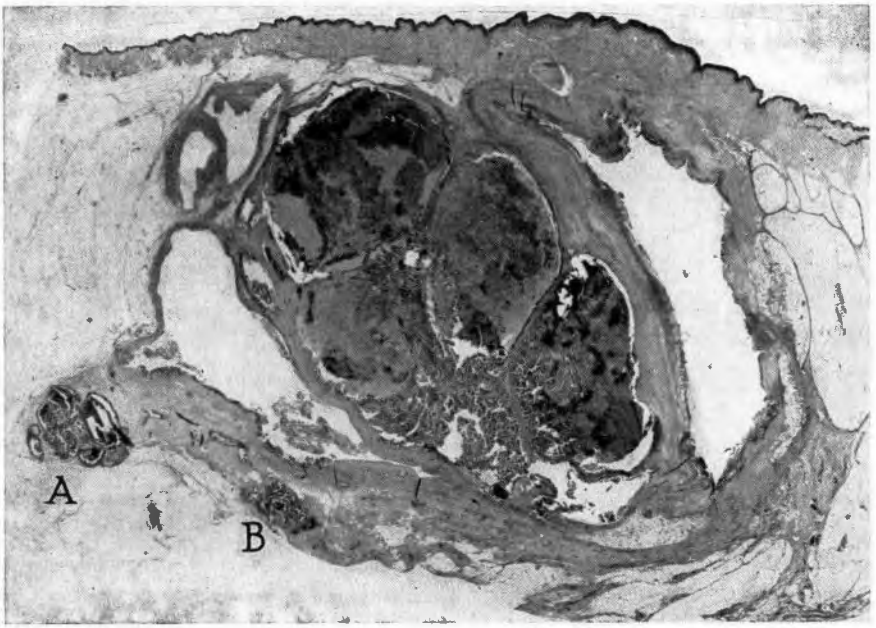

FIG. 410. A malignant papillary tumor with adjoining benign papillomas. The whole section of the breast shows the malignant tumor enclosing blood filled spaces and the small benign papillomas in an adjoining duct at A and B.

FIG. 411

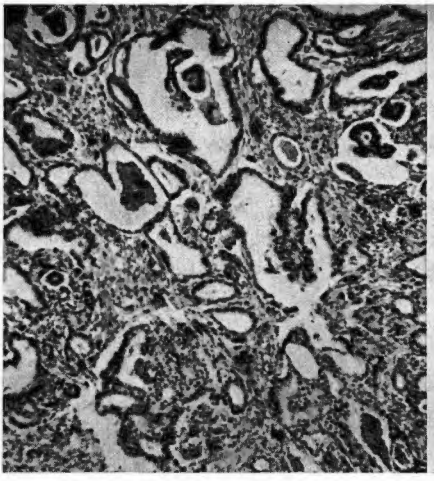

FIG. 412

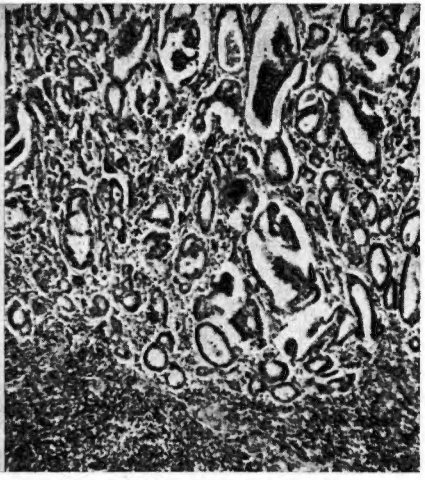

FIG. 411. Papilloma malignum. Photomicrograph of the primary tumor.
FIG. 412. Photomicrograph of the axillary metastases of papilloma malignum. Note the low-grade adenomatous structure of the tumor.

found in the axillary lymph nodes. These are the so-called adenoma or papilloma malignum. (Figs. 411, 412.)

In the majority of cases the branched stalks which are seen in benign papilloma are not found in the malignant growth, but the tumor grows in coils or sheets, with intervening areas of hemorrhage or necrosis or with numerous dilated cystic spaces. The margins of the malignant growth are for the most part sharply demarcated, separated from the surrounding normal breast by lymphoid cell infiltration. The absence of fibrous tissue splitting the cancer into cords or strands differentiates the tumor from scirrhous carcinoma.

Microscopic Diagnosis

In papillary cancer the epithelial cells surmounting fibrous stalks or forming loops or folds have a definite glandular character. They are of varied shapes and sizes but usually contain a moderate amount of cytoplasm of oval or columnar shape. The cells form rows so that regular or even margins are frequent. Many of the oval or columnar cells surround a central lumen forming acinar structures similar to, but larger than those seen in benign intracystic papilloma.

In benign intracystic papillomas the aborescent fibrous stalks supporting the neoplastic epithelium are prominent and well formed; and this fibrous portion of the growth often exceeds in amount the epithelial elements. The epithelium surmounting the fibrous core is orderly in arrangement, usually one to two layers in thickness, with an outer layer of tall, columnar cells with a frayed secretory border. Mitotic figures are scarce and the nuclei are usually regular in size and staining reaction.

In the malignant papillary tumors the fibrous stalk is inconspicuous, incompletely formed or absent and the epithelial coils which are many layers in thickness predominate. This predominance of epithelium gives the tumor in the gross its soft crumbling character. The loops of alveolar structures are many times larger than those seen in benign papilloma, and the lining cells are many layers in thickness. The basement membrane is frequently broken and the epithelial cells in small nests lie free in areas of connective tissue or in stroma infiltrated with lymphocytes. Mitotic figures are more common than in the benign papilloma and the size and staining of the nuclei are more variable. The most distinctive malignant feature is the invasiveness found at the margins. Nests of malignant epithelium at one or more points are separated from fat only by lymphoid cells. At other points foci of cancer are found budding into the fibrous stroma. Frequently large alveolar-like structures resembling comedo carcinoma extend from the capsule into the normal breast. In the present study no correlation could be found between the prognosis

and the orderly character of the papillary growth. Tumors, the general architecture of which resembles benign intracystic papilloma, are just as prone to produce metastasis and death as those with a less definite papillary structure, in which sheets or coils of intertwining malignant epithelium are found.

PROGNOSIS AND TREATMENT

Papillary adenocarcinoma may be cured by radical operation even in advanced cases. Among the five-year survivals which comprised 55 per cent of the 154 followed cases, tumors of 5 cm. or larger are nearly as common as those of smaller size. (Fig. 413.) In eight cases surviving more than five years the dimensions of the tumor exceeded 10 cm. In one of these patients a tumor of 14 cm. was removed by a radical mastectomy. Recurrence took place after four years. This was treated by excision and the patient died of other causes 11 years later. Another patient with a tumor of similar size died of cancer 17 years after mastectomy. The dissection was carried out above the clavicle because of metastasis to the glands of the neck. In other cases in which the patient died of the disease, late local recurrence was a striking feature. The recurrence in some instances appeared from 5 to 16 years after the radical amputation. Because of the large size of the tumor, there is a tendency to sacrifice only the skin overlying the mass with very little additional margin. This may account for the relatively high percentage of local recurrences in these circumscribed growths (23 per cent). Despite the size of the growth at the time of operation and the tendency to local recurrence, 55 per cent of 154 cases adequately traced survived the five-year period, and of these slightly more than half were alive after ten years.

The less favorable prognosis in younger patients with mammary cancer applies also to this circumscribed form. The five-year survival rate was 44 per cent in patients between the ages of 25 and 40 years. This, however, is slightly higher than even the most favorable cases of infiltrating or scirrhous cancer.

Because of the vascularity of these growths and pedicle-like arrangement of their nutrient vessels, these are among the most radiosensitive of the mammary carcinomas. It is advantageous, therefore, in the larger growths to combine irradiation and surgery to minimize the number of local recurrences and to control the extension of the disease in the supraclavicular region.

In the growths exceeding 5 cm. in diameter, aspiration or "punch" biopsy may be carried out to verify the diagnosis. Preoperative irradiation may then be given with divided-dose technic, using mul-

tiple fields including two for the breast, and three for the axilla and supraclavicular region. (See Chap. 30, p. 677.) Eight weeks after radiation a radical mastectomy may be performed.

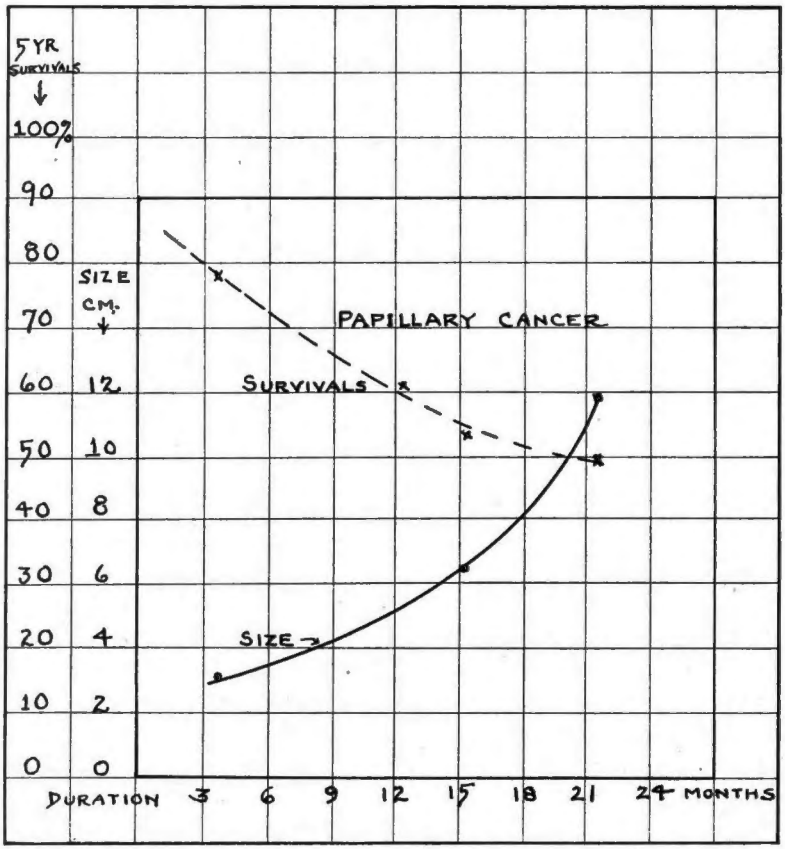

FIG. 413. The prognosis of papillary carcinoma in relation to size and duration of symptoms. The size of the tumor and the percentage of five-year survivals has been plotted against the duration of symptoms.

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23

Circumscribed Forms of Mammary Cancer: Gelatinous Carcinoma

Although rare, gelatinous cancer was among the first of the several varieties of mammary carcinoma to be described as a separate and distinct form. Its syrupy, jelly-like characteristics in the gross and the peculiar ground substance under the microscope make it readily recognizable and have permitted accurate classification. Lange has credited Otto, in 1816, with the first description. Robinson, in reporting a case in 1852, stated that only four similar tumors affecting the breast had been reported, one by Johannes Müller, one by Rokitansky, one in the London Hospital Museum, and one in St. Thomas's Hospital.

Robinson's case is of interest because the patient remained free of the disease for five and one-half years after excision. The patient, 56 years old,

> was under the care of the late Mr. Tyrell seven years ago (1827) for a tumor (not ulcerated) in the right breast, and another in the right armpit, both of which were removed by the knife and the wound healed perfectly in a month . . . About 18 months ago, a hardness was noticed on the termination of the wound towards the nipple . . . About one-third from the outer termination of the cicatrix is a small lobulated tubercle, which has existed four months, and which evidently increased. It is of purple colour, covered with crimson vessels, and surrounded by a similar stony induration, firmly attaching it to the chest.
>
> November 27 (1834): The ulcers had scarcely varied at all; the redness of the integuments of the right arm and the swelling somewhat subsided, but the hardness and tenseness continued. She had a troublesome cough,

wheezing, dyspnoea and sense of weight in the chest, with great emaciation; and although relieved by blistering, expectorants, hyoscyamus, and mild tonics, she died in the evening from effusion into the chest . . . At autopsy . . . the tumors in the course of the cicatrix had extended as far as the ribs, and implicated them. They were specimens of colloid cancer, and appeared much the same as during life, although not so vascular. One had a fibrous appearance, the other, a vascular; and into one of these blood had been effused. Upon incising it posteriorly, the gelatiniform appearance was beautifully shown. The lungs were congested, and the air-cells somewhat dilated, but they were not at all affected by malignant disease. There was about a pint of serous fluid in each side of the chest. The heart was healthy. The other viscera were not examined.

Gaabe, in 1908, found that this type of cancer was twice as curable as the ordinary form. Halsted, in 1915, described a peculiar sensation on palpation which he thought was diagnostic of gelatinous cancer. He stated that the tactile impression "might be defined as a delicate swish or crush of a jelly-like structure under tension." Lee, Hauser and Pack reviewed the literature on the subject, in 1934, and found the incidence given by various authors as 1 to 2 per cent of all cancers of the breast. They reported 30 cases, recorded in the Memorial Hospital, with 57 per cent of five-year cures.

The present study is based upon 83 cases of gelatinous carcinoma recorded among a total of 2,500 cancers of the breast. This study emphasizes the slow growth of these tumors, their low degree of malignancy and their tendency to local recurrence 5 to 30 years after treatment.

CLINICAL FEATURES

Age of Onset. Gelatinous carcinoma occurs as a rule in more elderly patients than ordinary mammary cancer. One-third of the cases in the present series occurred between the ages of 41 and 50 years and nearly an equal number occurred in patients between the ages of 60 and 79 years. (Fig. 414.)

The discovery of a lump in the breast was the first sign noted by the patient in 80 per cent of our cases. The painless character of the mass and its slow growth enhance the natural period of delay in consulting a physician. In 33 cases, the tumor was known to have been present for a year or more and in nine of these cases, the duration was five years or longer. In three instances, a mass was discovered during routine examination, the patient being unaware of its presence. One patient had noticed hardness of the affected breast for 20 years. The hardness apparently disappeared for several years but recurred eight years before admission and rapidly increased in the past year. During the past three years she had had a sanguineous

discharge from the nipple. When examined, there was diffuse induration of the entire breast and a soft fluctuating mass 3 cm. in diameter beneath the nipple. This patient died six years after radical operation with invasion of the mediastinum.

Gaabe has estimated that the duration of symptoms in gelatinous carcinoma is two and one-half times that of infiltrating cancer. Lange,

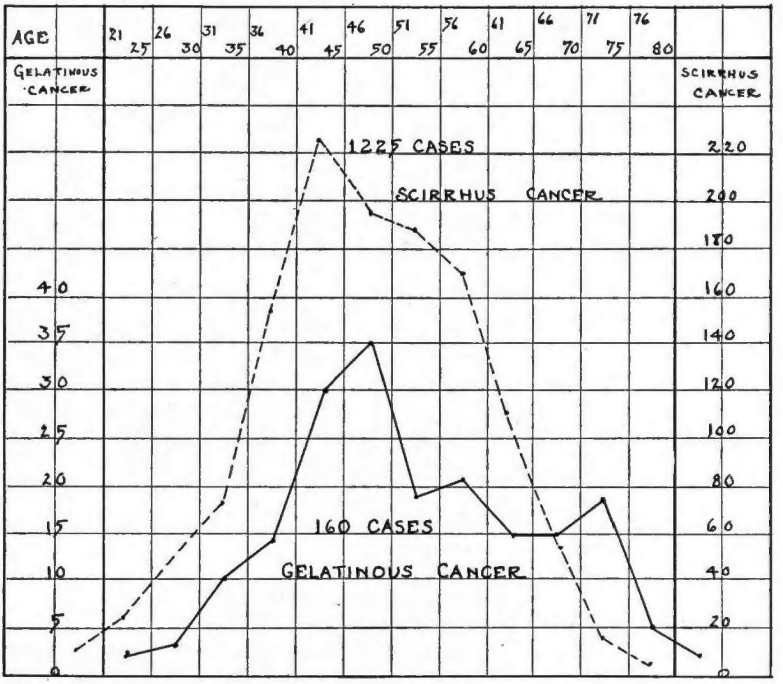


FIG. 414. The chart shows the comparison of the age incidence of 1,225 cases of scirrhous cancer with 160 cases of gelatinous cancer (including the author's series and those collected by Gaabe).

basing his conclusions on breast cancers reported by various German authors, states that ulceration of the skin in scirrhous cancer occurs from one to two years after the onset of symptoms. In the 75 cases of gelatinous carcinoma collected by him, the period elapsing before fixation of the skin averaged 33.9 months and ulceration occurred after 57.7 months.

The duration of symptoms, in terms of years, is corroborated by the similar period which may elapse between local excision and recurrence. In the case reported by Robinson, cited above, the first signs of local recurrence were five and one-half years after excision. In a similar case, recorded in this laboratory, local excision was per-

TABLE LXXI

DATA ON 83 CASES, GELATINOUS CANCERS

AGES		DURATION		SIZE		LOCATION	
20–24	1	Under 6 mos.	18	1–2 cm.	13	U.O.Q.	12
25–29	2	6 mos.–1 yr.	12	3–4 cm.	20	U.I.Q.	8
30–34	4	1–3 yrs.	24	5–6 cm.	18	Center	17
35–40	7	4–5 yrs.	6	7–8 cm.	6	L.O.Q.	5
40–44	13	Over 5 yrs.	9	Over 8	9	L.I.Q.	1
45–49	15	Found on routine	3	Av. size 5.3 cm.		Entire breast	5
50–54	8	Not stated	11				
55–59	9		83				
60–64	7						
65–69	7						
70–74	8	Av. duration—22 mos.					
75+	2						
	83						
Av. age	52						

INVOLVEMENT OF AXILLARY NODES

Nodes positive	32
Nodes negative	51

SYMPTOMS & FINDINGS		FOLLOW-UPS	
Tumor	80%	Followed cases	65 cases
Pain	20%	Living over 5 years	40 cases
Protrusion of nipple	8 cases	Dead under 5 years	25 cases
Discharge from nipple	9 cases	Excision only	19 cases
Cystic character	12 cases	Recurred under 5 years	18 cases
Bilateral	3 cases	Simple mastectomy	5 cases
Multiple tumors in same breast	7 cases	Recurred under 5 years	3 cases
		Five-year survivals	61%

formed in October, 1919. The recurrent tumor, which was half again as large, was noted in February, 1922. For this, a simple amputation of the breast was performed, and, in November, 1930, axillary lymph nodes which showed mucoid cancer were excised. The patient was well in April, 1937. Halsted performed excisions for recurrence, in 1903 and 1906, for a tumor which had had two previous excisions at four-year intervals. This patient died in an automobile accident in 1931, at the age of 73.

Size. Lee, Hauser and Pack have emphasized the large size of some of these growths. Gaabe found that 10 per cent of 88 cases were of unusual size. The present study emphasizes the relatively small size of the tumor in comparison with the long duration of symptoms. The average size of the tumor in 58 cases was 5.3 cm., and approximately 50 per cent had a diameter of 4 cm. or less. There were only five tumors, 10 cm. or more in diameter; the largest, 22 cm., was a recurrence after local excision. Three cases had a diameter of 8 cm., and one, 9 cm. (Fig. 415.)

Pain is usually not an early symptom. Approximately 10 per cent

of the patients noted a discharge from the nipple, usually of a sanguineous character, and an equal number had noted change in the size or color of the nipple, with or without itching or irritation. Discoloration or ulceration of the skin prior to examination was noted in 14 cases. The skin changes were present only in those tumors

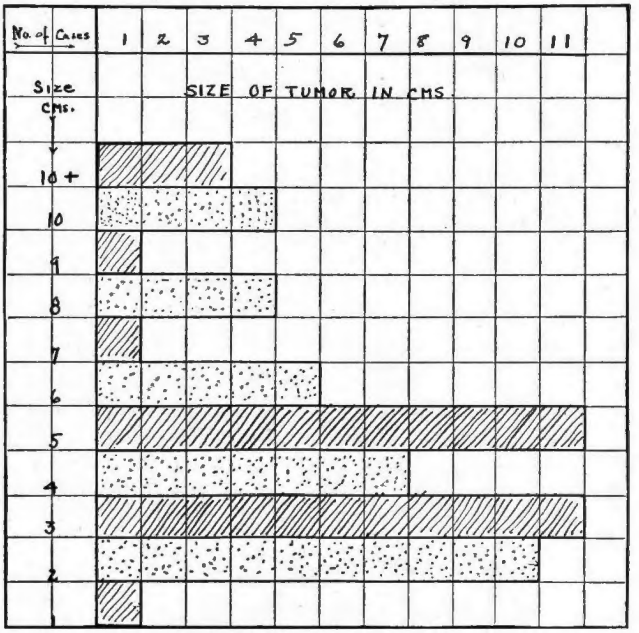


FIG. 415. Chart showing the maximum diameter of the tumor in cases of gelatinous carcinoma.

which were six or more centimeters in diameter. There was one exception.

DIAGNOSIS

There are four findings which suggest a diagnosis of gelatinous carcinoma: (1) The relatively small size of the tumor in comparison with the long duration of symptoms. (2) The protrusion and enlargement of the nipple on the affected side. Protrusion, rather than retraction, was noted by the examiner in eight cases and is probably of more frequent occurrence, since its diagnostic importance in gelatinous carcinoma has not been heretofore emphasized (Fig. 416) (3) The cystic character of the growth on palpation. The diagnosis of benign cyst was made prior to operation in 11 cases in the present

series. The differentiation from a benign cyst should not be difficult in these cancers because the tumors are often larger (4 to 6 cm.), and on aspiration do not yield the cloudy fluid obtained from a cyst of similar size. (4) The feeling of a "swish" on firm pressure, originally described by Halsted.

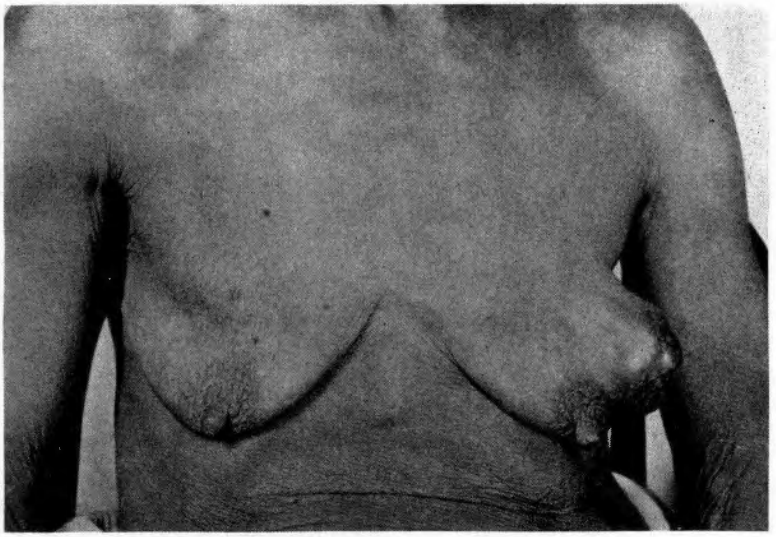


FIG. 416. Gelatinous carcinoma occurring in a colored woman, age 62. Note the bulging and enlargement of the nipple on the affected side. Enlargement and protrusion of the nipple may be a diagnostic sign in these growths.

Gelatinous carcinoma occurs most frequently in the outer upper quadrant and in the central portions of the breast. The location of the tumors studied in the present series and those reported by Lee, Hauser and Pack and by Gaabe, are shown in Table LXXII.

TABLE LXXII

LOCATION OF THE TUMOR IN 93 INSTANCES OF GELATINOUS CARCINOMATA

AUTHOR	UPPER OUTER QUADRANT	UPPER INNER QUADRANT	CENTER	LOWER OUTER QUADRANT	LOWER INNER QUADRANT	ENTIRE BREAST
Author's series	12	8	17	5	1	4
Lee, Hauser and Pack	4	4	10	0	3	1
Gaabe	15	3	0	6	0	0
Totals	31	15	27	11	4	5

In seven of the cases there were multiple tumors in the same breast.

In three cases both breasts were ultimately involved. In one, the involvement of the second breast occurred one year after the radical operation; this was a mucoid cancer. In the second case, the involvement three years later showed a scirrhous cancer with mucoid change. In the third case, a similar tumor appeared beneath the nipple in the opposite breast and enlarged nodes were palpable in the axilla five years after radical operation. In the 75 cases studied by Lange, three developed cancer in the other breast. In one, the tumor in the second breast was a colloid cancer. The second was diagnosed as a scirrhous and the third as a Paget's disease.

Differential Diagnosis

While the diagnosis of gelatinous cancer is usually made on the gross specimen or the microscopic section, there are 11 cases in the

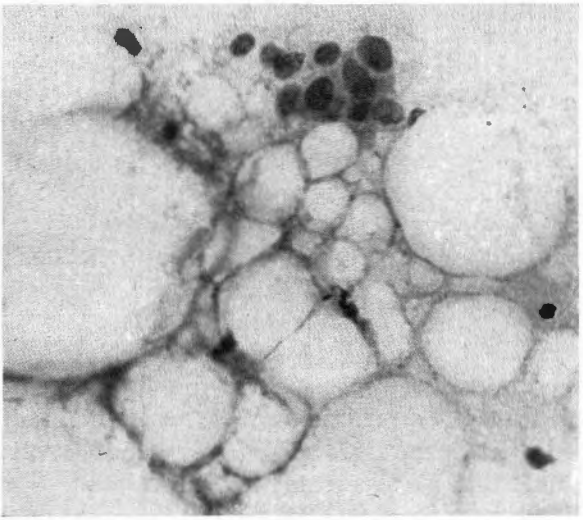


FIG. 417. Photomicrograph showing cancer cells in the mucoid material aspirated from a case of gelatinous carcinoma.

present series in which the nature of the tumor was correctly inferred from the clinical findings.

On the other hand, the tumor was incorrectly diagnosed as a benign cyst in 11 instances, in four cases, as intracanalicular myxoma and in an additional four cases, as benign intracystic papilloma or papillary carcinoma. In the remaining cases, where the diagnosis was not made clinically, the impression was that of ordinary mammary cancer. Where the diagnosis of benign cyst was made, sufficient importance was not given to the nearness of the tumor to the skin, the atrophy of the overlying fat, the size of the tumor, or its failure to

yield a characteristic cloudy fluid on aspiration. The distinction between a giant intracanalicular myxoma, or degenerating fibro-adenoma is more difficult. Usually the fibro-adenomas of corresponding size are opaque on transillumination, whereas in gelatinous carcinoma if the lesion is soft and sufficiently gelatinous the tumor will transilluminate. If a large size (18-gauge) needle is used for aspiration, the characteristic gelatinous material should be demonstrable (Fig. 417).

A central location, a sanguineous discharge from the nipple, and a boggy feeling with or without areas of fluctuation, occur in both gelatinous and papillary cancer. That the differential diagnosis may be impossible clinically is indicated by the pathologic finding of mucoid change in eight cases of papillary cancer recorded in this series.

PATHOLOGY

There are two groups of mammary cancers which contain this type of gelatinous material. In one, a shiny, translucent gel occurs throughout; in the other, the gelatinous change is found in one or more portions and solid cancer in the remainder of the growth. In the present series, 59 tumors showed gelatinous substance throughout, and 24 showed secondary mucoid change.

The gross specimens of typical gelatinous cancer may be cystic or solid, encapsulated or nonencapsulated. In carcinomas with complete gelatinous change, 16 of the cases were described as encapsulated and two as circumscribed. At exploration, the encapsulated tumors resemble a cyst or degenerated intracanalicular myxoma. One such tumor presented a blue dome because of its vascularity; another was polycystic. When the capsule of these cystic tumors is incised the soft, translucent jelly-like material, often flecked with hemorrhage, bulges or flows from the incision. The exuded material has frequently been compared to tapioca (Figs. 418, 419).

In the nonencapsulated gelatinous carcinomas, the mucoid material may invade the surrounding tissues, including fat and muscle, or the gelatinous material may be diffuse giving the cut surface a slimy, grayish cast or a honeycombed appearance (Figs. 420, 421). Three of the nonencapsulated tumors were fixed to the overlying skin and two had invaded the pectoralis muscle. In such solid nonencapsulated growths, pockets of mucoid material such as are found in encapsulated tumors may occur.

In six cases, gelatinous material was interspersed in tumors having the structure of papillary carcinoma (Fig. 422). In two other

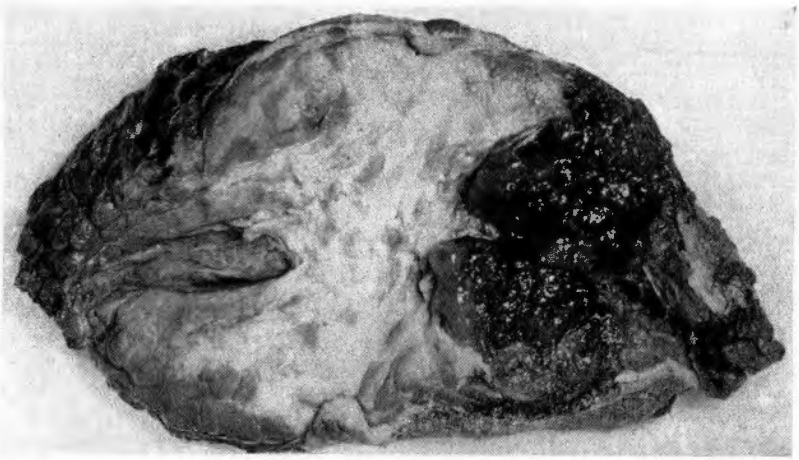


FIG. 418. Photograph of a gross specimen showing the bulging dark jelly-like material in a case of encapsulated gelatinous carcinoma.

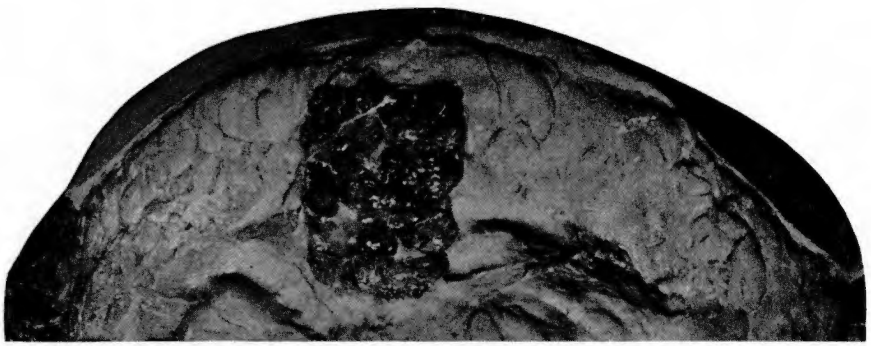


FIG. 419. Photograph of a gross specimen showing the encapsulated character of gelatinous growth, which feels like a cyst when palpated.

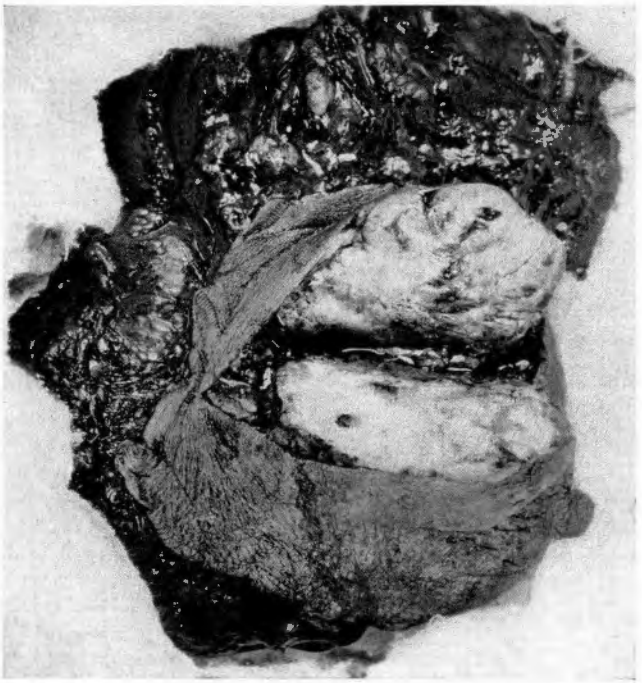


FIG. 420. Gelatinous carcinoma of solid character showing a characteristic glary surface.

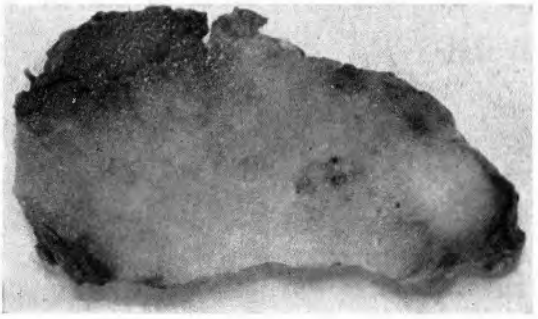


FIG. 421. A solid gelatinous growth removed at operation for recurrence, 19 years after mastectomy for the primary tumor.

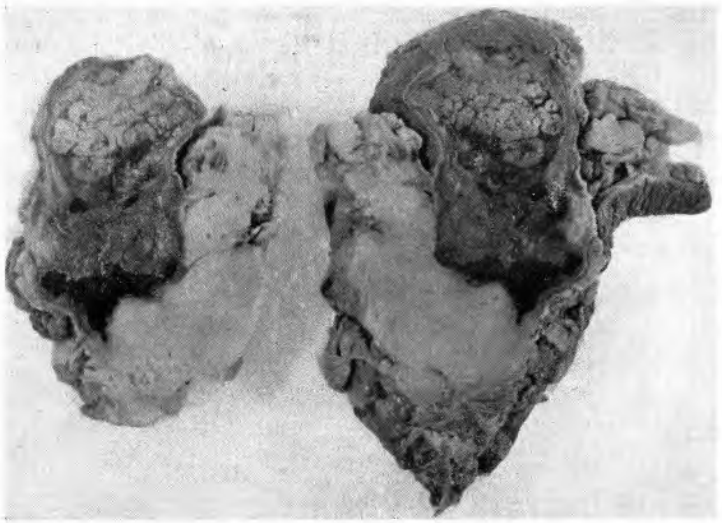
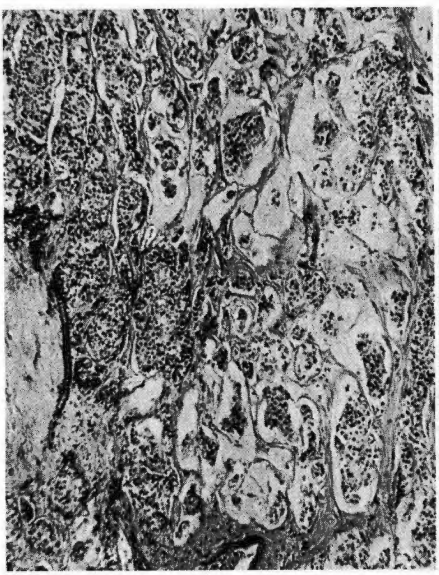


FIG. 422. Papillary carcinoma showing mucoid change. The papillary structure is seen at the upper margin of the growth and the gray gelatinous material at the lower. There is an intervening dark zone of hemorrhage.

FIG. 423

FIG. 424



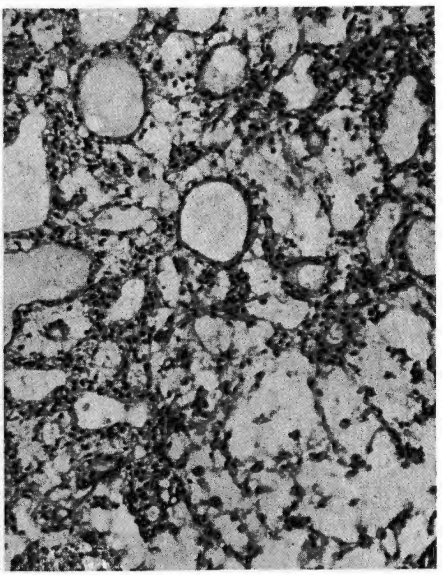


FIG. 423. Photomicrograph of infiltrating carcinoma with mucoid change. The majority of gelatinous carcinomas show cancer cells of this type but with more abundant gelatinous material.

FIG. 424. Photomicrograph of a gelatinous carcinoma resembling a mixed tumor of the parotid gland. The patient remained well 14 years following radical operation.

cases, the papillary carcinoma showed a typical structure and pockets of mucoid material were found in isolated portions of the tumor (Figs. 427, 428). More frequently, when only partial mucoid change

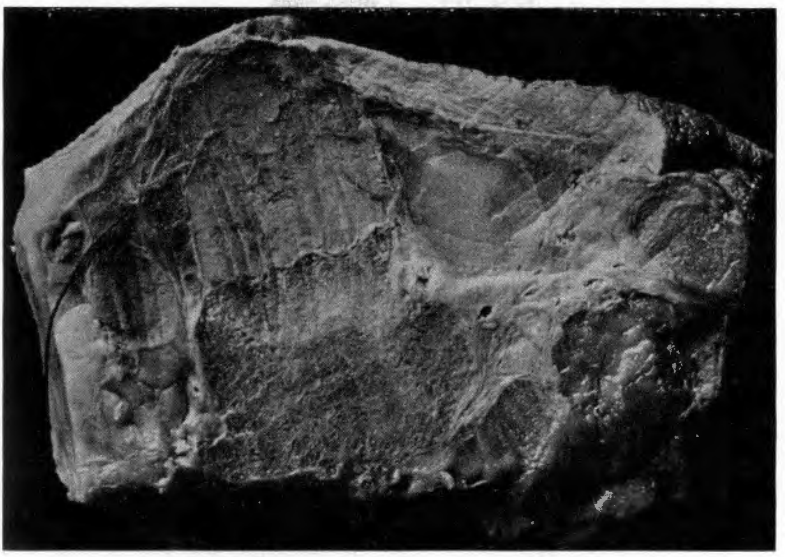


FIG. 425. Gross specimen of slowly growing scirrhous carcinoma with areas of gelatinous degeneration.

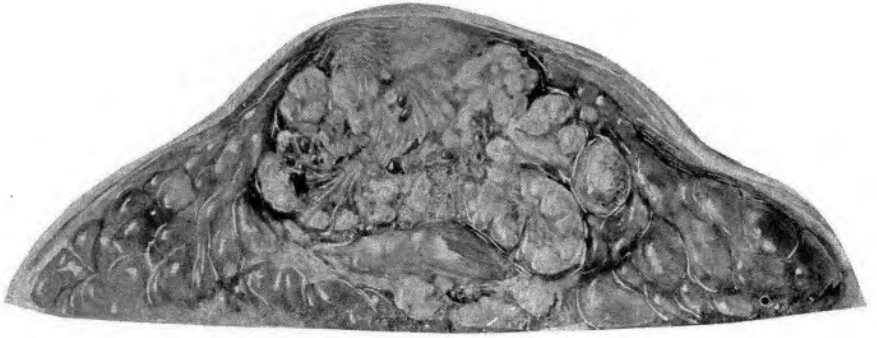


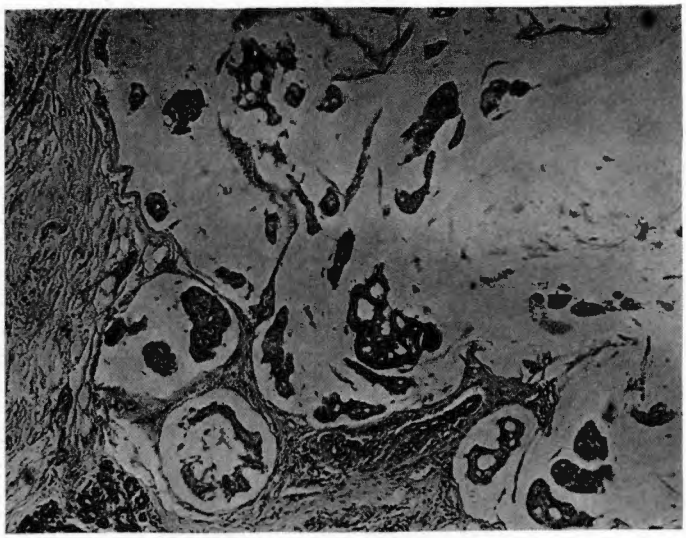
FIG. 426. Gross specimen of typical encapsulated gelatinous cancer.

is found, the tumor is a large, slowly growing infiltrating lobular cancer.

Microscopic Pathology

Gelatinous change has been described in nearly all varieties of mammary cancer. In general, the more slowly growing forms are

FIG. 427



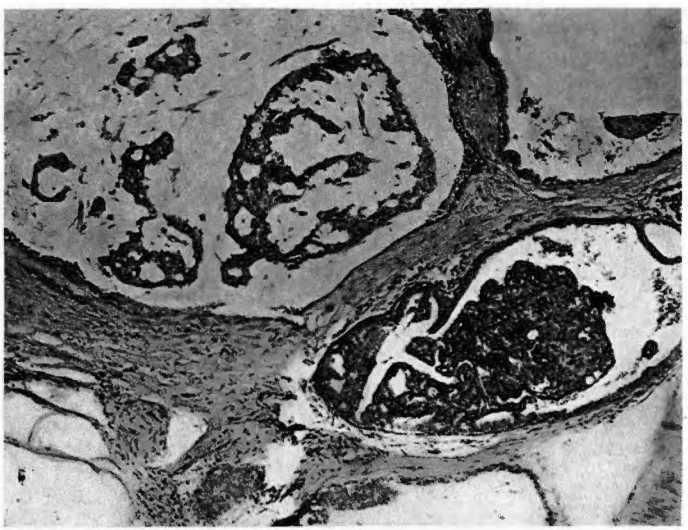
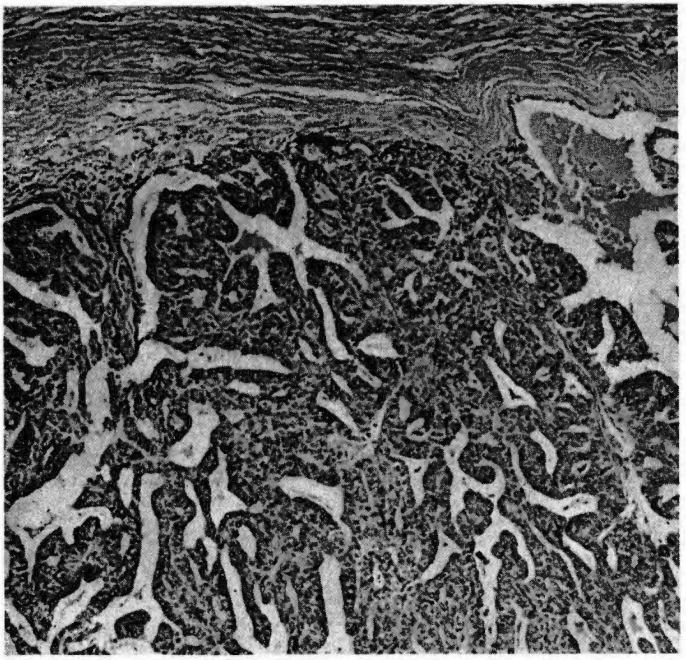


FIG. 428

FIGS. 427, 428. Photomicrographs of a small papillary tumor of the breast undergoing mucoid change. The patient, age 30, had two small tumors about 1 cm. in diameter, one near the right and one near the left nipple. The nodules were excised and the patient has remained well 14 years without further treatment. This case illustrates the origin of mucoid carcinoma from papilloma and the low degree of malignancy of such tumors in their early stage of development.

FIG. 429



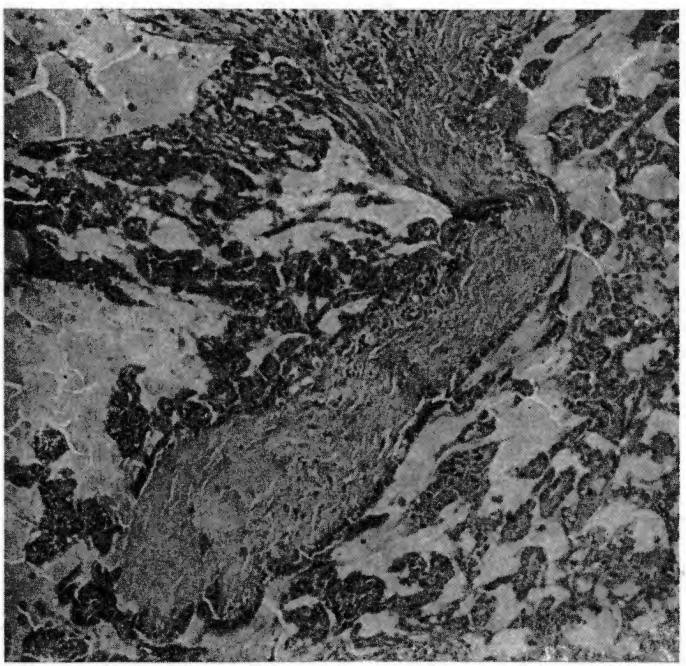


FIG. 430

FIGS. 429 and 430. Photomicrographs of a papillary carcinoma with mucoid change. This patient was operated upon four times, over a period of 30 years. She has remained well six years since the last operation. Figure 429 shows the papillary structure and Figure 430 the gelatinous portion.

affected, but this type of material may be found in isolated portions of more malignant forms. In such cases, the gel is apparently deposited in foci where interruption of blood supply or other factors have interfered with growth. Gelatinous carcinoma, therefore, can be divided microscopically into those cases in which the gelatinous material pervades the entire tumor and cases in which it is deposited

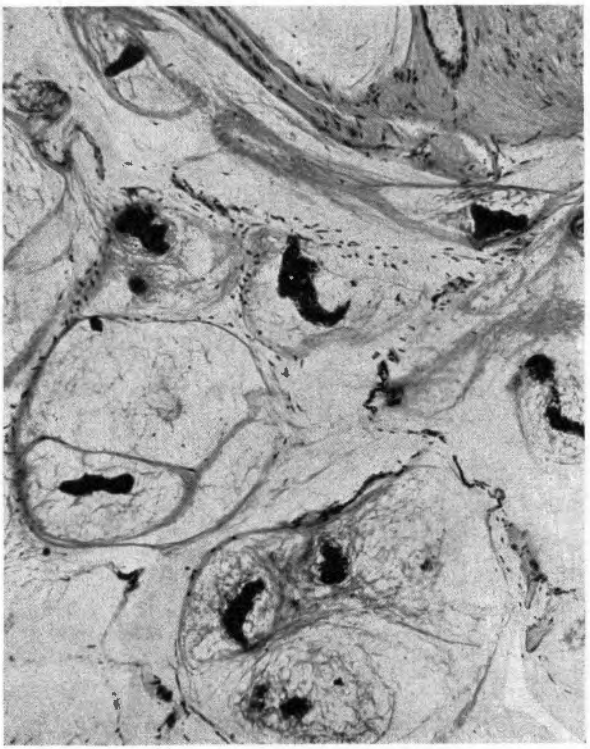


FIG. 431. Photomicrograph of gelatinous carcinoma where the mucoid change is crowding out the epithelial elements which resemble basal cells.

in isolated foci or sparsely through solid tumor growth. The majority of gelatinous carcinomas contain epithelium with definitely malignant features, resembling that found in infiltrating or papillary cancer, whether or not the mucoid substance is diffuse and abundant or scarce (Fig. 423). Among the carcinomas of the breast in which gelatinous material predominates, there is, however, a group of cases containing epithelium of the basal-cell type. (Fig. 431.). Judging from the relatively benign character of the epithelium and from the large amount of mucoid substance, the prognosis in these growths should be unusually good. This assumption is borne out by the cases of this character in this series.

Origin of the Gel. Kaufman, Lange and Ewing are among those who have sought to trace the origin of the gelatinous material to stromal degeneration. The abundance of the gel and the crowding out of epithelial elements in some of these growths favors such an

FIG. 432

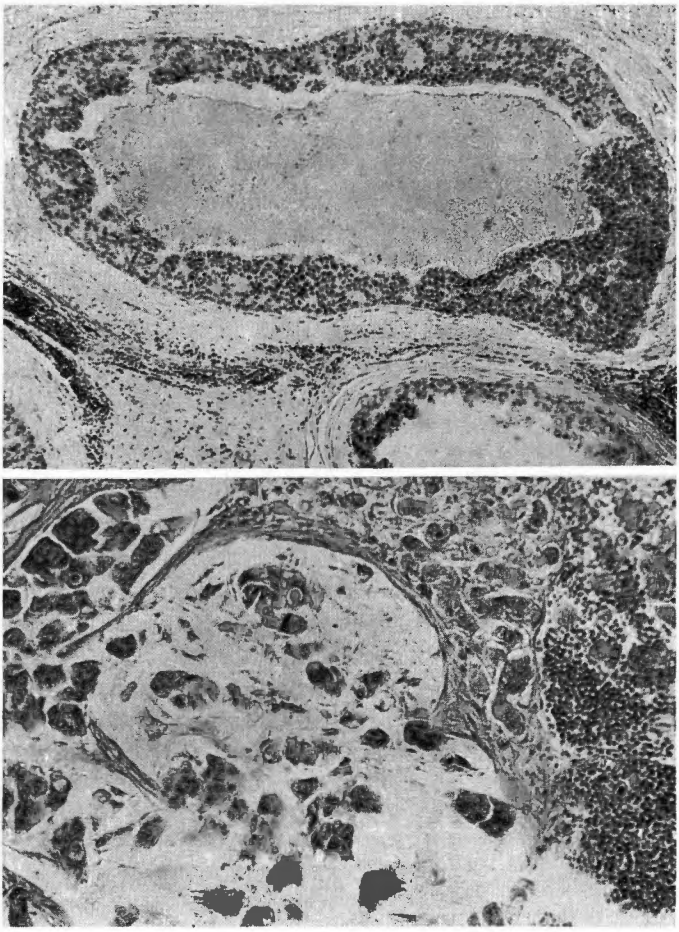


FIG. 433

FIGS. 432-433. Photomicrograph of comedo carcinoma in which gelatinous change occurred in the metastatic nodules of the lymph node but not in the primary growth. Above is illustrated the structure of the primary growth; below cancer cells with mucoid secretion in the metastasis to the lymph node.

interpretation. (Fig. 431.) The gelatinous material, moreover, does not take the specific stains for mucin. Ribbert and Gaabe, as well as most recent contributors, hold that the gel results from the

secretory activity of the malignant epithelium. There is a preponderance of evidence in support of such a view. The occurrence of the gel in metastatic deposits in the lung and lumph nodes, where fat and fibrous material are sparse or absent, indicates an epithelial origin (Figs. 432, 433). Moreover, in papillary tumors and adenocystic basal-cell cancers of the breast undergoing mucoid change, the gel can be seen forming within the acinar structures of the tumor away from stromal elements (Figs. 428, 430).

PROGNOSIS AND TREATMENT

A study of the results of treatment in gelatinous carcinoma emphasizes the frequency of late recurrence and a long survival period, in spite of incomplete or unsuccessful surgery. A period of 5 to 10 years of freedom from symptoms following treatment does not necessarily indicate permanent cure. There were 14 late recurrences. Eight of these proved fatal between the sixth and tenth year. Three patients died of metastases, 14 to 18 years after the complete operation. Three patients had repeated excisions for the disease over a period of 11 years and are well more than 10 years after the last operation.

Of 83 gelatinous cancers, 65 have been adequately traced and 40 of these, or 61 per cent, survived the five-year period; the remaining 25 died of the disease (Fig. 437). If the cases with complete gelatinous change only are considered, there are 76 per cent of five-year cures, and if among these only those which showed basal cells are considered, the five-year survivals are 100 per cent. The treatment of choice in these cases is radical mastectomy. These growths are radioresistant. The five-year survival rate is high in this series even though a group of incomplete operations are included.

TABLE LXXIII

AN ANALYSIS OF THE FIVE-YEAR MORTALITY RATE BASED UPON THE TYPE OF CELL

TYPE OF CANCER	NO. OF CASES	NOT TRACED	DEAD WITHIN 5 YEARS	DEAD OTHER CAUSES	DEAD AFTER 5 YEARS	WELL OVER 5 YEARS	PER CENT 5-YEAR CURES
Basal-cell cancer, with complete mucoid change	25	6	0	3[1]	3	13	100
Papillary or scirrhous cancer, with complete mucoid change	34	8	11	2	4	9	54
Scirrhous cancer, with partial mucoid change	24	4	13	1	3	3	30

[1] One of these patients died postoperatively.

FIG. 434

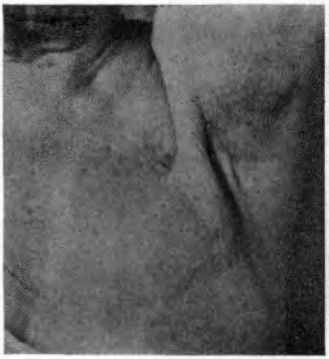


FIG. 435

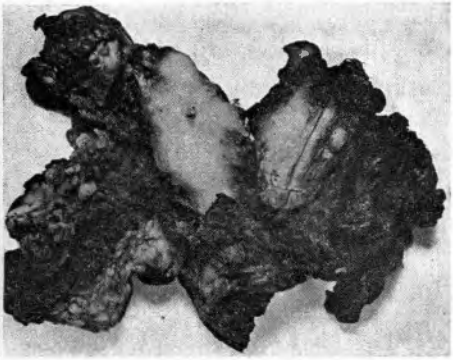
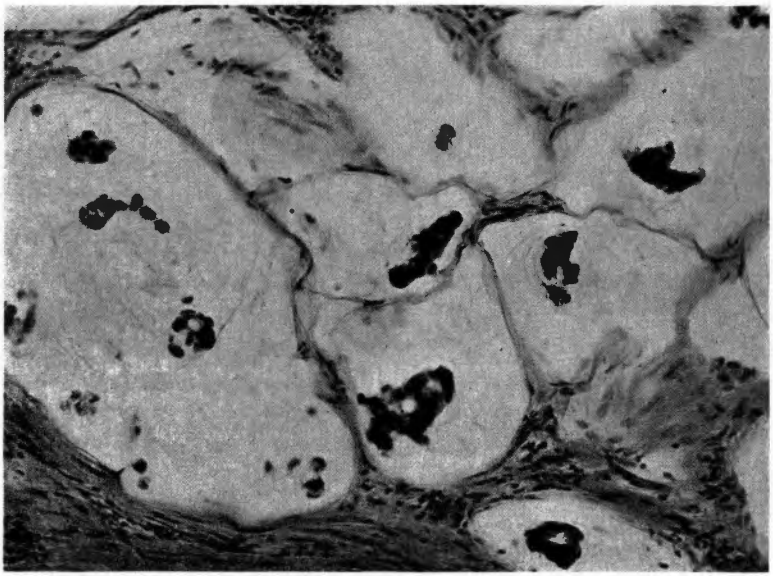


FIG. 436



FIGS. 434, 435, and 436. Photograph of the patient, gross specimen and photomicrograph of a case of gelatinous carcinoma treated by mastectomy, in 1896. Dissection of the axilla and removal of the pectoral muscle with recurrent cancer was performed in 1915. The patient died, in 1931, with mediastinal metastases, 35 years after the first operation.

With radical mastectomy promptly performed, the five-year cure rate should approximate 80 per cent.

In 7 cases, the initial treatment was excision followed by further partial operations (simple mastectomy and excisions) or by irradia-

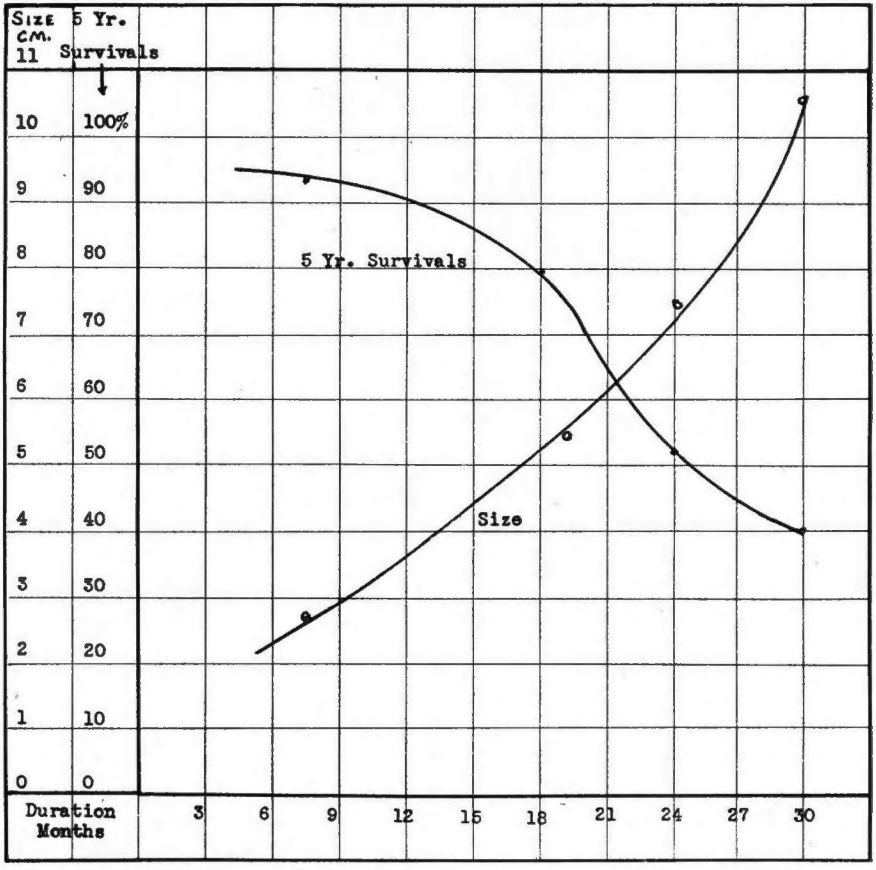


FIG. 437. The prognosis of gelatinous carcinoma in relation to size and duration of symptoms. The size of the tumor and the percentage of the five-year survivals have been plotted against the duration of symptoms.

tion. In five cases, simple mastectomy was the initial treatment, followed by further surgery in only one instance.

No cures were established by simple excision alone with the exception of the case illustrated in Fig. 427. One case, treated in addition by deep roentgenotherapy, is living six years. One case was treated by excision in 1919, by simple mastectomy in 1922, and by excision of diseased axillary nodes in 1930 and was well in 1938. Another patient was treated by excision in 1895 and 1899; received

further dissections by Halsted in 1903 and 1906 and died from accidental death in 1931. One patient treated by simple mastectomy was well 16 years later and another was well after six years. The histories of two cases initially treated by incomplete operation who survived for more than 15 years, but eventually succumbed to the disease, are given below.

Case 1. The patient, a colored female, 40 years old, was treated for enlargement of the thyroid with iodine, 12 years ago.

Four and one-half years ago, she noticed a small lump in the upper outer quadrant of the left breast. This increased gradually to the size of a walnut. She struck it with a piece of wood after which it grew larger and became painful.

The mass was excised elsewhere, in 1916, at which time it was 6 cm. in diameter. There is no pathologic note on the specimen.

One year later, in 1917, she noted a recurrence in the upper outer portion of the scar of the incision. This has gradually increased in size during the past three years and during the past two weeks (1920) it had become painful. Examination showed a normal thyroid gland. The left breast was enlarged and showed a scar 14 cm. long at the site of the previous excision. In the midportion of the scar there were two masses, one, 9 cm. in diameter medial to the scar and another, 21.5 cm. in diameter lateral to the scar. The overlying skin was attached to the masses and was slightly edematous. Both masses gave the sensation of fluid under tension on palpation, and over the larger mass there was an area 4 cm. in diameter, which gave the impression of fluctuation. Two enlarged lymph nodes were palpated in the left axilla.

A radical operation was performed July 28, 1920. Both the masses showed hemorrhagic and gray, glistening translucent material on section. In the larger tumor a small cyst had formed.

Pathologic examination showed gelatinous carcinoma. There were no metastases to nodes; the large axillary nodes showed tuberculosis adenitis.

The patent reported that she was well in 1924; was not heard from again. Her attending physician reports that she died of recurrent carcinoma of the breast February 24, 1938, 18 years after the radical operation and 22 years after the first excision.

Case 2. The patient, at the age of 36, in 1896, had her left breast removed for cancer.

There is no note on the duration of symptoms or clinical findings prior to operation. The pectoralis minor was not removed and part of the axilla was not dissected. A pathologic note by Dr. G. P. Briggs of New York in 1896, states that "the tissue removed last February, consists chiefly of development of myxomatous tissue in the walls of the alveoli, the tumor removed is unquestionably a carcinoma which has undergone early degeneration into a mucoid substance of indefinite character. The degeneration has involved chiefly the carcinomatous cells, beginning in those nearest the alveolar wall and often leaving a central bunch of cells which are nearly normal. Where breast tissue can still be recognized, proliferation of epithelial cells and infiltration of the fibrous stroma with small round cells is often seen. Tumors presenting extensive degeneration into homogeneous gelatinous material have usually been designated as

colloid and I think this breast tumor is most properly called a colloid carcinoma."

This letter of Dr. Briggs, written in 1896, described the tumor removed by Dr. Bull.

Nine years later a mass appeared just below the axilla which gradually increased in size. In July, 1915, Dr. Bloodgood operated upon the recurrent tumor and performed a partial excision of the mass in the apex of the axilla. He found it impossible to remove all the tumor because of its proximity to the larger nerves and vessels. Following this, the patient remained fairly well, but, in 1919, a mass appeared in the region of the clavicle. The patient received deep roentgenotherapy, in 1919, 1920, and in 1922. In 1926, an indurated mass developed, suggesting a recurrence beneath the clavicle. Further irradiation was given. In April, 1931, Dr. Dandy performed an operation for the relief of pain because of symptoms of nerve pressure in the brachial plexus. At this operation tumor tissue microscopically verified, was removed from the nerves. Pain, however. soon recurred with swelling of the arm and lymphedema.

In November, 1931, the arm was amputated. Erysipelas developed in the wound and the patient died, November 21, 1931, 35 years after the first operation with mediastinal metastases. At all the operations, subsequent to 1896, mucoid carcinoma could be demonstrated in the axilla or supraclavicular regions (Figs. 434-436).

In diffuse gelatinous carcinoma with malignant epithelial cells of the infiltrating scirrhous type, 10 cases had metastatic involvement of the lymph nodes. Only one of these patients was cured, and this one remained well 14 years. Three had recurrence or metastases at the end of five years.

Six cases of gelatinous carcinoma with basal cells had metastases to the axillary lymph nodes. One died postoperatively, and another, one year later of accidental death. Three died of the disease, 7, 18 and 35 years, respectively, after radical operation, and one was reported well 16 years later.

Of 24 cases with partial mucoid change 16 had axillary involvement. Two survived the five-year period, and 14 are known to be dead of the disease.

In fatal cases the lungs were the most frequent site for internal metastases. Such involvement was reported in six cases. The liver, brain and skeleton were each involved twice.

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24

Stratified Epithelial Cancers

(Paget's Disease of the Nipple, Transitional-Cell Duct Cancers, and Neo-Mammary Cancer)

The nipple, the ducts and the glandular tissue of the breast may be involved by cancers composed of large transitional cells. The components of the malignant tissue in these tumors resemble epidermoid cells, the lining cells of the large ducts, or sweat-gland epithelium. Since the description of cancer of the nipple by Paget in 1874 and Butlin's microscopic study of the disease in 1876, cells in these growths are often referred to as Paget's cells. The tumor tissue forms a membrane or grows as a solid sheet, rather than in alveolar fashion, hence the term epitheliomatous cancer. When affecting the nipple, the cancer cells have an intradermal location.

These transitional-cell cancers comprise about 10 per cent of all forms of mammary carcinoma and present a variety of clinical forms. That described by Paget produces eczema, ulceration and destruction of the nipple, invades the adjoining ducts and later extends into the glandular tissues. The clinical and pathological features of Paget's disease have been the subject of numerous contributions in recent years. Cases of extramammary Paget's disease also have been reported; the disease had affected the skin, the mucous mem-

brane of the male and female gentalia, or the mucous membrane of the nose or lip. There were 72 cases of Paget's cancer of the breast in the present series.

TABLE LXXIV

DATA ON 72 CASES OF PAGÈT'S CANCER

AGES		DURATION		MARITAL STATUS	
26–39	10	Under 1 year	18	Single	14
40–49	10	1–4 years	25	Married	50
50–59	25	5 years +	18	Married—childred = 0	6
60–69	10	Not stated	11	Married—children = 1	8
70+	6			Married—children = 2 or more	12
No data	11		72		
Total	72	Average duration—35 months			
Aver. age 53.6				Average children per family	2

SYMPTOMS OF ONSET		CLINICAL FINDINGS	
Scaling, ulceration, weeping, etc., of nipple	41	*Nipple only involved	19
Red, granular nipple	17	Nipple involved, surrounding region indurated	13
Pimple or acne of nipple	3	Nipple and breast involved	40
Discharge from ducts at nipple	4		
Retraction of nipple (1 congenital)	4		
Mass in breast	3		
Bilateral	4		

*Of these cases, pathologic study subsequently showed cancer in the ducts in 8, and metastasis in the axillary nodes without cancer in the breast in 3.

Axillary nodes involved	25
Axillary nodes not involved	23

FOLLOW-UPS

Nipple only affected on clinical examination—32 cases (Surrounding zone of induration in 13 cases)		Nipple and breast involved—40 cases	
Incomplete operation	6	Complete operation	40
Recurred under five years	3	Dead under five years	23
Living five years +	3	Living five years +	2
		Not traced	15
Complete operation	26		
Living five years +	19		
Not traced	7		

Total number of cases followed 50
Five-year survivals (48%) 24

While much study has been devoted to the significance of the intradermal cancer cells in Paget's disease, there is a second group of cases less frequently reported in which the cancer affects chiefly the mammary ducts. Thus Muir described an "intra-duct carcinoma"

which may arise in multiple foci and grow in the ducts forming a "sort of injection of them." In the present study there were 35 duct cancers which did not involve the nipple but formed a mass in the ducts beneath. Histologically the tumor tissue is identical with that

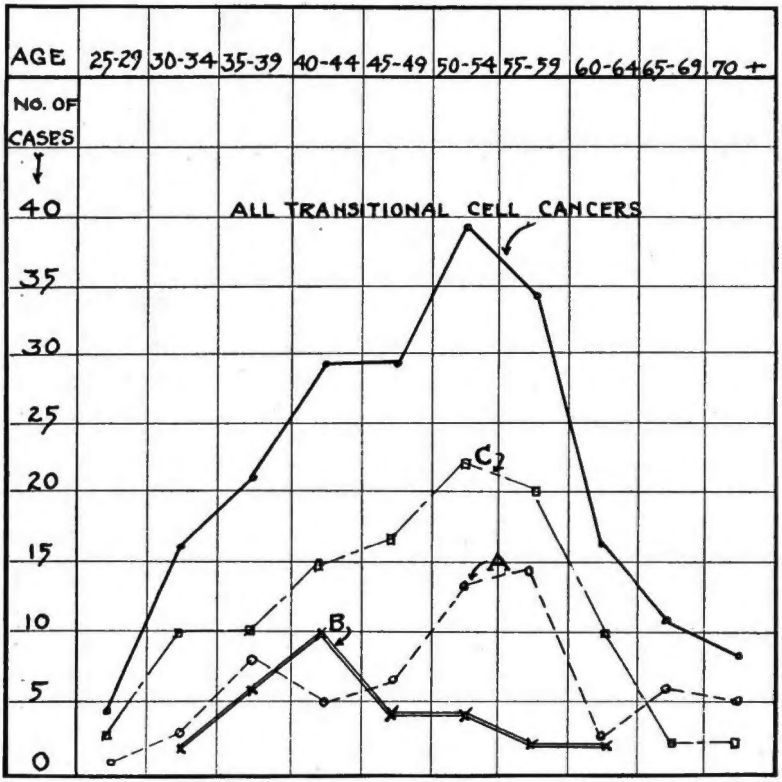


FIG. 438. Chart showing the age distribution of the three individual forms of stratified epithelial cancers. A, Paget's, B, Duct, and C, Neomammary cancer.

formed in Paget's cancer of the nipple, but as a rule, younger patients are affected and the clinical course is more rapid and malignant. The terms epitheliomatous duct cancer and Paget's or pagetoid cancer of the ducts are applied to this group.

In a third group of cancers, the appearance of the malignant cells is similar, but the tumor arises deep in the substance of the breast, and neither the nipple nor the large ducts adjacent to it are primarily affected. Some of these cancers grow to relatively large size and undergo cystic degeneration before the time of examination and have been described as cancer cysts. Others that remain relatively circumscribed have a glandular structure, and resemble sweat-gland

cancers. The term "medullary" which varies in its significance according to the pathologist making the report, is often applied to this group. There were 135 such cases in the present study. A relatively large number of these were among Negroes. The term neomammary cancer is applied by the author to this group because of the histologic resemblance of the cancer to the tissue of the primitive nipple pouch. (Fig. 438.)

These three groups of carcinoma form transitional epithelium rather than mammary glandular epithelium. The relation of this transitional epithelium to the down-growth of epidermoid cells which forms the nipple pouch in the embryo and which provides the openings for the larger ducts, has been discussed in Chap. 18. Paget's cancer of the nipple and the epitheliomatous intraductal cancers are related to the nipple pouch both in their location and in their histology. The group of cancers arising deep within the mammary tissues have similar histologic features. They form a lining membrane of transitional epithelium or alveolar structures resembling the sweat glands, but whether they arise from derivatives of the primitive nipple pouch, or owe their microscopic peculiarities to a process of metaplasia is difficult to determine.

PAGET'S DISEASE OF THE NIPPLE

Paget's cancer is characterized by invasion of the nipple or areola and the mouths of the larger ducts by malignant cells resembling, but not identical with, those seen in transitional-cell cancers of the skin or mucous membranes. The clinical histories are of two types: those cases in which symptoms referable to the nipple precede a tumor in the breast, and the others in which a lump in the breast precedes the lesion of the nipple. The former is the more common. (Figs. 439, 440.)

Regardless of the mode of onset, all cases of Paget's cancer included in the present study ultimately involved the nipple. The cancer begins either in the large ducts beneath the nipple or in the basal-cell layers of the nipple at the point of junction with the ducts. In practically every case the upper parts of the ducts are involved when the nipple is affected and radical mastectomy must be performed to establish a cure. At times an apparently insignificant lesion of the nipple without the presence of a fissure or ulcer, and without a palpable mass in the breast beneath, may be the first indication of cancer which has penetrated deeply into the adjoining ducts.

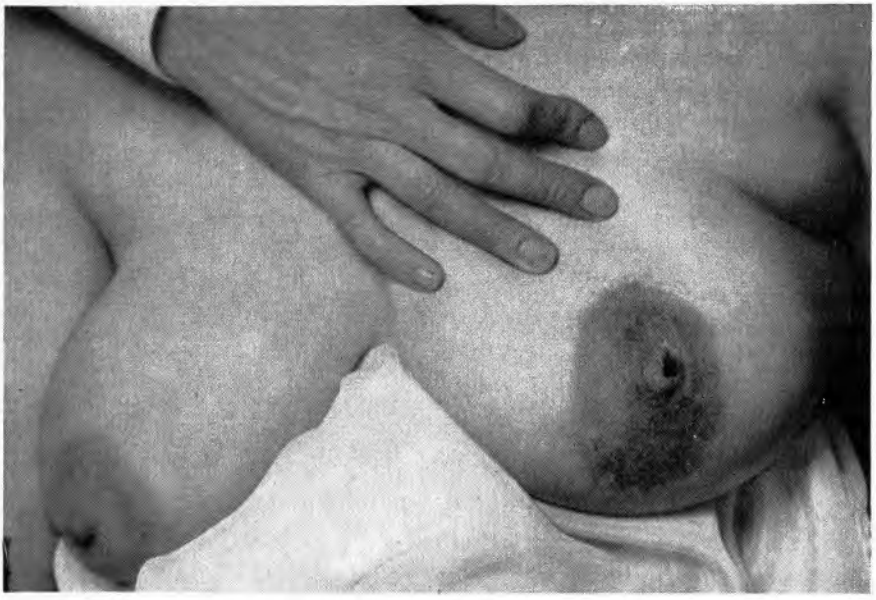


FIG. 439. Photograph of the patient showing involvement of the nipple by Paget's cancer.

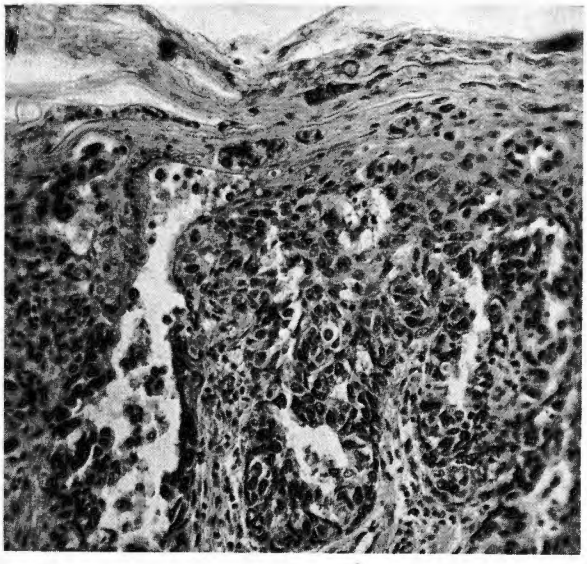


FIG. 440. Photomicrograph of the case shown in Figure 439.

Clinical Features

Age of Onset. There are three clinical features of Paget's disease which suggest that this condition has its origin in epidermal structures or their derivatives. The first is the elderly age of the patients affected. Two thirds of the seventy-two patients were 50 or more

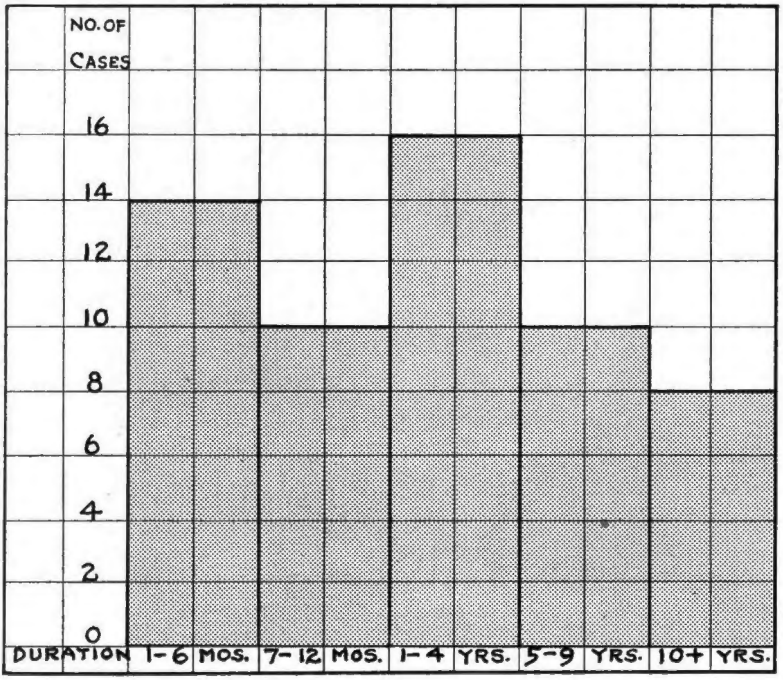


FIG. 441. Chart showing the duration of symptoms in Paget's disease.

years of age and twelve of these were 65 years or more. Weiner collected 58 cases of extramammary Paget's disease involving the skin or mucous membranes of the genitalia. In 45 cases in which the age was tabulated, 28 were 60 or more years of age. (Fig. 438.)

Duration of Symptoms. The second feature relates to the long duration of symptoms. (Fig. 441.) In 63 per cent of the cases studied, the duration of the symptoms was in terms of years rather than months, the average for the group being just less than three years. This long prodromal period is also characteristic of extramammary Paget's cancer. In all the extramammary cases reported in the literature, symptoms had been present for a year or more. Third, the symptoms given by the patient, with three exceptions, were related to the nipple whether or not a mass was found in the breast. Itch-

ing, burning, pain, or soreness was noticed first but in some instances discharge, crust, or scabs of the nipple were observed as the initial symptom. Fissure or ulceration usually developed in the cases which were proved to be malignant, although in some instances the nipple was red, large, and finely granular. Gradual retraction

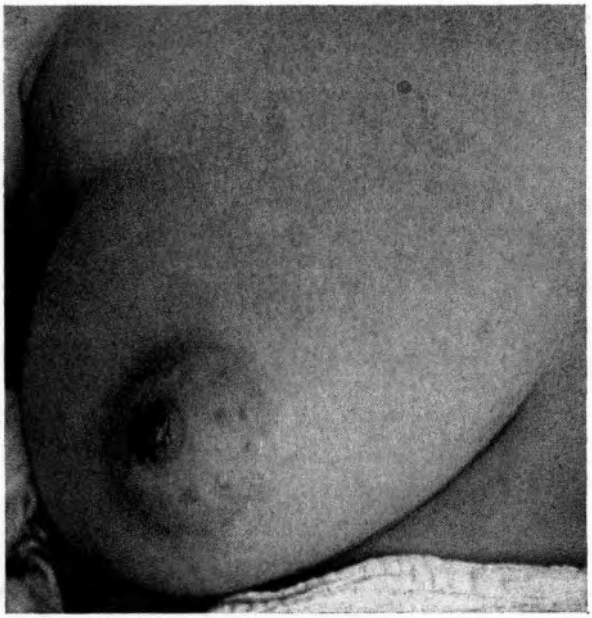


FIG. 442. The appearance of the nipple in one stage of Paget's disease—a red granular nipple.

and disappearance of the nipple may occur. In two cases, the area of ulceration was in the areola, not in the nipple. (Figs. 442-444.)

Diagnosis

The diagnosis of Paget's cancer is suggested either by ulceration or by a red, granular appearance of the nipple. Ulceration is preceded by the formation of scabs or scales which are accompanied by itching. These are usually scratched or rubbed off, but reappear until finally a shallow ulcer which weeps or bleeds is formed. Occasionally a heavy crust covers the nipple or the entire region about the areola, and cracks or fissures appear which bleed or discharge purulent material. This group of cases which is characterized by eczema of the nipple comprises about 57 per cent of the total. (Fig. 445.) In a second group of cases (23 per cent), the nipple becomes enlarged, red, granular, and tender, and bleeds or weeps from

pin-point areas. (Fig. 442.) Congenital retraction of the nipple does not predispose to Paget's disease and in only one case in the present series was a congenitally retracted nipple affected. In three other cases, however, retraction of the nipple was a symptom of onset of the disease, the inverted nipple gradually being replaced by ulceration.

FIG. 443 FIG. 444

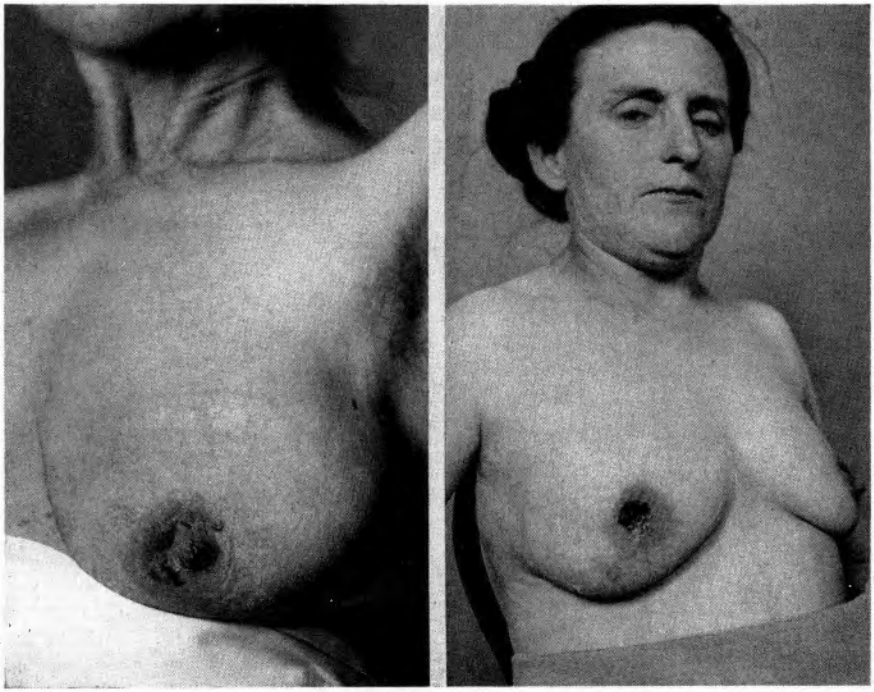


FIG. 443. Paget's disease. A patient with fissure of the nipple and eczema of the areola.
FIG. 444. Paget's disease. A patient in whom the nipple has been replaced by ulceration.

Three patients complained of a mass in the breast which was noted before change in the nipple was observed. In three other cases, one or more pimples in the nipple or areola was the first trouble noted.

Where ulceration or fissure of the nipple has occurred, a discharge of blood, pus or serum is common, but such a discharge from an intact nipple is not usually a symptom of Paget's disease. Four cases, however, proved to be exceptions.

Case 1. One patient, 52 years old, complained of a bloody discharge from the nipple of three months' duration. A nodule 0.5 cm. in diameter which transilluminated darkly was felt just above the nipple. This mass was excised together with the nipple and the frozen section interpreted

as benign. Paget's cancer, however, was found in the paraffin sections and a complete mastectomy was performed. The patient was well two years later.

Case 2. A woman, 55 years old, had had a watery discharge from the nipple for 21 months. This disappeared but the nipple became red and irritated. At biopsy, Paget's cancer was found in the nipple and adjoining ducts. Radical mastectomy was performed and the patient was well 9 years later.

Case 3. A woman, 64 years old, had had a bloody discharge from the nipple without irritation or ulceration of that organ. No operation was advised and the patient was kept under observation. At the end of five years, ulceration and weeping of the nipple occurred. Biopsy and radical mastectomy were done for Paget's cancer in 1925. The patient died of other causes in October, 1934, at the age of 81 years.

Case 4. A woman, 55 years old, had noted a sanguineous discharge from the nipple for 30 months. Following this, the nipple became raw and bled from the surface. At this time she noted a mass about 3 cm. in diameter in the breast just inside of the nipple. Radical mastectomy was performed but death from metastasis occurred one year later.

The common findings on examination in cases of Paget's cancer are an eczematous or granular nipple. In the eczematous nipple, a shallow ulceration or fissure is formed which weeps or oozes. The edges are covered by scales or crusts of dried secretion. A few drops of blood are usually produced by manipulation. The nipple is flattened or retracted. The granular nipple is enlarged, red, and tender. A small amount of blood or serum exudes from minute raised and denuded papillae. The zone immediately surrounding the nipple is indurated, or one or more distended ducts are palpated. In advanced cases of Paget's disease, the nipple is replaced by an ulcer and an indurated mass is felt in the central zone of the breast or toward the periphery. In three cases, multiple masses were palpated in the breast, and in four cases the opposite nipple was involved by crust, scales, or granulations which proved to be benign, when the tissues were pathologically studied. Palpable axillary nodes were present in approximately 50 per cent of the cases studied.

In 19 cases in the present series the nipple alone was involved on clinical examination, and neither an indurated zone nor masses were palpated. When the nipple and adjoining ducts were excised and studied microscopically, cancer was found in one or more of the large ducts in eight cases. In three cases typical Paget's cells were found only in the nipple, the radical mastectomy was performed, and although no cancer was found in the breast, the axillary nodes were involved by metastasis. In the remaining eight cases the cancer was apparently confined to the nipple. Three of these cases were treated by radical mastectomy and remained well for two years, six

years and 17 years respectively. In the other five cases, the initial treatment was excision of the nipple with a core of tissue containing the larger ducts in four and simple mastectomy in one. Only one case treated by excision remained well 10 years. The patient treated by mastectomy was well after four years. In the other three cases the cancer recurred and the complete operation was performed

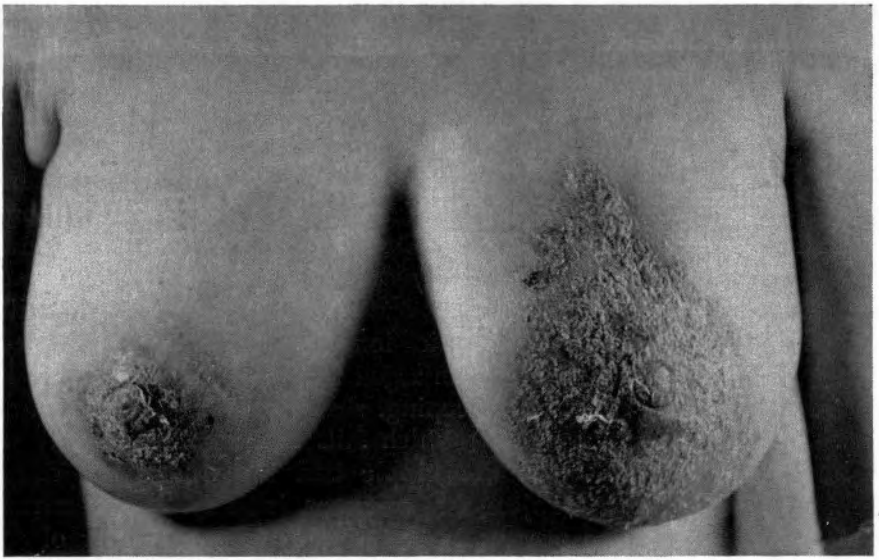


FIG. 445. A patient with extensive bilateral eczematous involvement of the nipples.

subsequently after a course of irradiation. One of these patients is dead and the other two are living two years later. These cases emphasize that Paget's disease almost invariably involves the mammary ducts, and that an incomplete operation is dangerous.

Differential Diagnosis

Differentiation of Paget's Cancer from Benign Keratosis of the Nipple. The clinical diagnosis of Paget's disease is more readily made when, in addition to an eczematous or granular nipple, a hard infiltrating mass is palpated in the breast. Such a mass was present in 40 of the 72 cases. This is a grave prognostic sign and only two of the 40 patients survived the five-year period.

The clinical distinction between benign and malignant lesions of the nipple cannot be made with certainty in cases of keratosis and ulceration in which a mass palpating like cancer is not found in the underlying breast. During the corresponding period in which 72 cases of Paget's cancer were observed, 97 benign lesions of the

nipple were reported. In 52 of these cases of keratosis, a few of which were complicated by ulceration and red granular nipple, the benign nature of the lesion was established because the lesion healed and disappeared after three to four weeks of daily applications of petrolatum applied after the nipple had been cleansed with soap and water. In the other 45 cases healing did not occur when such cleansing and protective measures were instituted. These cases, with 5 exceptions, were treated by excision. Microscopic study failed to reveal evidence of malignancy. In the 5 exceptional cases observed prior to 1920, simple mastectomy or the radical operation was performed because the lesions were considered clinically malignant although pathologic study failed to confirm this.

In the lesions of the nipple without evidence of mammary involvement an attempt should be made to establish diagnosis without sacrificing the nipple for biopsy. Benign epidermal warts or keratomas of the nipple are relatively common and small scales and crusts overlying the surface will usually disappear quickly if daily cleansings followed by the application of petrolatum are carried out. If, however, the nipple is enlarged and granular or if there is a discharge from the ducts, weeping, shallow ulceration or fissure (without relation to lactation) which fails to respond promptly to simple hygienic measures, the nipple and the underlying ducts should be excised and subjected to microscopic study. Paget's cancer of the nipple may be present in the absence of a fissure or of an ulcer.

In some cases of enlarged granular nipple, usually with a sanguineous discharge, excision with microscopic study will reveal a benign intracystic papilloma growing within the ampullae of the nipple. Such cases have been reported by Cohn, Cheatle and Cutler, and others. (See Chap. 14.) In one case in which the areola was involved by ulceration, an ordinary squamous-cell cancer without involvement of the breast was found. The possibility of a chancre of the nipple must be borne in mind and a Wassermann reaction should not be omitted from the management of all cases of suspected Paget's disease of the nipple.

Pathology

A pathologic study of the breast in cases of Paget's cancer shows dilatation of the larger ducts in the nipple zone in addition to the keratotic or ulcerated nipple. Occasionally these ducts are filled with blood or inspissated secretion. In other cases they are distended with cancer cells. (Figs. 446, 447.) In one case a small encapsulated mass of cancer cells measuring 5 mm. was found just beneath the nipple.

A definite infiltrating mass in the mammary tissue outside the nipple zone occurred in 55 per cent of the cases. With few exceptions these cases also showed metastasis to the axillary lymph nodes. In 3 cases the nipple and axillary nodes were involved and no cancer could be demonstrated in the mammary tissue.

FIG. 446 FIG. 447

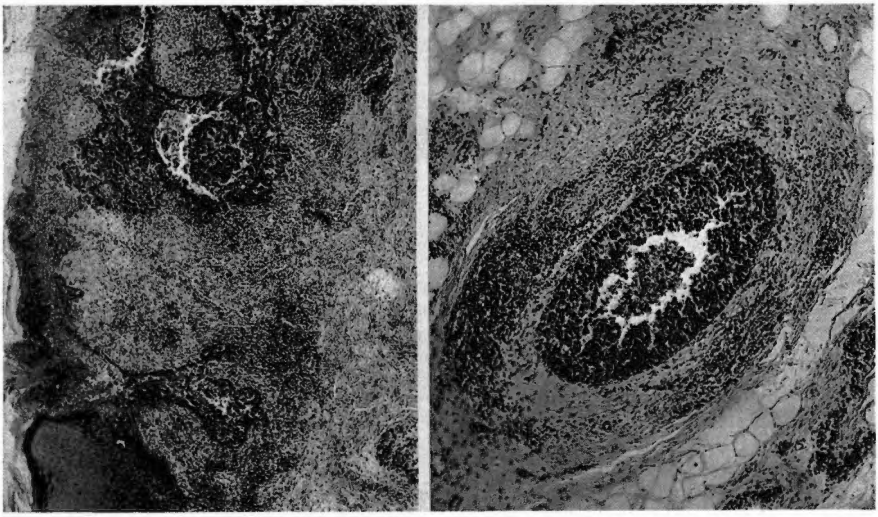


FIG. 446. Paget's cancer with involvement of the ducts. Photomicrograph showing the involvement of the nipple. The cancer cells are forming tubules indicating that the structures involved are related to the nipple pouch from which the opening of the large ducts are derived in the embryo.

FIG. 447. Photomicrograph showing the involvement of the ducts by cancer cells.

All cases classified as Paget's cancer in the present series showed large cells with deep staining or vesicular nuclei and pale staining cytoplasm in the epidermis of the nipple. Mitotic figures were frequent. (Fig. 448.) In 3 cases these Paget cells were found only in the epidermis of the nipple when the breast and axillary contents were examined after radical mastectomy. In the remaining cases pathologically examined the larger ducts were involved and the cells in the nipple were infiltrated beyond the basement membrane. (In three of these cases the ducts were not involved but there were axillary metastases.) The ducts were lined by many layers of malignant epithelium with necrotic debris or secretion in the enclosed lumen. (Fig. 449.) Where the ducts only were involved in addition to the nipple, the growth in the ducts showed the histologic picture of duct cancer, described in the next section. When the breast tissue

was invaded, the pathologic appearance resembled superficially that of scirrhous carcinoma. On further microscopic study, however, the cells are larger, more irregular in shape, contain numerous mitotic figures and tumor giant cells, approaching epidermoid carcinoma in their histology, although no keratinization is found.

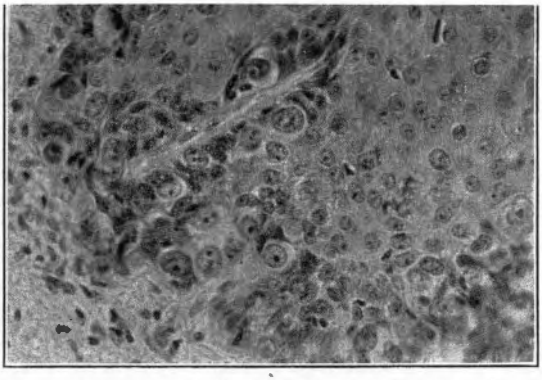


FIG. 448. Photomicrograph showing the histology of Paget's cells. Note the mitotic figures in the lower portion of the picture.

The histogenesis of Paget's disease has been the subject of much discussion and controversy in the past 50 years. From the standpoint of the embryology of the breast, and from the histologic study of numerous cases, four facts seem well established:

FIG. 449. Gross specimen from a breast amputated for Paget's disease. The photograph shows distention and invasion of the large ducts by cancer.

1. The cells in Paget's cancer are derivatives of the early downgrowth of epidermis which forms the nipple bud in the embryo, and are not derived from the functioning mammary epithelium which comes from the primary sprouts of the mammary bud (Chap. 1).

2. The malignant tissue in Paget's cancer may arise within the epi-

dermis of the nipple or in the ducts beneath but usually arises at the junction of the two.

3. Regardless of their point of origin, the cancer cells have the potentiality to differentiate into duct epithelium; not only do they invade and line pre-existing ducts but they also form new ones. (Fig. 446.)

4. Although all forms of mammary cancer occasionally may invade the large ducts and ultimately involve the nipple, the intradermal cells in Paget's cancer are not of metastatic origin but arise in situ. This is indicated by the failure of other forms of cancer, when metastasizing to the nipple, to give rise to typical Paget's cells.

Prognosis and Treatment

In the present series 32 cases of Paget's cancer showed no mass within the breast proper clinically. Six of these cases had incomplete operations (3 simple excision and 3 simple mastectomy). Three of these patients remained well beyond the five-year period.

In the 26 cases treated by radical mastectomy (in this group where the cancer was confined to the nipple and adjoining ducts) none so far traced has failed to survive the five-year period. Seven have not been traced and 19 were living after five years. Three of the surviving patients ultimately died of the disease, two after six years and one after 10 years.

There were 40 cases of Paget's cancer in which the nipple showed changes and a mass was present in the underlying breast. All of these cases were treated by radical mastectomy. Twenty-three died of the disease within five years, the majority within a period of 1 to 2 years. Fifteen have not been traced. Two cases survived the five-year period. One of these died after 6 years, the other is well 10 years later.

Irradiation and conservative operations are insufficient to eradicate the disease. Cohn has reported instances where irradiation was followed by healing of the lesion of the nipple, but continued growth and spread of the disease occurred in the breast beneath.

Keratosis, fissures, ulcerations, and red granular changes in the nipple should be treated by excision of the nipple with a margin of skin and a core of underlying ducts and fatty tissue, if the lesion fails to heal within three to four weeks after cleansing and protective measures. The excised tissue should be subjected to microscopic study, and if cancer is found, radical mastectomy is indicated. In those cases where cancer is not found in the underlying breast tissue, cures will be effected by this treatment. Where cancer tissue is demonstrated in the mammary gland, the chances of the patient surviving the five-

year period are less than 10 per cent (8 per cent in this series). Such patients should have the benefit of postoperative irradiation.

In all, 50 cases of Paget's cancer have been traced and of this number 24, or 48 per cent, survived the five-year period.

TRANSITIONAL-CELL DUCT CANCER—PAGET'S DUCT CANCER

A group of 35 duct cancers were studied, in which the histologic features were identical with those of Paget's cancer except for the

FIG. 450

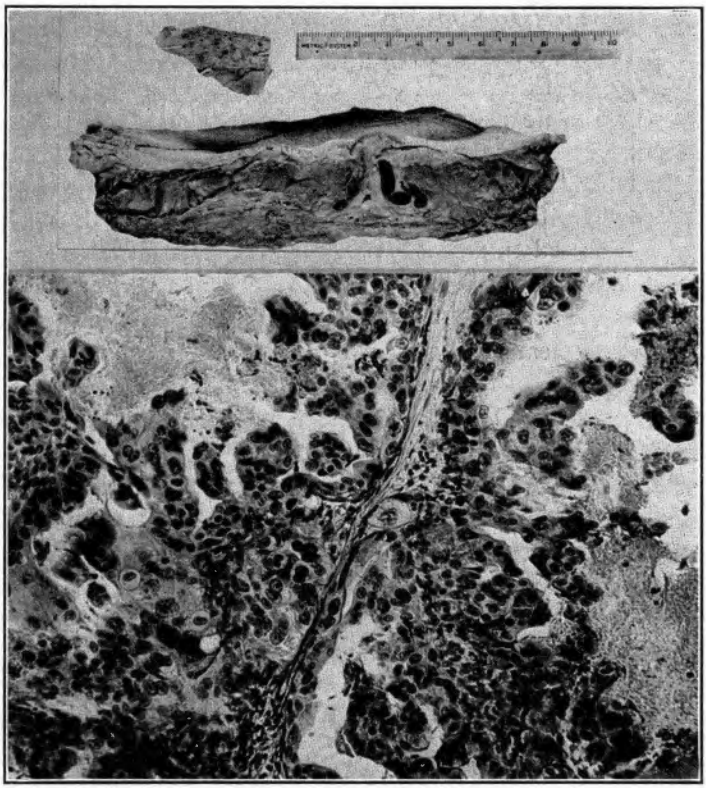


FIG. 451

FIGS. 450, 451. Gross specimen and photomicrograph of cancer arising in the large ducts beneath the nipple.

absence of involvement of the nipple. In these cases the tumor tissue lines the larger ducts, invades the surrounding breast tissue, and extension to the skin and axillary nodes occurs relatively early in the clinical course. (Figs. 450-452.) The duration of symptoms is brief; the majority of patients had noted tumor, pain or a drawing

sensation in the region of the nipple for six months or less. The peak of age incidence was between 39 and 49 years, 72 per cent of the patients were less than 50 years old. Discharge from the nipple (usually bloody) was present in seven cases, and in an equal number

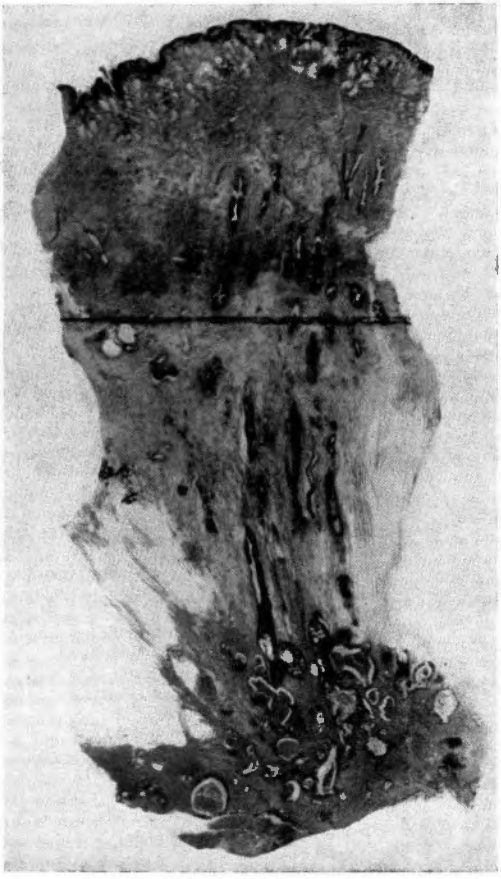


FIG. 452. Cross section of the nipple showing the ducts invaded by duct cancer.

pain, itching, twisting, or pulling sensations were referred to the nipple.

Many of the features of these cancers suggest a relation to Paget's disease. The cancer cells have the same epidermoid features and the major part of the growth is just beneath the nipple although invasion and ulceration of this organ did not occur. The tumors apparently arise in the central ducts some distance from the nipple, rather than in the mouths of larger ducts. Two thirds of the cases showed such a location; the remainder were either in the outer upper quadrant or

in the lower hemisphere of the breast. The fact that none of the tumors was over 5 cm. in diameter at the time of operation suggests that involvement of the nipple, with the clinical picture of Paget's

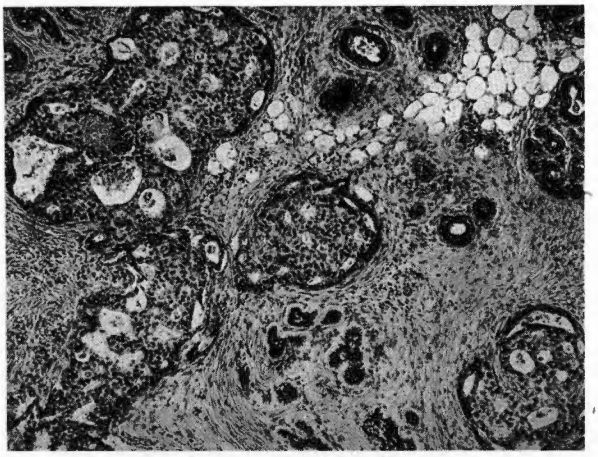


FIG. 453. The histology of duct cancer. (See also Figure 454.) Low-power photomicrograph showing the cancer penetrating the branches of a duct.

disease might have occurred at a more advanced stage. As a rule, however, the patients affected are younger than those with Paget's disease, and the progress of the disease is more rapid.

These growths also have certain features in common with comedo

TABLE LXXV

DATA ON 35 CASES OF TRANSITIONAL-CELL DUCT CANCERS

AGES		DURATION OF SYMPTOMS		LOCATION		SIZE	
30–34	4	1– 2 mos.	13	Central zone	= 28	1.5 cm.	1
35–39	6	3– 5 mos.	4	Upper outer quadrant	= 8	2 cm.	3
40–44	10	6– 8 mos.	2	Lower hemisphere	= 6	3 cm.	5
45–49	4	9–11 mos.	2	Upper inner quadrant	= 1	4 cm.	9
50–54	4	12–15 mos.	4			5 cm.	2
55–59	3	2– 4 yrs.	5			6 cm.	5
60–70	3						

Average age—44.8

Average duration of symptoms—9.8 mos.

Average size —3.5 cm.

LEADING SYMPTOMS		RESULTS OF TREATMENT	
Tumor	16	Dead of tumor	17
Nipple discharge	7	Well 5 years +	8
Enlargement of breast	5	Not traced	10
Itching, pulling, etc., referred to nipple	7	Five-year survivals—32%	

cancer. Both involve the large ducts, produce symptoms referable to the nipple and in the gross specimen there are dilated ducts from which plugs of cancer cells may be expressed. These duct cancers, however, grow more rapidly and become hard infiltrating growths that involve the skin and axillary nodes after a few months of symptoms. The malignant features are more pronounced and more readily recognized on clinical examination. The extension of the disease through the surrounding milk channels gives the impression, on palpation, of an ill-defined, hard, infiltrating mass, which involves

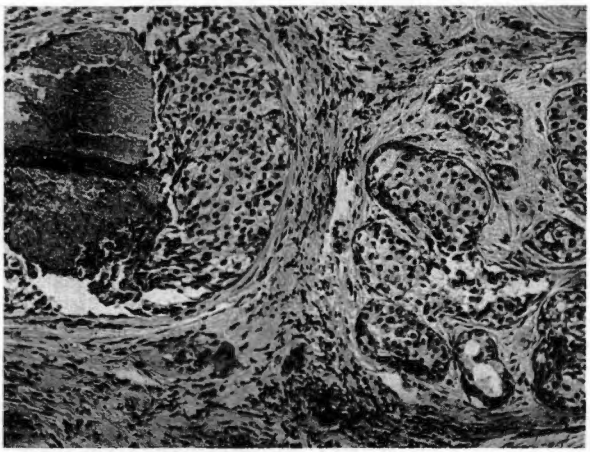


FIG. 454. High-power photomicrograph showing the abundant cytoplasm and variable nuclei in the tumor cells.

the subcutaneous region. The overlying skin is thickened, indurated, or adherent. In some instances the extension of the disease in the ducts produces small secondary nodules. These are usually superficial, hard, and readily palpated.

Under the microscope these cancers are characterized by large, pleomorphic cells with extremely malignant features. The cancer cells form a heavy ring of epithelium within the duct wall, enclosing a core of necrotic and amorphous material. Islands of malignant cells also invade the stroma. (Figs. 453-456.)

The results of follow-up studies confirm these malignant features. Twenty-five of the 35 patients were followed until death or for more than five years. Seventeen died of the disease, usually within a period of one to three years, and but eight survived the five-year period. This gives a five-year survival rate of 32 per cent.

Radical mastectomy is recommended for these cancers. There is insufficient information to warrant a statement regarding their radiosensitivity.

FIG. 455

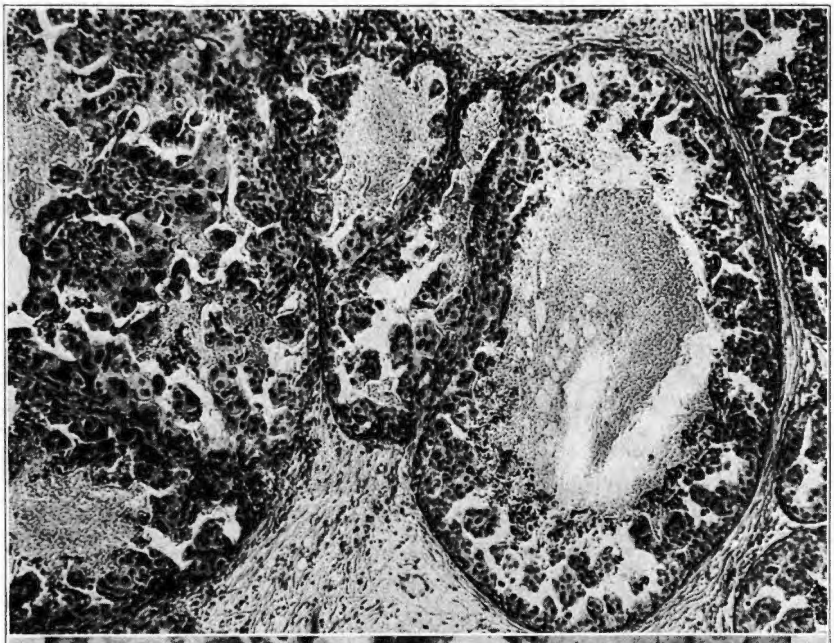


FIG. 456

FIGS. 455, 456. Medium (Fig. 455) and high-power (Fig. 456) photomicrographs of a duct carcinoma, showing large malignant cells similar to those seen in Paget's disease of the nipple.

NEOMAMMARY CANCER

(Intramammary Stratified Epithelial Cancers: Circumscribed Epidermoid Cancer: So-called Medullary Cancer, Sweat-Gland Cancer and Cancer Cysts)

Stratified epithelial cancers may occur deep in the breast and resemble histologically either nonkeratinizing epidermoid carcinoma

FIG. 457

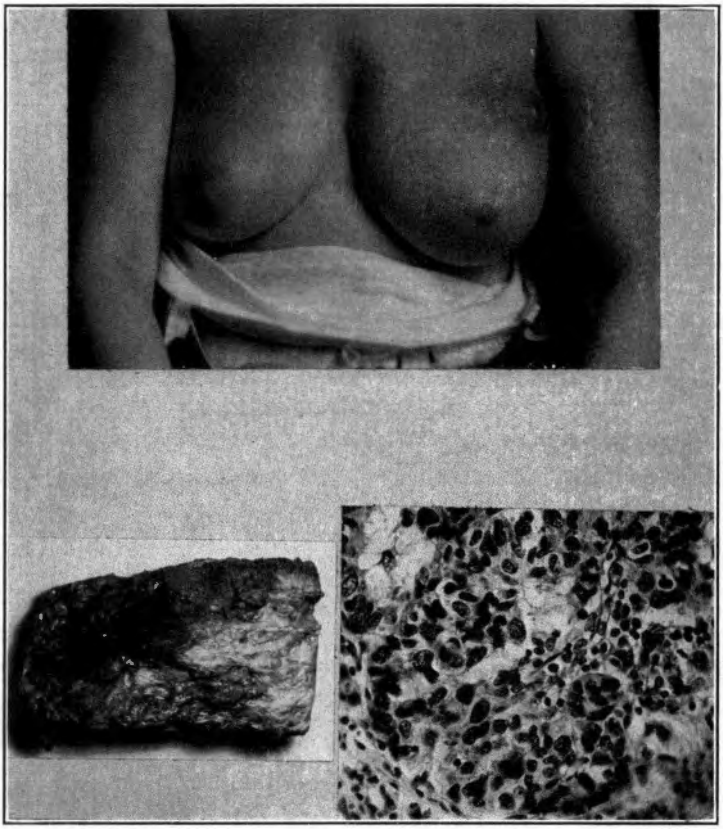


FIG. 458 FIG. 459

FIGS. 457, 458, 459. Photograph of the patient, gross specimen, and photomicrograph from a case of neo-mammary or so-called medullary cancer.

of the skin or cancer arising in sweat glands. (Figs. 457-459.) While in most instances either epidermoid or glandular features predominate, in some instances a combination of both is found. When it is realized that the breast is a modified sweat gland derived from the epidermis, it is easy to comprehend why these tumors originating in archaic epithelium resemble the epidermis in their undifferentiated

portions and the sweat glands in the more highly differentiated parts. Despite their highly malignant appearance under the microscope, these cancers in which glandular features are prominent have a relatively good prognosis even when of large size and when they occur in women younger than 40 years. In this particular group of mammary cancers there is an increased incidence in the colored race, and a family history of mammary cancer is more frequently given.

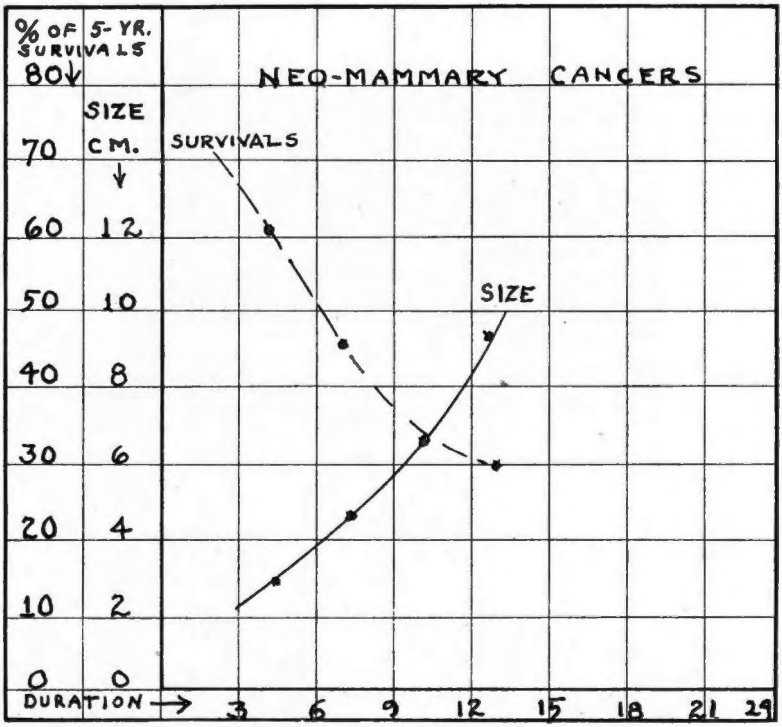


FIG. 460. The growth curve of neo-mammary cancer. The size of the tumor and the percentage of five-year survivals have been plotted against the duration of symptoms.

In the hospital records, the solid growths were usually classed as medullary cancers because of the succulent or juicy surface of the cut tumor and the large malignant character of the tumor cells on microscopic examination. The larger growths, because of their cystic degeneration, were classed as cancer cysts. The term neomammary cancer applies to the entire group.

Clinical Features

Age of Onset. The ages of the 135 patients in this group are slightly more advanced than those for mammary cancer in general.

The youngest patient was 28 years old, the oldest 72 years. The peak of distribution is in the fifties. (Fig. 438.) The large cystic growths, however, are seen more often in patients younger than 50 years. Eighty-two per cent of the patients were married, with an average of three children per family. The number of colored women affected was twice as great as in the other forms of mammary cancers.

Size. Because of their deep location and painless growth, these cancers are rarely noted until they have reached a size of 3 cm. or

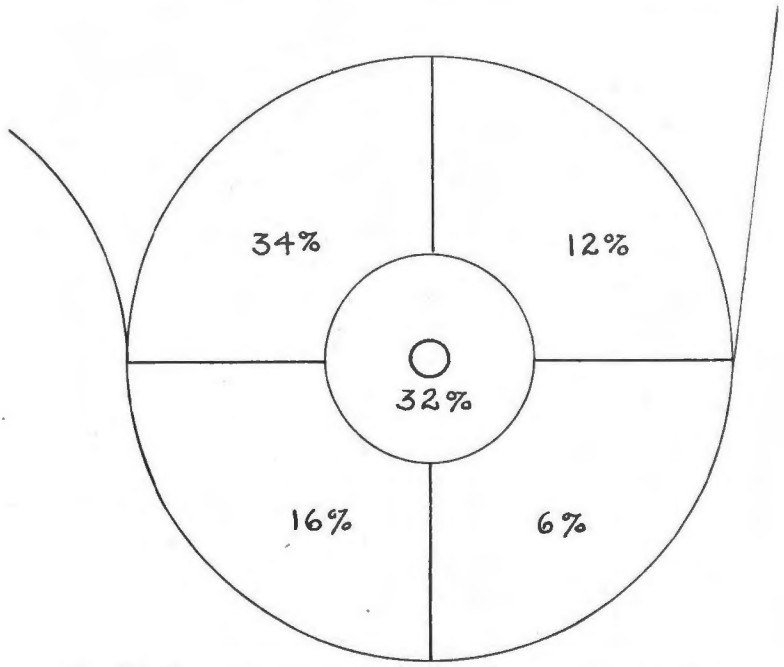


FIG. 461. Chart showing the distribution of neo-mammary cancer.

more and only one-third of the tumors were less than 5 cm. in diameter at the time of examination. The average duration of symptoms for the smaller solid growths was six and one-half months compared to ten months for the larger cystic tumors. (Fig. 460.)

The asymptomatic nature of these tumors is emphasized by the fact that trauma was responsible for their discovery in 30 per cent of the cases, and in an additional 15 per cent the enlargement of the axillary nodes rather than the primary growth was first noted. A few of the patients complained of enlargement of the breast rather than tumor. Discharge from the nipple is rare (3 cases) unless cystic degeneration has occurred.

The mass is usually regular in outline, circumscribed, and freely

movable. The tumor bulges from, rather than adheres to, the deeper structures. (Fig. 457.) It may give the impression of a cyst or of a benign fibro-adenoma, but more often the tumor has a solid rubbery feeling or palpates like a water-soaked sponge. It casts a dark shadow on transillumination. When the tumor occurs in the axillary tail of the breast the metastatic nodes may be as large as the primary growth. As in other cancers the outer upper quadrant is the most frequent location, but an unusual number (39 per cent) are in the lower hemisphere, or beneath the nipple, deep in the breast. (Fig. 461.) This location and a tendency to occur in brunettes with swarthy complexions have been stressed by Lee, Pack, and Scharnagel who have classed some of these growths as sweat-gland cancers. Dimpling or edema of the overlying skin is found in the larger tumors and a serous or bloody discharge from the nipple occurred in six of 36 cancers which had undergone cystic degeneration. Enlarged lymph nodes were usually felt in the low or mid-axillary regions at the time of the examination.

Diagnosis

The following findings suggest the diagnosis of neomammary cancer:

1. A boggy, cystic tumor more than 5 cm. in diameter occurring in a colored patient.
2. A bulging, solid tumor deep in the breast and beneath the nipple that is smooth in outline and casts a shadow on transillumination.
3. A similar solid, circumscribed tumor occurring in the axillary tail of the breast with a solitary enlarged axillary node of 2 cm. or more in diameter.
4. A tumor 5 cm. or more in diameter, which in spite of its large size and slow growth has a relatively brief duration of symptoms (4 to 8 months).

Cancer Cysts (cystic neomammary cancer)

Because of their peculiar structure, the larger neomammary carcinomas forming thick-walled cysts have been studied as a group. These were formerly classified as cancer cysts. (Fig. 462.) This is an obsolete and confusing classification since it includes large infected, infiltrating lobular cancers with a necrotic core, papillary cancers with bloody, fluid contents within the central cavity, squamous-cell cancers arising in epidermoid cysts, as well as the neomammary cancers under discussion.

There were 36 cystic neomammary cancers in the present group. These were large, circumscribed tumors as a rule occurring in women in middle life, between the ages of 35 and 55 years. Thirteen of the 36 patients were colored (the normal ratio would be 6 of 36). The tumors were asymptomatic until they had reached fair size. Although the average duration of symptoms was 10 months, the average size of the growth was 7.3 cm. at the time of examination.

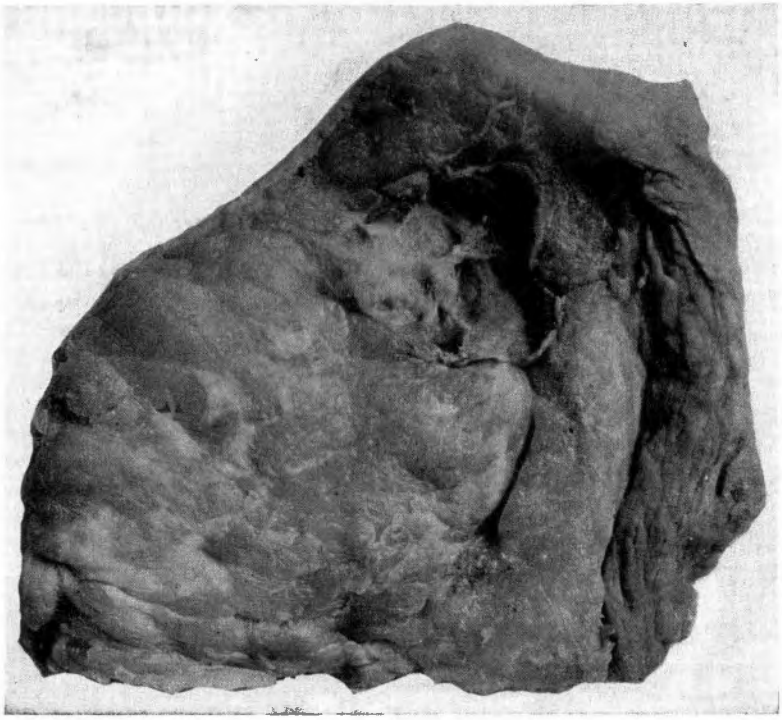


FIG. 462. Gross specimen of a cancer cyst. The irregular wall of the cavity is shown.

These are movable, encapsulated growths, that may show atrophy of the overlying fat or dimpling in the neighboring skin. They have an elastic or cystic feeling. The mass may be bulging, spherical and fluctuant giving the impression of a benign cyst, a galactocele, or an abscess. When explored, there is often a capsule and the outside of the tumor has a grayish white dome (rarely bluish). On incising the thick wall, greenish, whitish or a bloody fluid exudes, and the inner wall is irregular, ragged or nodular.

These large growths are rarely cured in spite of the encapsulated or circumscribed character of the mass.

Pathologic Features

The study of the gross specimens enables one to trace the evolution of the cystic from the solid stratified epithelial cancers. The smaller tumors have a grayish white or semitranslucent appearance

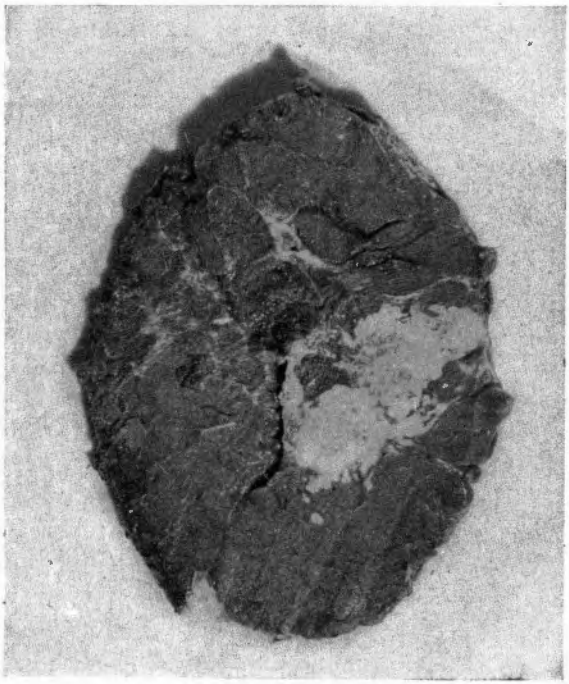


FIG. 463. Gross specimen of a circumscribed solid neomammary cancer.

and are usually well circumscribed. (Figs. 463, 464.) With increased size, foci of necrosis and degeneration give the cut surface a grumous or cheesy appearance which sometimes resembles a gumma. (Figs. 465-467.) Later the degenerating areas in the center of the tumor coalesce and liquefy leaving a thick, ragged or nodular wall of cancer tissue surrounding a cavity which contains purulent, greenish or bloody fluid.

The microscopic appearance of these tumors resembles Grade-III epidermoid carcinoma of the skin or mucous membranes. The large tumor cells grow in sheets or coils embedded in a lymphoid stroma rather than fibrous tissue and have numerous areas of necrosis. The tumor cells form a membrane with the free margin along a necrotic area. The cells are large and the nuclei vary greatly in size and in staining characteristics. Mitotic figures are frequent. (Figs. 465-467.)

In the majority of the growths there is little or no tendency to gland formation and in some of these cases small amounts of keratin or a few epithelial pearls may be formed. (Fig. 468.)

One third of the cancers studied contained large, pale and granular cells with an alveolar or acinar arrangement, simulating a sweat-gland cancer. This histologic structure was not found in the cancer cysts but in the solid circumscribed growths. (Fig. 469.)

One of the striking features of these tumors with an alveolar arrangement of cells is the peculiar myxomatous reaction in the stroma

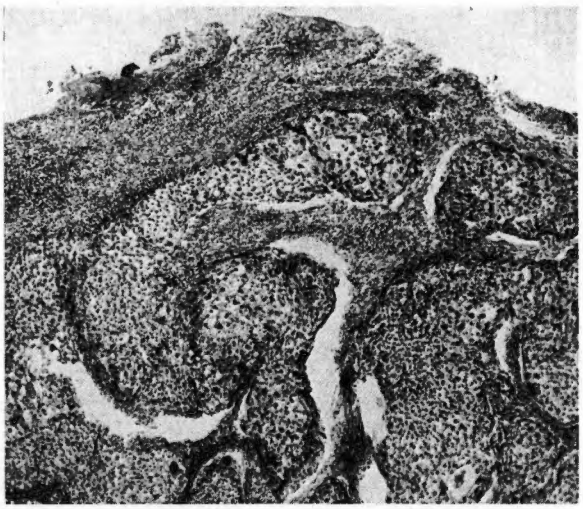


FIG. 464. Photomicrograph of the tumor shown in Figure 463.

of the adjacent mammary lobules. (Fig. 500.) This reaction, sometimes seen in the sweat-gland tumors of the abdominal wall near the umbilicus, together with the pale granular cells of the tumor and their alveolar arrangement are grounds to classify these tumors as sweat gland in origin. The deep location of the tumors, however, suggests that they originate from primitive mammary structures related to the nipple pouch rather than from preformed sweat glands in the subcutaneous tissues (Figs. 470, 471).

Prognosis and Treatment

Because of the large size of these tumors at operation, the skin and axillary involvement frequently found, and the highly malignant appearance of the tissue under the microscope, it might be expected that the majority of these cases are relatively hopeless. This is by no means true, and a number of patients with cancers of large

FIG. 465

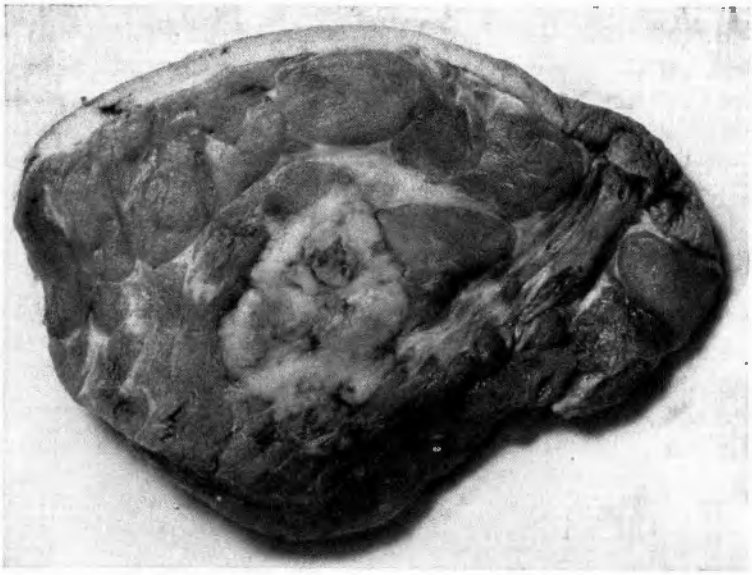


FIG. 466

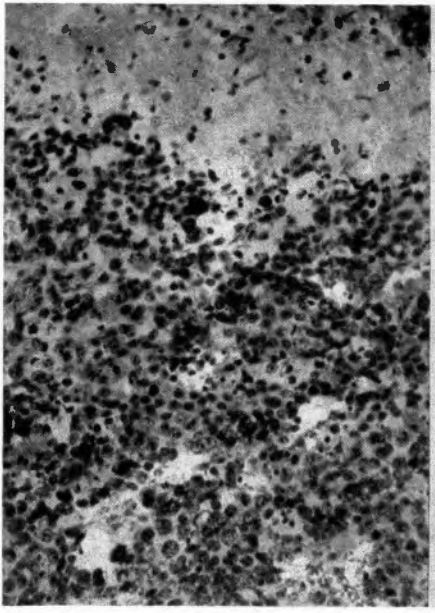
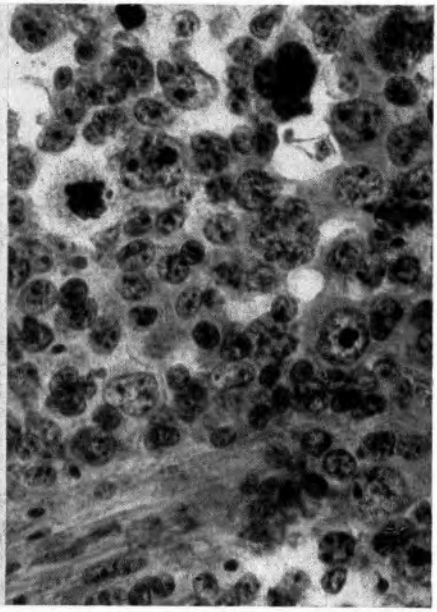


FIG. 467



FIGS. 465, 466, 467. Gross specimen, low- and high-power photomicrograph of a neomammary cancer. The tumor is undergoing necrosis at its center. The histology of the tumor is characterized by pleomorphic cells with frequent mitotic figures.

size, with axillary involvement, survived the five-year period. (Fig. 460.)

A colored woman who had nine children had a tumor which had been present six years. The mass was 6 cm. in diameter and the overlying skin

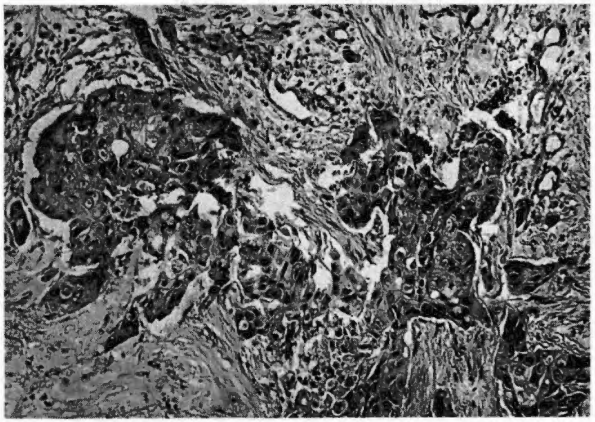


FIG. 468. Photomicrograph of a neo-mammary cancer with squamous cell features.

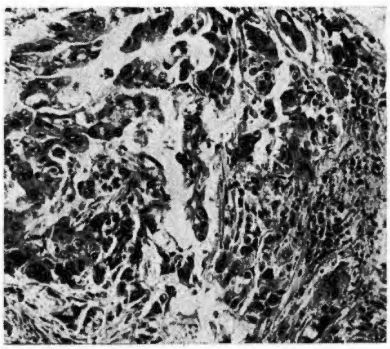


FIG. 469. Photomicrograph of a neo-mammary cancer with an alveolar arrangement resembling sweat glands.

was ulcerated. Metastases to the axillary glands was verified at operation. Yet this patient was well eight years after the radical mastectomy was performed.

In a similar case operated on in 1906, local recurrence took place in 1913, seven years later and the patient died of cancer in 1914.

In another case the tumor had been present three years and was 6 cm. in diameter; the patient died of metastases seven years later.

In another patient the tumor had been present three years in the right breast. Involvement of the left breast occurred two years after radical operation. Local recurrence took place in the second breast three years later. The patient died of metastases six years after the first operation.

Radical mastectomy is the treatment of choice for these circumscribed transitional-cell carcinomas of the breast. In the larger cystic cancers, the five-year survivals are 13.8 per cent whereas in the smaller

FIG. 470

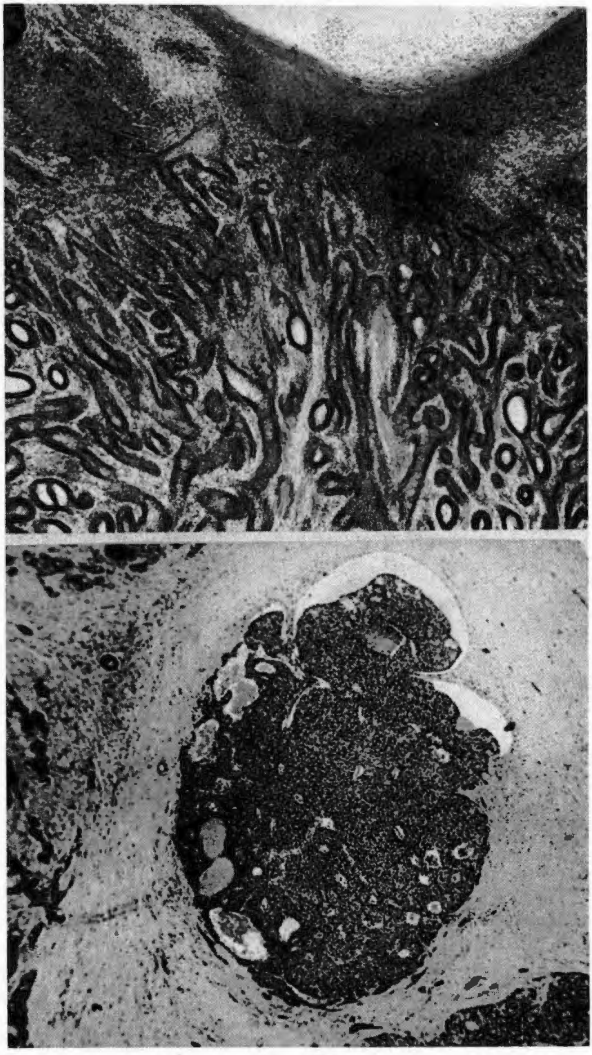


FIG. 471

Resemblance of Vascular Neomammary Cancer to Sweat Gland Structure.
FIG. 470. Photomicrograph showing benign sweat gland adenoma of the eccrine type.
FIG. 471. Photomicrograph showing vascular neomammary cancer with islands resembling eccrine sweat gland tumor.

solid tumors, 46.3 per cent of the cases live beyond the five-year period. Among the 36 cancer cysts, 29 patients were followed. Four

TABLE LXXVI

DATA ON 135 CASES OF NEOMAMMARY CANCER

AGE		DURATION		SIZE		LOCATION	
25–29	3	1– 3 mos.	34	1– 3 cm.	20	U.O.Q.	27
30–34	10	4– 6 mos.	25	4– 5 cm.	32	U.I.Q.	12
34–39	8	7–12 mos.	32	6– 7 cm.	28	L.O.Q.	10
40–44	14	13–24 mos.	12	8–12 cm.	15	L.I.Q.	4
45–49	17	2+ yrs.	4	12+	5	Nipple zone	29
50–54	24					Entire breast	7
55–59	20						
60–64	12	MARITAL STATUS				DISCHARGE FROM NIPPLE	
65–69	4	No data	33	Married—0 children	12		
70+	1	Single	18	Married—1 child	18	Solid tumors	3
		Married	84	Married—2 children	10	Cystic tumors	7
				Married—3 children	17		
				Married—3+ childr.	23		

Average no children per family—3

FOLLOW-UPS

Cancer cysts	*36*	*Solid tumors*	*99*
Followed	29	Followed	69
Living 5 yrs.+	4	Living 5 yrs.+	32
Dead under 5 yrs.	25	Dead under 5 yrs.	37

Among 98 followed cases, 36 are well, = 36.6% five-year survivals

of these were well six to 10 years after operation, and the remaining 25 were dead of the disease. Among the small solid growths, there were 69 patients who were followed until death or for more than five years. Thirty-seven of the patients died of the disease and 32 survived more than five years. Ten of these were well 10 or more years after operation. In all, there were 36.6 per cent of five-year survivals. The degree of malignancy in this group of cancers is less than would be expected from their size and microscopic appearance.

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25

Microscopic Diagnosis of Mammary Cancer

With the turn of the last century, when mammary cancer passed from an incurable to a curable disease, the emphasis shifted from pathologic anatomy to histopathology. The advanced stages of untreated cancer formerly seen could be diagnosed with certainty in the gross, and little was added by microscopic study. Now, when the disease is seen frequently in its early stages, and can be arrested by radical surgery or irradiation, microscopic sections are essential to confirm and to record the malignant nature of the condition. The correlation of the microscopic picture with the results of treatment is also important, and has made more accurate the microscopic differential diagnosis in doubtful cases. Such a correlation also supplies data for the prognosis of the disease and for the interpretation of histologic changes which may precede or accompany the development of cancer in the breast.

From a practical standpoint, the microscopic study of malignancy in the breast is important:

1. To confirm the clinical impression of cancer before undertaking radical surgery or irradiation.
2. To differentiate between benign and malignant conditions in doubtful cases.
3. To classify and grade mammary cancers as a guide to treatment and prognosis.

BIOPSY IN CONFIRMATION OF MALIGNANCY

A microscopic preparation of the cancer should be available to confirm diagnosis and for future reference before undertaking radical surgery or irradiation. An aspiration or punch biopsy is not a substitute for an adequate frozen or paraffin section unless the presence of malignancy is UNQUESTIONABLY demonstrated. The interpretation of a doubtful aspiration or punch biopsy should not be influenced by the clinical impression. An indurated zone of tissue such as occurs in mastodynia may surround a small cyst or an area of adenosis and simulate cancer; a large fibro-adenoma occurring toward the menopause may produce dimpling of the skin or retraction of the nipple; periductal mastitis or residual puerperal mastitis may cause edema and fixation of the overlying skin; and a thick-walled cyst may simulate mammary cancer. Even in large clinics needlessly radical procedures have been performed for such benign conditions in the presence of equivocal aspiration biopsies. Such mistakes, although rare, can be avoided if a competent pathologic report is awaited before beginning treatment. Surgical biopsy followed by chemical or thermal cauterization and a delay of several days to permit an adequate pathologic examination are preferable to procedures based upon an incorrect diagnosis.

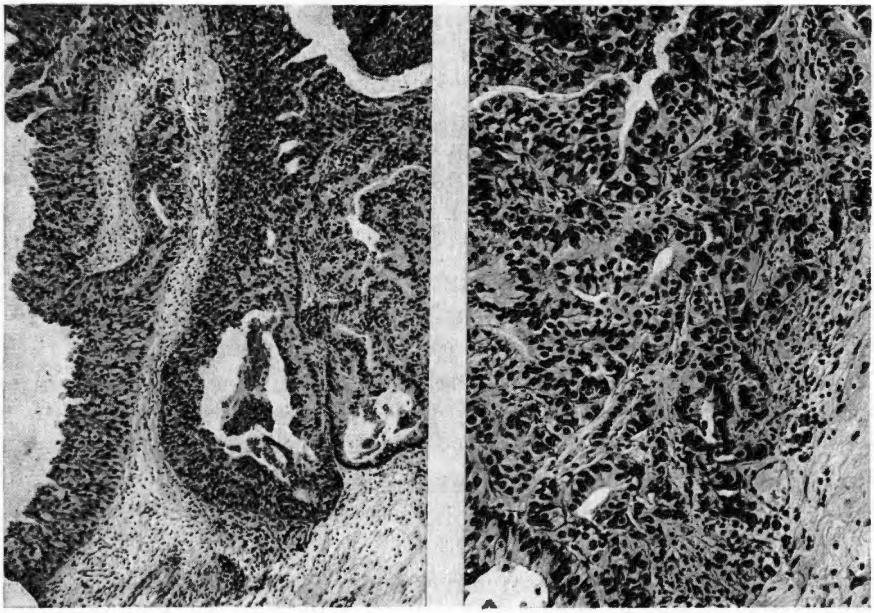
MICROSCOPIC DIFFERENTIATION BETWEEN BENIGN AND MALIGNANT LESIONS

A variety of lesions in the mammary gland may give rise to difficulties in microscopic diagnosis. The distinction between benign and malignant papillomas, between adenosis and comedo adenocarcinoma, between duct adenoma and duct carcinoma. between benign fibro-adenoma and fibro-adenoma undergoing cancerous or sarcomatous change, and between residual mastitis and cancer arising in mastitis may require the best sections obtainable and a most careful and detailed study.

Benign and Malignant Papillomas

Benign papillomas which exceed 3 or 4 cm. in diameter are rare, although the cysts surrounding the papilloma and containing serosanguineous or bloody fluid may exceed 10 cm. in diameter in exceptional cases and enclose a small benign growth. Larger papillary

FIG. 472 FIG. 473



Early Malignant Change in Intracystic Papilloma.

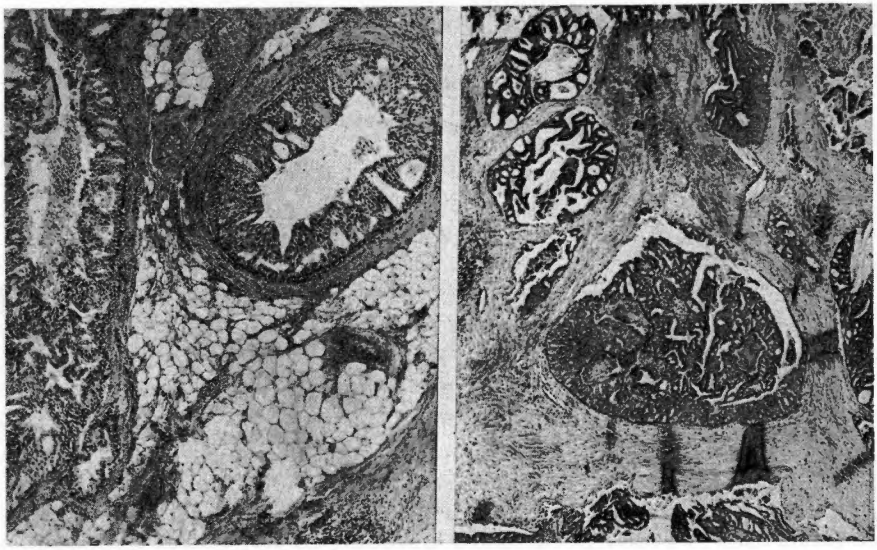
FIG. 472. Photomicrograph showing the base of the papilloma with folds of epithelium penetrating into the connective tissue.

FIG. 473. The same area under higher magnification showing the penetration of the basement membrane by the tumor cells. Note the variation in size and the staining characteristics of the nuclei.

growths or multiple papillomas of appreciable size should be regarded with suspicion. Malignant change is first observed in the base of the growing tumor. (Figs. 472, 473.) In the early stages of cancer, the epithelial tissue near the stalk of the papilloma grows in solid sheets and the basement membrane is penetrated. (Figs. 472, 473.) The nuclei of the cells and their cytoplasm are increased in size. The staining characteristics of the nuclei are variable and the number of mitotic figures is increased. Later, the malignant epithelium invades the stroma beyond the base of the stalk and papillary masses are

found as discrete, new tumors in the neighborhood of the primary growth. Some of these epithelial masses will form plugs of adenocarcinoma confined to, but distending, the ducts resembling the malignant tissue seen in comedo cancer. Because of their solid clumps of malignant cells, these secondary epithelial masses can be distinguished from multiple small benign papillomas which are at times found in the ducts adjoining a larger intraductal papilloma.

FIG. 474 FIG. 475



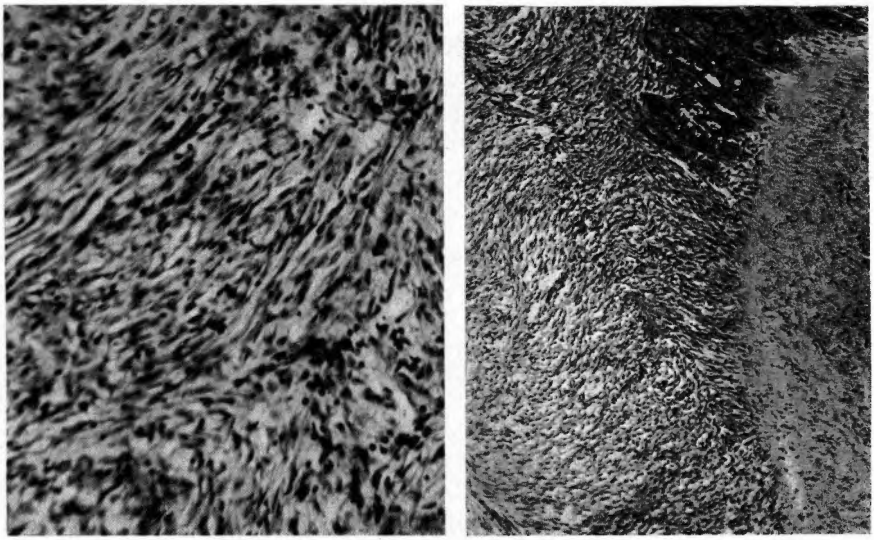
FIGS. 474, 475. Adenocarcinoma developing from benign papilloma. The photomicrographs show the formation of secondary epithelial masses resembling comedo carcinoma in the fat and connective tissue just beyond the base of the papilloma. (See Color Plate II.)

Fibro-Adenomas with Malignant Change

The majority of fibro-adenomas are readily distinguished grossly and microscopically from mammary cancer. As a rule, fibro-adenomas which have a distinctly benign and encapsulated character in the gross are not malignant even though atypical epithelial proliferation may be found under the microscope. Epithelial proliferation within the fibro-adenoma may occur in pregnancy, but usually the epithelium retains its benign characteristics in spite of the rapid enlargement of the tumor. In only one case observed by the author did malignancy occur, and in this large sheets of cancerous epithelium

were a distinguishing feature. (Fig. 154.) Rapidly growing, intracanalicular myxomas may show papillary epithelial hyperplasia. The epithelial cells are large and pale, of the sweat-gland type without malignant features, and have a distinct basement membrane. Occasionally, squamous-cell metaplasia may occur in large myxomas. In such cases, squamous-cell cancer may be present but is readily iden-

FIG. 476 FIG. 477



Microscopic Contrast Between Giant Myxoma and Fibrosarcoma of the Breast.
FIG. 476. Photomicrograph of a benign cellular giant myxoma showing the small and slender character of the nuclei in the stroma of these tumors. (See Color Plate III.)
FIG. 477. Photomicrograph of fibrosarcoma arising in mammary myxoma showing the pleomorphic character of the nuclei. (See Color Plate III.)

tified by its infiltrating character and the presence of epithelial pearls. (Fig. 498.)

Large fibro-adenomas or myxomas are more often affected by sarcomatous than by carcinomatous change. In such cases, the tumor is of large size and occupies most of the breast so that there is little practical difference between performing a simple mastectomy for the large benign tumor and one which includes the pectoral fascia if sarcoma is suspected. Histologically, the fibrosarcomas occurring in giant myxoma are distinguished by interlacing whirls of small spindle cells with occasional tumor giant cells with two or more large dusty nuclei. (Figs. 476, 477.)

Pleomorphic Fibro-Adenoma

In rare instances, the adenomatous tissue in fibro-adenoma may undergo marked proliferation. Lobular structures, which are rarely a prominent feature of these benign growths, may dominate the microscopic picture. Some of these are circumscribed formations with increased numbers of enlarged acini lined by one or more rows of epithelium of the sweat-gland type, the epithelium in some places forming solid clusters without a central lumen. (Fig. 478, 479.) In other places, there are large irregular lobules without encapsulation and with rows of proliferating epithelium extending into the fibrous tissue—the so-called epithelial spilling which is more common in adenosis. The large size of the pale epithelium in the encapsulated lobules, and the infiltrating character of the cells in the nonencapsulated lobules make it difficult to decide against a diagnosis of mammary carcinoma. The term "pleomorphic fibro-adenoma" has been proposed for these growths. (See Chap. 13.) Only four such cases have been observed in our entire series. Two were treated by radical mastectomy and two by local excision followed by irradiation. All of the patients are living four or more years after operation and none has developed axillary metastases. The conclusion, therefore, is that these are benign growths with atypical forms of epithelial proliferation. The histories of the four cases are given briefly below:

Case 1. A white female, 40 years old, noticed a lump in the outer mid zone of the breast of three months' duration. A biscuit-shaped mass, nonencapsulated, measuring 4.5 cm. in diameter and 2 cm. thick, was excised in March, 1937, and postoperative irradiation was given. Although not definitely encapsulated, the borders are well demarcated. On incision, the cut surface presented an appearance similar to a fibro-adenoma except it was more reddish in color. The patient was reported well in January, 1944.

Case 2. A white female, 28 years old, had noticed a lump in the breast for two years. Preoperative irradiation was given. A nonencapsulated tumor, 2 cm. in diameter was excised in November, 1940. Further irradiation was given. The patient has remained well for four years.

Case 3. A white female, 24 years old, had a rapidly increasing swelling in the lower quadrant of the right breast which had been present for only two months. Examination revealed a tumor the size of a small lemon. It was hard and irregular to palpation and the overlying fat was atrophic, but there was no definite adherence to the skin. The bisected tumor in the gross resembled cancer. A radical mastectomy was performed in June, 1936, and the patient was well in June, 1944. (Figs. 478, 479.)

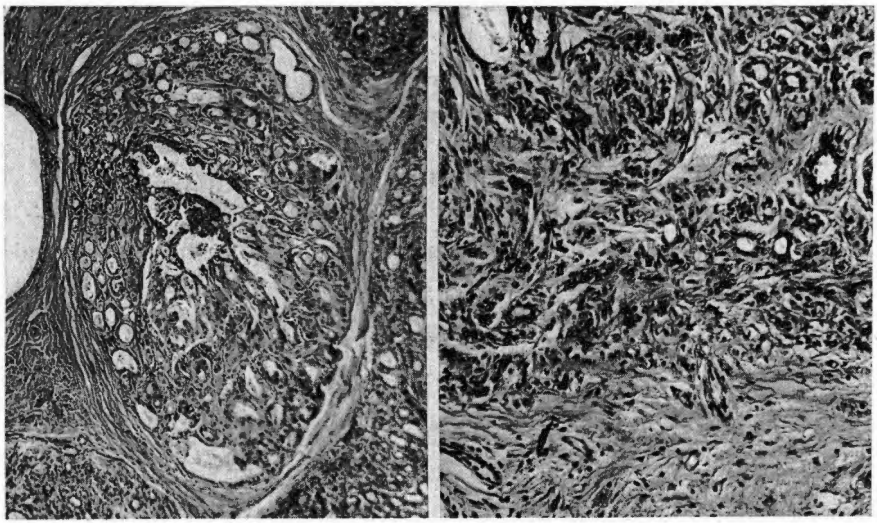
Case 4. A white female, 46 years old, with three children, felt a lump in the right breast four weeks previously. On examination there was a

definite mass of the mastitis type in the mid zone of the upper hemisphere. The palpable mass was larger than a silver dollar. Radical mastectomy was performed in February, 1930. Bisection of the tumor showed a small blue-domed cyst the size of a five-cent piece with an area in the wall that resembled cancer grossly. The patient has remained well for 10 years.

Adenosis and Comedo Cancer

Adenosis or Schimmelbusch's disease may be associated with mammary cancer. Infiltrating mammary cancers complicating this condi-

FIG. 478 FIG. 479



Microscopic Features of Pleomorphic Fibro-adenoma.

FIG. 478. The photomicrograph shows sweat-gland metaplasia in a circumscribed lobule in a cellular fibro-adenoma.

FIG. 479. Photomicrograph showing non-encapsulated epithelial proliferation of another large lobule, from the same tumor shown in Figure 478. The gross specimen of this unusual fibro-adenoma resembled carcinoma and radical mastectomy was performed. The lymph nodes were negative. The patient has remained well for six years.

tion may have their onset in a sclerotic, fibrosed area and under such circumstances rarely offer any difficulties in microscopic diagnosis. (Fig. 480.) Comedo carcinoma which may occur in association with adenosis is more difficult to differentiate. Solid duct adenomas composed of benign epithelium are relatively common in adenosis and, under low power, may resemble the intraductal growth of comedo cancer. There are two important distinctions. The intraductal growth in comedo cancer rarely forms a solid compact plug under the microscope. Instead there is a central zone of necrosis;

the surrounding ring of cancer tissue, lining the duct, has numerous small secondary channels where the tumor is giving rise to minute new tubules or forming acinar spaces. (Fig. 481.) The second distinguishing feature is found under high power: the duct adenomas occurring in adenosis are composed of small epithelial cells of uniform size with relatively small nuclei and small amounts of cyto-

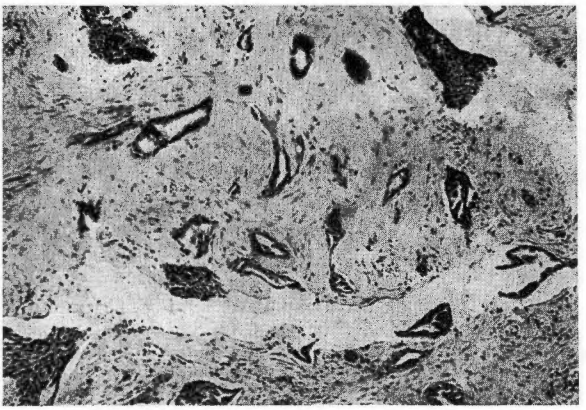


FIG. 480. Low grade lobular cancer developing in a sclerotic area of adenosis. (See Color Plate III.)

plasm. On the other hand, in comedo cancer the epithelium contains numerous cells of larger size with pale and swollen nuclei and occasional mitotic figures. (Fig. 482.) In many cases of comedo carcinoma the epithelium in one or more places invades the surrounding fat and fibrous tissue. This feature, when present, establishes the diagnosis of malignancy.

Small papillary adenomas and papillary cystic adenomas may be found in Schimmelbusch's disease or adenosis. These are usually of a definite benign appearance and while there is an increased susceptibility to cancer in such patients these small epithelial formations cannot be considered precancerous. (Figs. 483, 484.)

The precancerous changes in adenosis comprise the solid duct adenomas and stellate epithelial islands separated by large amounts of sclerotic fibrous tissue. The duct adenomas may persist and may be found in cases of comedo cancer (Figs. 485, 486), and the fibrosed stellate adenomas may be found in early cases of infiltrating carcinoma (Fig. 488). In spite of the fact that many patients with solid adenoma of the ducts have remained well 5 to 20 years following simple excision, it is safest to interpret these as beginning

FIG. 481

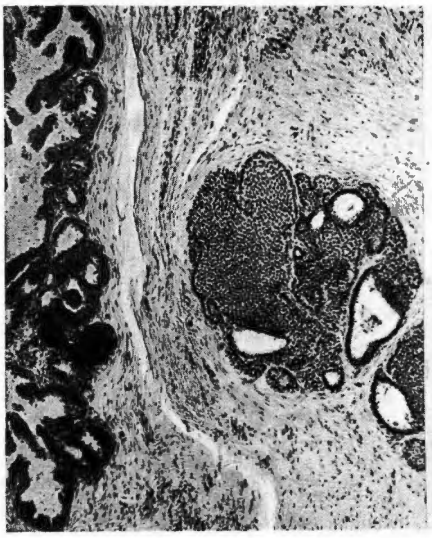


FIG. 482

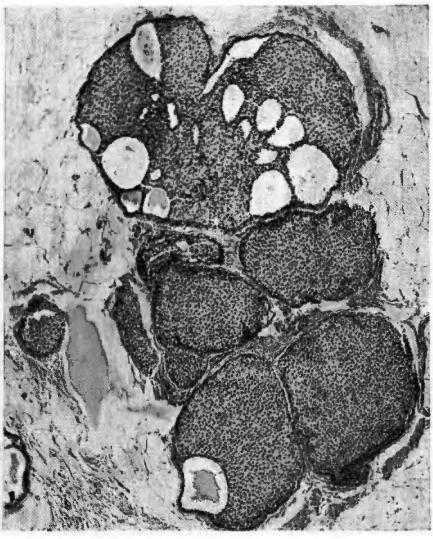


FIG. 481. Benign duct adenoma occurring in adenosis. The photomicrograph shows a cystadenomatous lobule in the left hand portion and a duct adenoma in which the cells still have a benign morphology in the right hand portion. (Compare with Figure 482.)

FIG. 482. Comedo carcinoma with beginning invasion of the fatty tissue. The photomicrograph shows distention of the preformed ducts with enlarged tumor cells and the formation of new islands of epithelium outside of these channels. (Compare with Figure 481.)

FIG. 483

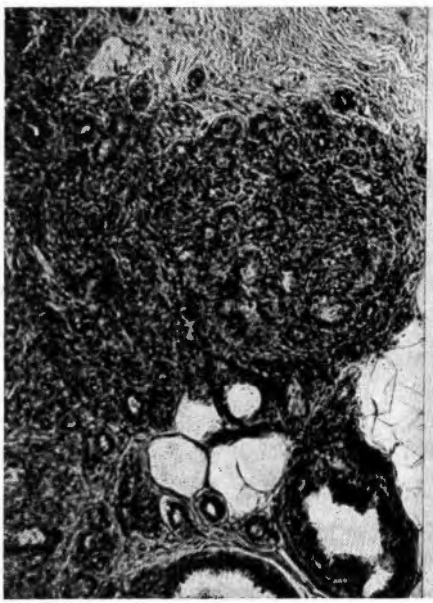
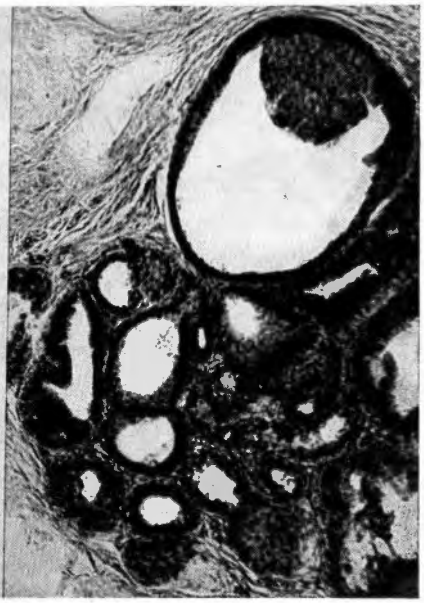


FIG. 484

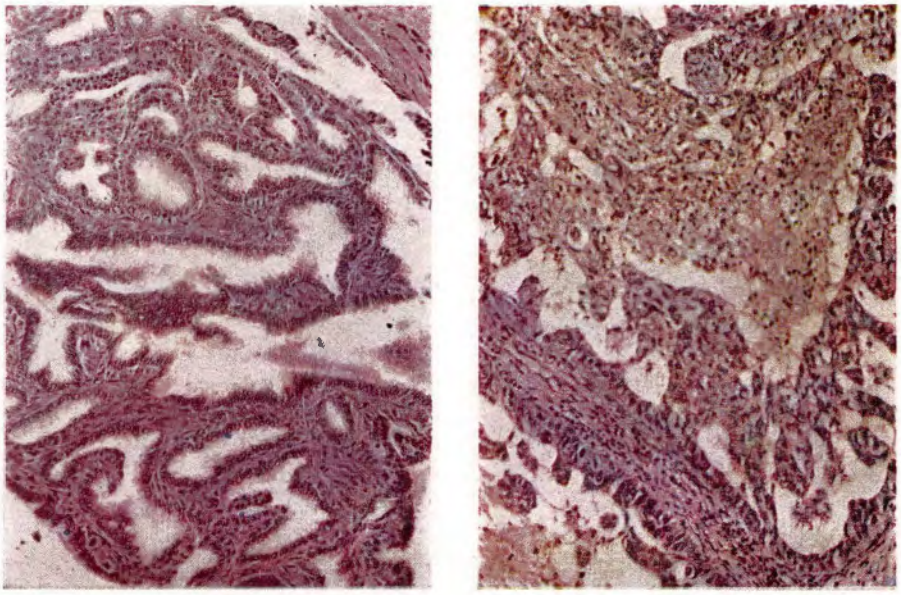


Adenosis with Epithelial Spilling and Minute Intracystic Papilloma.

FIG. 483. Photomicrograph showing characteristic irregular lobule formation with epithelial spilling in benign adenosis.

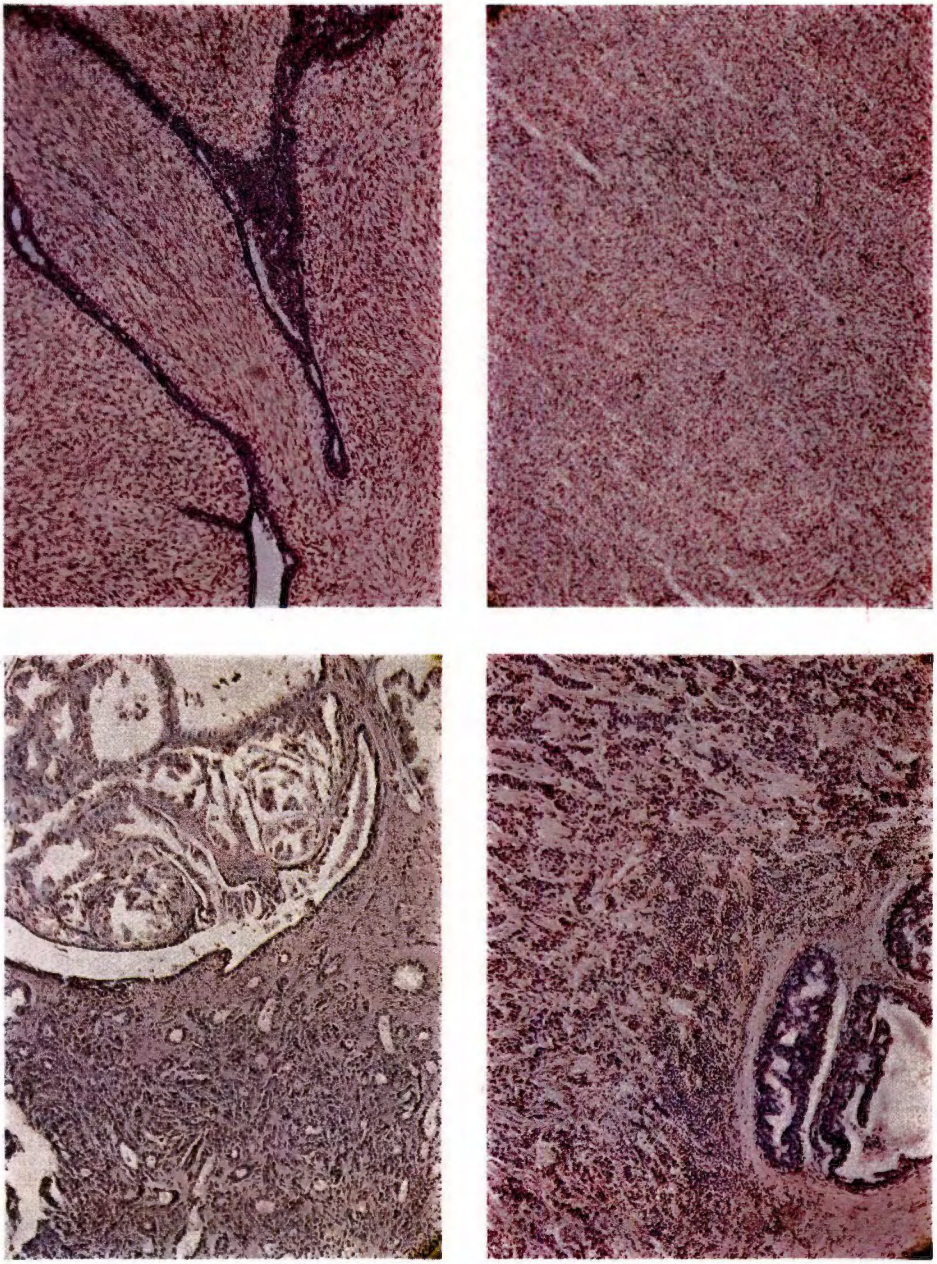
FIG. 484. Photomicrograph of the same case showing a small intracystic papilloma.

Color Plate II



(Left) Structure of benign papilloma.
(Right) Structure of papillary carcinoma.

Color Plate III



(Top, left) Photomicrograph of a benign cellular giant myxoma showing the small and slender character of the nuclei in the stroma of these tumors.

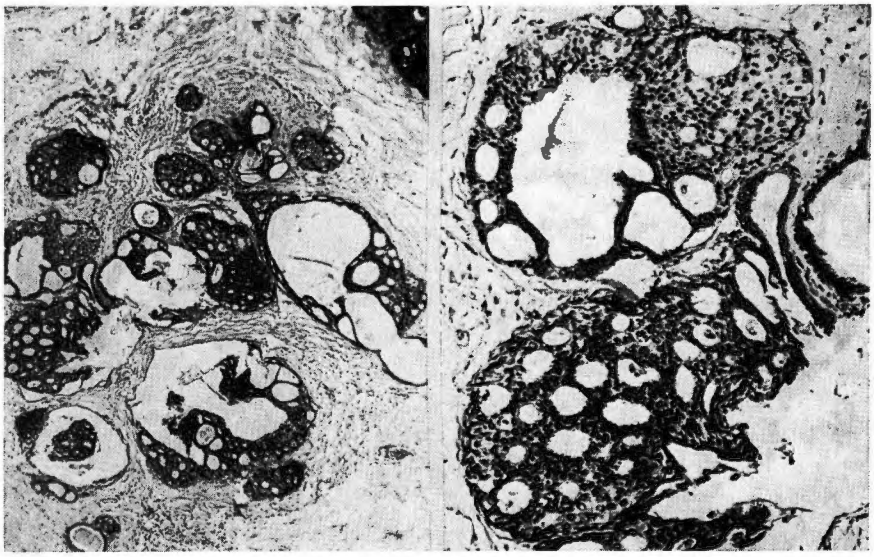
(Top, right) Photomicrograph of fibrosarcoma arising in mammary myxoma showing the pleomorphic character of the nuclei.

(Bottom, left) Pleomorphic fibro-adenoma showing sweat-gland metaplasia of the epithelium to the left and hyperplastic lobule formation to the right.

(Bottom, right) Lobular cancer developing in a case of adenosis. The photomicrograph shows the malignant epithelium developing independently in the stroma without relation to preformed lobules.

comedo cancer and perform radical mastectomy whenever there is a tendency to central necrosis or enlargement of the cells. In fibrosed tissue with stellate adenoma the same radical procedure should be carried out if the fibrosis is marked and the enclosed adenomatous areas are numerous and contain cells with enlarged nuclei.

FIG. 485 FIG. 486



Duct Adenoma in Adenosis Undergoing Malignant Change.

FIG. 485. Low-power photomicrograph showing beginning comedo carcinoma in a case of adenosis.

FIG. 486. High-power photomicrograph from the same area shown in Figure 485. Note the enlarged cancer cells in the upper right hand corner. This patient was treated by simple excision and developed recurrence and axillary metastasis one year later. (Compare with Figure 487.)

In estrogenic mammary cancer in the rat, solid duct adenoma may precede the formation of typical comedo cancer by as little as three weeks and the two types of duct pathology may be found in the same section. (Fig. 233, Chap. 12.) Fibrosing stellate adenoma does not occur in the rat because of the sparsity of fibrous tissue but microscopic fibroadenomas frequently form in the surrounding region when cancer occurs in pre-existing adenosis. (Fig. 265, Chap. 13.)

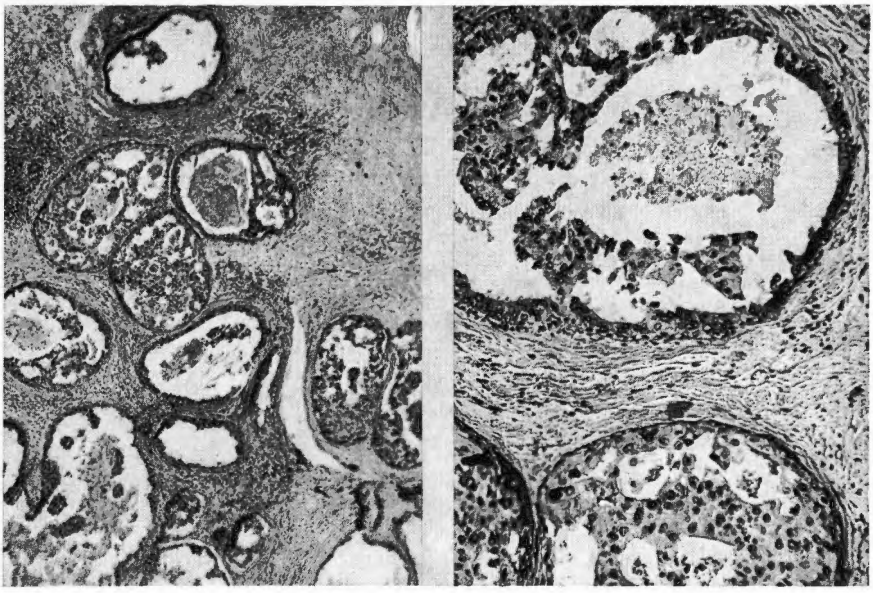
Fibrosing Adenoma and Infiltrating Carcinoma

The irregular lobular formation in adenosis is often accompanied by epithelial sprouts which penetrate the fibrous tissue without a well-defined basement membrane. This "epithelial spilling" when it

is associated with increased fibrosis may be difficult to distinguish from infiltrating lobular cancer.

At times, this proliferating epithelium undergoes so-called sweat-gland metaplasia; the cells enlarge and their nuclei stain densely, making the resemblance to mammary cancer more pronounced. The distinguishing feature with low-power microscopic examination is a

FIG. 487 FIG. 488



FIGS. 487, 488. Fully developed comedo carcinoma occurring in adenosis. Low and high-power photomicrographs showing fully developed cancer. This patient was treated by radical mastectomy. The glands were negative. The patient is well ten years later. (Compare with Figure 486.)

continuity of the irregular epithelial sprouts with the original lobule formation. The proliferating epithelium adds to the size of the lobule and gives it a fringed or irregular border but does not form separate lobular structures. Normal tubules and acini persist in the midst of the proliferating epithelium. (Fig. 489.) These enlarged pathologic lobules with epithelium spilling when associated with increased fibrous stroma have been termed "fibrosing adenoma." In the author's experience, they are not associated with mammary cancer unless the amount of fibrosis is sufficient to obliterate the major portion of the epithelial elements and thus to form small separate islands which no longer resemble nor have any visible relation to the original large hyperplastic lobules. (Fig. 490.)

Cancer in Mastitis

In chronic infectious mastitis, inflammatory tissue infiltrates the stroma and penetrates about the tubules and lobules which are gradually broken up and destroyed. During the process of lobular disintegration, the disorganized fragments of epithelial tissue may resemble mammary cancer. The individual cells may be swollen or pyknotic in appearance and may be scattered in strands or small foci in a dense lymphoid matrix. Microscopic diagnosis is difficult because

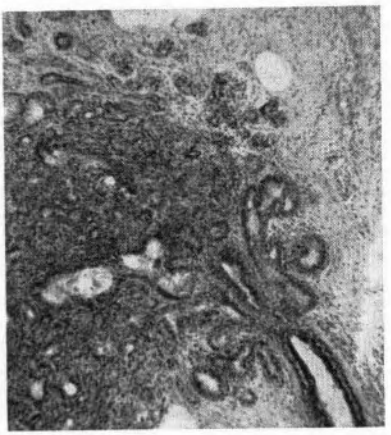


FIG. 489. Epithelial spilling or so-called fibrosing adenoma in a case of adenosis. The photomicrograph shows the infiltrating character of the benign lobular epithelium. (Compare with Figure 490.)

mammary cancer may have its onset in residual puerperal mastitis or in the scar of a former abscess. The chief points of differentiation are: first, the extent of the epithelial disarrangement; and second, the degree of variation in the appearance of the individual cells. In mammary cancer, arising in the scar or the residuum of infectious mastitis, there is usually ample malignant tissue and the cancer cells are found throughout one or more fields growing in characteristic fashion with a uniform size and structure in the individual cells. In infectious mastitis the foci of epithelial derangement are small and surrounded by far larger zones which are infiltrated by wandering cells and which are devoid of epithelial elements. The disintegrating epithelial cells in mastitis vary from a small shrunken size to larger swollen masses in which the cytoplasm of several individual cells may become confluent and simulate a foreign-body giant cell. (Fig. 145, Chap. 6.)

Interpretation of Intraductal Papilloma and Comedo Carcinoma

There are occasional differences among pathologists not in regard to the diagnosis, but the degree of malignancy of certain mammary lesions. Intraductal papillomas of macroscopic size without invasion of the surrounding tissue are nonmetastasizing tumors. About nine per cent of these papillomas may at a subsequent date undergo malig-

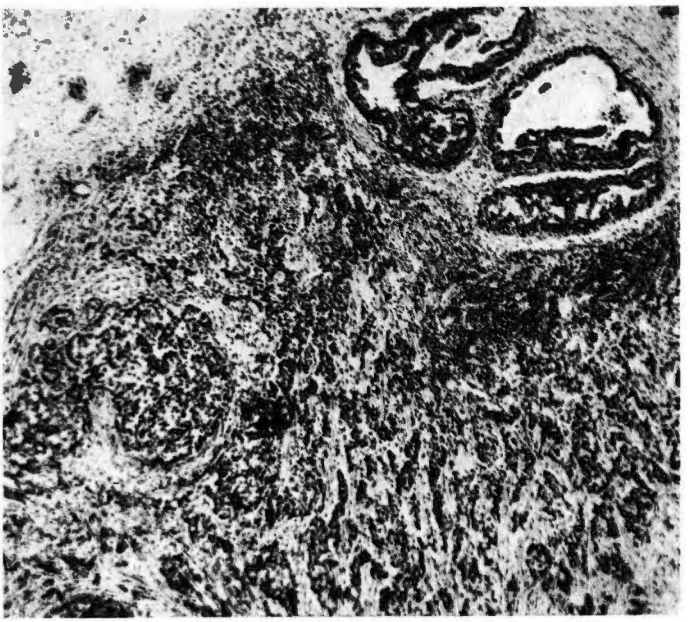


FIG. 490. Lobular cancer developing in a case of adenosis. The photomicrograph shows the malignant epithelium developing independently in the stroma without relation to preformed lobules. (See Color Plate III.)

nant change giving rise to metastasizing papillary adenocarcinoma. The distinction between the two, however, can be definitely made on the basis of microscopic findings as outlined above. Nevertheless, there are still pathologists who prefer to classify benign papillomas as Grade I adenocarcinomas. This practice can only lead to confusion in the interpretation of the end-results of surgery and radiation in the treatment of mammary cancer. Obviously, the five-year survivals are much increased if these benign lesions are considered among the cured cases. Among 59 papillomas treated by simple excision, and followed three to 35 years, 48 remained well. Eight cases had a second operation for another benign papilloma, and three were ulti-

mately treated for papillary adenocarcinoma. While there may be some room for discussion concerning the method of treatment, the fact that the majority have remained well following simple excision is certainly proof of their benign character.

Bloodgood, because of the number of cures obtained in cases of comedo cancer, suggested that the noninfiltrating form might be treated conservatively. The author has traced 9 cases of comedo carcinoma treated by local excision or simple mastectomy. Most of these were reported in Dr. Bloodgood's series. Only two have remained well beyond the five-year period (six and 11 years respectively). The remainder developed recurrences or axillary metastasis. This is sufficient evidence to reaffirm the malignant features of all grades of comedo carcinoma.

MICROSCOPIC CLASSIFICATION AND GRADING OF MAMMARY CANCERS

The histologic structure of the cancer furnishes valuable information in regard to its curability and radiosensitivity. For this reason, the study of properly prepared sections with the object of classifying or grading the cancer should be included as part of the pathologic diagnosis. Four microscopic features have been used in the histologic grading of mammary carcinoma: (1) the arrangement or pattern of the epithelial growth; (2) the characteristics of the individual cells; (3) the reaction of the stroma; (4) the penetration of normal tissue boundaries. A papillary adenomatous structure, a comedo pattern with the cells confined to pre-existing ducts, and a gelatinous stroma or matrix are features which have been recognized and generally accepted as favorable prognostic signs. Conversely, a diffuse proliferation of the epithelium without definite arrangement, marked variation in the size, shape and staining characteristics of the nuclei of individual cells, and frequent mitoses are generally accepted as unfavorable prognostic findings. A similar significance is attached to the penetration of pre-existing boundaries which indicates an invasive tendency.

Circumscribed Adenocarcinomas

Grade I. In the previous discussion of mammary cancer the circumscribed adenocarcinomas, which include the papillary, comedo and gelatinous cancers, have been treated separately and an attempt has been made to correlate the pathologic features peculiar to these forms of cancer with their clinical behavior. Haagensen, in a careful

correlation of histologic structure with the end-results of treatment, has confirmed the relative low degree of malignancy of these forms of mammary cancer. He states that "According to this plan tumors were arbitrarily placed in Grade I when they had a papillary or comedo character, when the adenoid arrangement of the cells was marked, when gelatinous degeneration was present." In Haagensen's group of Grade-I adenocarcinomas, the five-year survivals varied from 76 to 84 per cent according to whether the lymph nodes were or were not involved. In our own series there were 386 cases of circumscribed adenocarcinomas among 2,534 mammary cancers. The five-year-survival rate of these low-grade cancers was 64 per cent.

TABLE LXXVII

FIVE-YEAR SURVIVALS IN CIRCUMSCRIBED ADENOCARCINOMAS (GRADE I)

NO. OF CASES	TYPE	FIVE-YEAR SURVIVALS
106	Comedo	76.2%
197	Papillary	55.0%
83	Gelatinous	61.0%
386	Totals	62 %

Circumscribed forms of adenocarcinoma are usually distinguished by their sharply delimited margins in the gross and their distinct glandular structure under the microscope. Comedo cancers contain columnar cells with a brush-like secretory border in contact with the central opening of the duct or the newly formed nodules. The papillary cancers contain glandular epithelium growing in coils or branching cauliflower fashion. The gelatinous cancers contain small basal cells with an acinar arrangement embedded in characteristic mucoid matrix.

The radiosensitivity of circumscribed adenocarcinomas apparently varies in accordance with the degree of vascularity. The avascular gelatinous cancers are radioresistant. The papillary adenocarcinomas which are often highly vascular are radiosensitive and the site of the tumor may be converted into an area of infarction by external irradiation. The comedo carcinoma is less sensitive than the papillary form, and those that invade the ducts diffusely are more readily controlled through radiation than those which form a discrete large mass.

Infiltrating Lobular Cancers

As previously pointed out in Chapter 19, the separation of infiltrating lobular cancers into groups with different degrees of malignancy on the basis of their microscopic features is a plausible

FIG. 491 FIG. 492

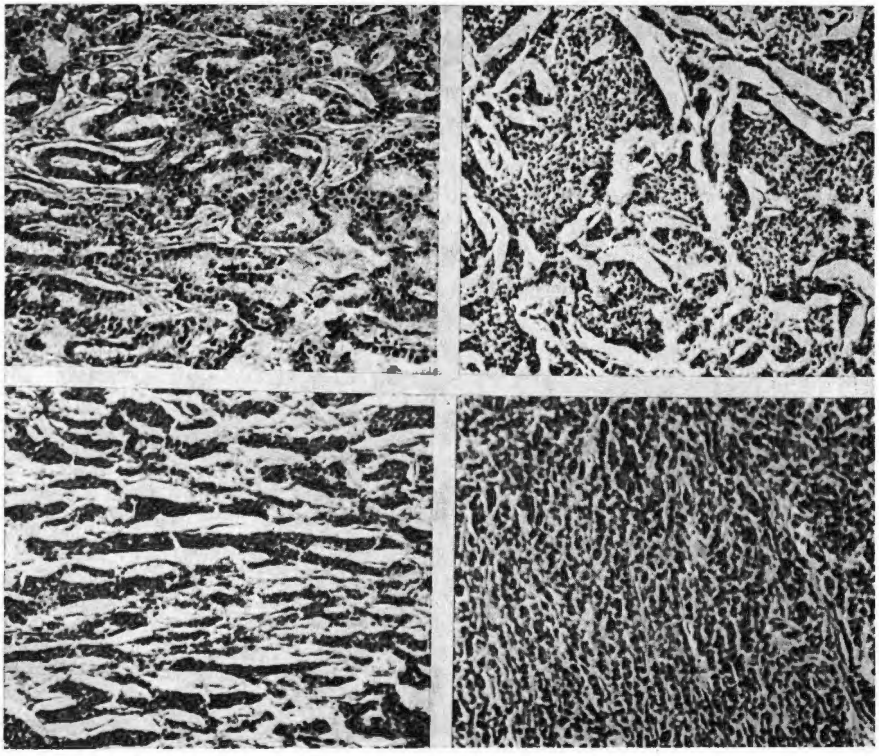


FIG. 493 FIG. 494

The Microscopic Grades of Lobular Cancer.
FIG. 491. Grade I: The tumor has a definite adenoid arrangement.
FIG. 492. Grade II: Solid alveolar masses are characteristic of the tumor.
FIG. 493. Grade III: The tumor is growing in cords, or rows.
FIG. 494. Grade IV: There is a dense and diffuse proliferation of tightly packed malignant cells.

undertaking if the circumscribed forms of adenocarcinoma and the stratified or transitional epithelial cancers have been previously excluded.

Grade I. The presence of well-developed acinar structures, since it indicates a high degree of differentiation, is evidence of a low

degree of malignancy. Lobular cancers with such an adenoid arrangement embedded in reactive fibrous tissue have been placed among the Grade-I cancers by Haagensen, Greenough, Broders and others. In our own series these cancers with a well-developed adenoid structure have a prognosis as favorable as the circumscribed adenocarcinomas and hence belong to Grade I. The five-year survivals in this pure adenoid group were 66 per cent. The adenoid lobular cancers with the lowest degree of malignancy are those in which the acinar structures are well separated by fibrous tissue (Fig. 480); these constitute a little less than 8 per cent of all the infiltrating lobular cancers. On the other hand, this adenoid structure is often associated with larger solid islands of epithelium and merges with the group of Grade-II lobular cancers.

Grade-II lobular cancers are those composed of solid islands of epithelium well rimmed by fibrous tissue. Some of these islands form plugs within the ducts but most of them form solid alveoli of irregular polygonal shape. The nuclei of the cells are usually of uniform size and are separated by a moderate amount of clear cytoplasm. These are Grade-II carcinomas with a five-year survival rate of 39 per cent in our series.

Grades III and IV. The majority of infiltrating lobular cancers are composed of cords of epithelial tissue which penetrate in rows of two or three or in single file into surrounding fibrous tissue. Where Grade-III malignancy is found some of the cells will accumulate in small islands of the solid alveolar type and small imperfect tubular structures will be found. In Grade-IV malignancy, the cells are without such arrangement and show only a diffuse proliferation with very moderate amounts of intervening fibrous tissue.

TABLE LXXVIII

FIVE-YEAR SURVIVALS IN 1,482 INFILTRATING LOBULAR CANCERS

GRADE	NO. OF CASES	FIVE-YEAR SURVIVALS
I	108	66%
II	313	39%
III	892	31%
IV	169	22%
Totals	1,482	34%

Infiltrating lobular cancers are moderately radiosensitive. The highly cellular infiltrating forms may show marked regression following irradiation. Those with an abundant fibrous stroma are, on

the other hand, radioresistant. Unfortunately, the larger tumors, particularly those which have undergone ulceration and secondary infection and which give the poorest surgical results, are difficult to treat by external irradiation. The more diffuse infiltrating forms, without a single mass of appreciable size, respond more favorably.

Transitional Cell Mammary Carcinoma

Grade III. The transitional-cell forms of mammary cancer which include Paget's disease, duct cancer and neomammary cancer have a relatively high degree of malignancy. As a class, therefore, they may be placed with a fair degree of accuracy among Grade-III cancers. These cancers are readily distinguished by their large transitional cells which approach squamous cells in appearance. As a group the five-year survivals vary between 32 and 48 per cent. In Paget's cancer, the prognosis depends upon the extent of involvement of the breast and in neomammary cancer, the size and extent of the growth are also important considerations. The neomammary cancers which show a sweat-gland arrangement have a better prognosis than the average and those with squamous cells have a worse prognosis than the group as a whole. Duct cancers with transitional-cell features have a uniformly bad prognosis. Unfortunately, there is very little data on the radiosensitivity of this group of tumors other than what has been learned in regard to Paget's disease. Judging from experience with this form of cancer when it involves the deep mammary tissues, the stratified epithelial tumors which invade the breast are radioresistant. The grouping of the transitional-cell cancers in Grade-III malignancy is not based upon any individual microscopic finding, but upon the clinical and pathologic features of the group as a whole. Neither the size of the cells, the degree of necrosis nor the amount of lymphoid stroma which may be conspicuous features of these tumors has been found significant for prognosis.

TABLE LXXIX

FIVE-YEAR SURVIVALS IN TRANSITIONAL CELL MAMMARY CANCER (GRADE III)

NO. OF CASES	TYPE	FIVE-YEAR SURVIVALS
72	Paget's cancer	48 %
35	Duct cancer	32 %
135	Neomammary cancer	36.6%
242	Totals	39.5%

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26

Rare Forms of Mammary Cancer and Tumors of Accessory Mammary Tissue

Since the mammary gland is derived from the epidermis and is a modified appendage of skin, it is not remarkable that cancers are occasionally found in the breast which are more common in the skin or its other derivatives. Such cancers include squamous, basal-cell and sweat-gland types.

In the study of our material, true squamous, basal-cell and sweat-gland cancers are extremely rare. From time to time, however, various groups of carcinomas which are peculiar to the breast have been looked upon as analogous to or related to the forms of skin cancers just mentioned. Thus, Bloodgood has spoken of pure comedo cancer as being of the basal-cell type, and low-grade gelatinous carcinomas as having a similar origin. MacCallum speaks of Paget's disease and other transitional cell cancers arising in the substance of the breast as being composed of squamous epithelium. Ewing has repeatedly stressed the relation of some forms of mammary cancer (particularly those classified by the author as neomammary cancer) to the sweat

glands, and has recently stated that in his material about 25 per cent are of this type. Such assumptions may or may not be justifiable from the standpoint of histogenesis. Nevertheless, they have not been found helpful in the classification of mammary carcinoma from the practical viewpoint of diagnosis, treatment and prognosis, and hence, have not been followed in the discussion of mammary carcinoma in the foregoing chapters. The squamous, basal-cell and sweat-gland carcinomas which are described in the present chapter are identical with such tumors elsewhere in the body and are therefore different from the true mammary carcinomas, which from time to time may be considered as histogenically related to such epithelial structures.

SQUAMOUS-CELL MAMMARY CANCER

Paget's disease of the nipple, duct cancers and neomammary cancers (so-called medullary carcinoma) may resemble, histologically, forms of epidermoid carcinoma found in the skin or mucous membrane. Such mammary cancers, however, are composed of transitional epithelium and under the microscope are readily distinguished from true squamous-cell cancers. Typical epidermoid carcinomas originating in the breast and unconnected with the skin are rare. Deaver and McFarland reported four cases, and Stout reported a similar number. More recently, Pasternack and Wirth reported an adeno-acanthoma and a deep-seated epidermoid carcinoma was described by Foot and Moore who calculated from their material that epidermoid carcinoma constituted 0.5 per cent of mammary cancers. Haagensen found two squamous-cell cancers among 164 mammary carcinomas.

Origin

There are three groups of intramammary epidermoid carcinoma among our cases: (1) squamous-cell cancers arising in epidermoid cysts; (2) squamous-cell metaplasia with malignant change arising in fibro-adenomas; (3) Grade IV neomammary cancers (medullary carcinomas) with a scattering of squamous cells. Squamous-cell cancers arising in the epidermis of the areola or in the skin overlying the breast have also been observed.

Epidermoid Cysts. Squamous-cell cancer may develop in epidermoid cysts embedded in the breast (Chap. 15). There were six such cases in our series. The distinguishing features of the cancers in this group were the cystic character of the gross specimen, the

atheromatous contents of the cyst, and the fragments of epidermoid membrane lining the cyst, found upon microscopic examination. Pearl formation was conspicuous and, in general, the histologic structure indicated a low degree of malignancy. This is borne out by the results of treatment. Only one of the six patients is known to have died from metastasis. Four remained well beyond the five-year period, and the other died three years after operation, from an unstated cause. (Figs. 309-310.)

With two exceptions, these patients were 60 years of age or over at the time of examination. One was 54 and the other case was in a colored woman of 32 years who, for a period of two years, had noted a tumor, 3 cm. in diameter, in the upper outer quadrant of the left breast. The mass was painful and adherent to the overlying skin. This patient was reported dead (the cause of death was not recorded) three years after radical mastectomy. One of the patients, who was 61 years of age, stated that a mass which had grown rapidly in the past six months had been present for 10 years. In the remaining four cases, the tumor had been noted for less than a year. One of these growths was centrally located, another was in the lower hemisphere, and the remainder in the upper hemisphere of the breast. On palpation, these tumors are hard, spherical in outline, movable in the surrounding structures, but attached as a rule to the overlying skin. They cast a shadow on transillumination.

THE INCIDENCE of malignant change in epidermoid cysts has been variously reported. Two squamous-cell cancers (1.3 per cent) were found among 150 benign dermoid cysts of the neck (Geschickter); whereas in the breast there were six malignant cases among a total of 34 (17 per cent). Caylor reported 12 cancers (3.4 per cent) among 236 epidermoid cysts in various locations, and Bishop reported 11 carcinomas (9 per cent) among 119 cysts. In Bishop's series, the average age of the patients with malignant change in epidermoid cysts was 64.2 years, which is roughly 10 years more than the average age of patients with malignant intramammary epidermoid cysts in our series.

Malignant changes in intramammary epidermoid cysts have not been reported frequently in the literature. Pasternack and Wirth were able to find four well-described cases. One case reported (Kaufmann) was in a woman aged 45. The mass was as large as a hen egg, and an infiltrating, lobular carcinoma was also present. Konjetzny's patient, aged 34, had a tumor the size of a fist which was discovered during pregnancy. Lahm's case was a woman, 34 years old, and showed small multiple atheromatous cysts. Lecene's case was a woman aged 54. The tumor, which was about the size of an egg,

was centrally located. These cases were reported as malignant degeneration in cholesteatomas. Menville in a discussion of simple dermoid cysts in the breast recorded in the Surgical Pathology Laboratory included seven cases with malignant change. Six of these are the cases referred to by the author in the foregoing discussion.

The following tabulation from Menville contrasts the clinical and pathologic features of benign and malignant epidermoid cysts of the breast.

TABLE LXXX

MALIGNANT CHANGE IN EPIDERMOID CYSTS

(Cases: 36; Universal symptom: tumor)

	BENIGN	
	29 cases (81 per cent)	
(1)	Average duration	3.9 yrs.
(2)	Average age incidence	47.7 yrs.
(3)	Sex distribution:	
	Female	100 %
(4)	Single cyst	73.1 %
(5)	Multiple cysts	6.89%
(6)	Location:	
	Right breast	40 %
	Left breast	60 %
(7)	Dermoid cyst	
	(sole pathology)	45 %
(8)	Dermoid cyst incidental to malignant lesion	18.2 %
	Incidental to benign lesion	36.8 %
(9)	Infected dermoid cyst	27.6 %
(10)	Giant cells with dermoid cyst	20.7 %
(11)	Result: No recurrence or malignant change.	
	MALIGNANT	
	7 cases (19 per cent)	
(1)	Average duration	2.3 yrs.
(2)	Average age incidence	54 yrs.
(3)	Sex distribution:	
	Female	100 %
(4)	Cyst formation	42.9%
(5)	Location:	
	Left breast	85.7%
	Right breast	14.3%
(6)	Dermoid	
	(sole pathology)	72 %
(7)	Dermoid plus benign breast pathology	14 %
	Plus malignant breast pathology	14 %
(8)	Infected dermoid	29.5%
(9)	Giant cells with dermoid	0
(10)	Result: Two of seven cases dead; one from metastasis and the other from unknown cause.	

Squamous-Cell Metaplasia. The second group of intramammary epidermoid cancers are those arising in connection with squamous-cell metaplasia which usually affects a pre-existing fibro-adenoma. Pasternack and Wirth collected 31 cases from the literature in which the lining epithelium in ducts or cysts of large fibro-adenomatous tumors had undergone partial replacement by squamous epithelium. In 21 of the cases, the tumors affected were giant myxomas or cystosarcomas.

Oliver reported squamous epithelial metaplasia in three cases of fibro-adenoma of long standing, from among the 600 fibro-adenomas

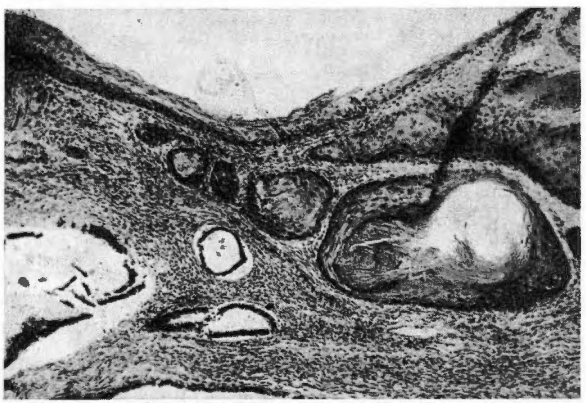


FIG. 495. Squamous-cell metaplasia occurring in a fibro-adenoma of long standing. The photomicrograph shows cysts lined by squamous cells and islands of similar tissue with epithelial pearls.

analyzed by the author in Chap. 13. (Fig. 495.) Apparently, the transformation of the glandular epithelium into squamous cells is the result of long-continued estrogenic stimulation in these benign tumors. Thus, in a girl of 16 with a benign fibro-adenoma of seven years' duration, the large size of the tumor and its constant growth throughout adolescence suggests estrogen as the likely agent responsible for the squamous-cell metaplasia observed on pathologic study. In the two remaining cases reported by Oliver, the patients were near the menopause (46 and 50 years of age). The tumors had shown rapid, recent growth and were clinically malignant. Both patients remained well more than five years following radical mastectomy, and frankly malignant features were not present. In both cases, however, there was marked squamous-cell metaplasia. In one, the possibility of early malignant change cannot be ruled out. In this connection it is of interest to note that squamous-cell metaplasia is often noted in estrogenic mammary cancer in the rat. (Figs. 496, 497.)

In the squamous-cell carcinomas reported by Foot and Moore and by Haagensen, the metaplastic origin of the squamous cells from glandular or duct epithelium could be traced under the microscope.

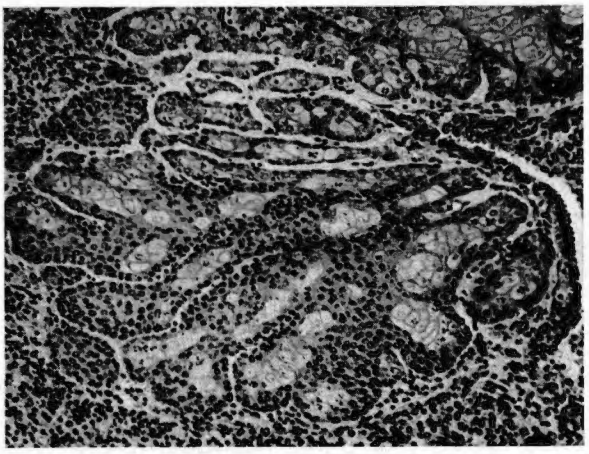


FIG. 496. Squamous-cell metaplasia in the rat's breast resulting from estrogenic hyperstimulation. (See also Figure 497.)

While the clinical histories of Haagensen's cases were not reported, the patient studied by Foot and Moore had a tumor of 20 years'

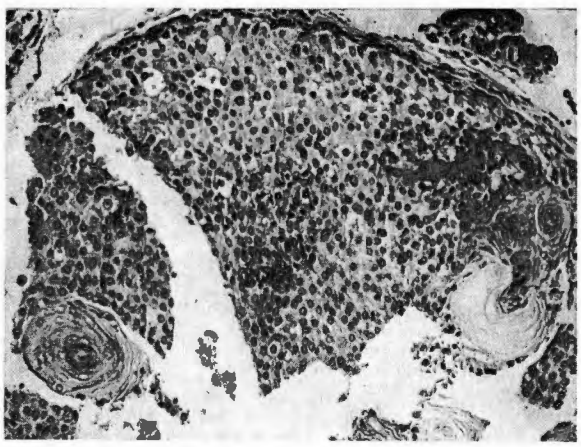


FIG. 497. Squamous-cell metaplasia with epithelial pearls in estrogenic mammary cancer in the rat.

duration prior to the onset of the malignant growth. In the case of Pasternack and Wirth, a previously benign tumor had been present for 17 years.

The author has studied three cases of squamous-cell cancer arising on the basis of metaplasia in pre-existing fibro-adenomas. In all of these cases, there was a history of a pre-existing tumor of long duration. The tumors were large, hard and circumscribed. On microscopic examination, the bulk of the mass was composed of fibrous or myxomatous tissue with islands of squamous cells scattered through the stroma. (Fig. 498.) In places the squamous epithelium lined the wall of cystic cavities, often in reduplicated rows resembling a normal mucous membrane of stratified epithelium.

Case 1. (Case referred by Dr. L. A. Keasby, Lancaster, Pa.) A woman, 81 years old, suffering from chronic nephritis, had a large tumor in her

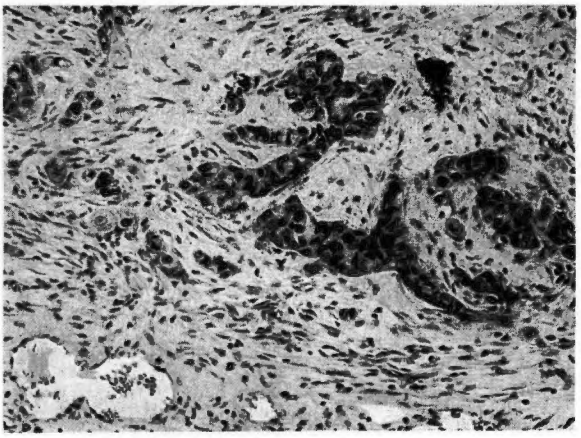


FIG. 498. Squamous-cell cancer complicating pre-existing fibro-adenoma. The photomicrograph shows squamous cells penetrating the stroma of a fibro-adenomatous tumor which had been present for 15 years.

breast which had been discovered on routine examination two years previously. No accurate history of its duration could be obtained. A simple amputation was done in 1929 because of the patient's age. The tumor measured 6 x 5 cm., and was firm and circumscribed but contained a cystic cavity with pedunculated fibrous intracystic masses. On its under surface friable, nonencapsulated tumor tissue was found. Pathologic study showed squamous-cell cancer growing from the wall of a cystic cavity in an intracanalicular myxoma. The patient died three years later from nephritis complicated by terminal pneumonia. Autopsy was not obtained.

Case 2.[1] A woman, 50 years old, noted a sticking sensation in the left breast just above the nipple. This was the site of an abscess lanced during her first lactation 12 years ago. A nodule appeared at this site and the left nipple had remained retracted since that time. Examination showed a mass about 8 cm. in diameter, firm but circumscribed, adherent to the skin, but movable on the deep structures; it was just above and to the outside of the nipple. The nipple was retracted.

[1] Case referred by Dr. George R. Moffitt, Harrisburg, Pa.

At operation a circumscribed tumor was found which on microscopic section showed squamous-cell cancer invading fibrous tissue. Radical mastectomy was performed on May 11, 1936, and the patient was reported well on November 17, 1941.

Case 3. A colored woman, 31 years old, had a tumor of 15 years' duration which had grown progressively during the past three years. In September, 1916, the mass, which measured 6 x 5 cm., was excised. It was a cystic fibro-adenomatous growth, but was attached to muscle. Squamous-cell cancer was found in the cyst lining. A radical mastectomy was performed three weeks later. The patient died with skin and osseous metastases in October, 1919.

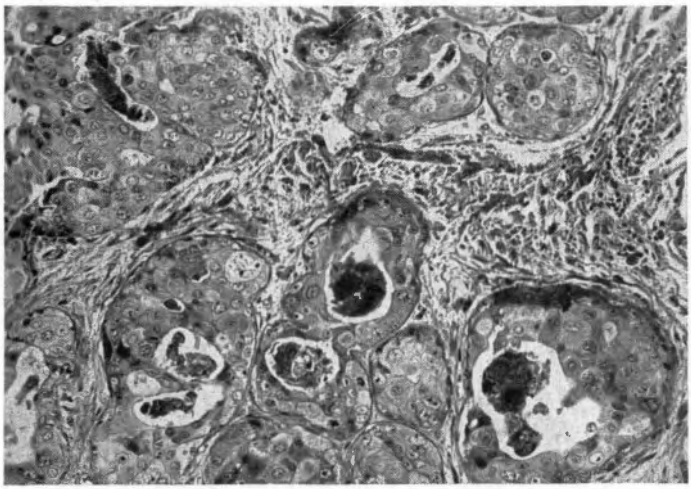


FIG. 499. Neomammary (medullary) cancer with squamous cells. The photomicrograph shows the tendency for the highly malignant and cellular tumors of this group to form epidermoid tissue.

Cancers with squamous epithelium arising in fibro-adenomatous tumors have been variously interpreted. Ewing has discussed the cases in the early literature under the heading of teratoid mixed tumors and some have been reported as carcinosarcomas. Thus, Saphir and Vass, who reviewed 32 cases of so-called carcinosarcoma of the breast, discuss one case of adeno-acanthoma arising in a cellular myxomatous stroma. This is apparently the case of Pasternack and Wirth referred to above which was a circumscribed tumor of 17 years' duration and which contained typical squamous cells.

Neomammary Cancers. Another group of mammary epidermoid cancers is found among the circumscribed medullary group, or neomammary cancers, which have been described in Chap. 24. In these cases, a resemblance to epidermoid carcinoma is frequently seen but typical pavement epithelium with keratinization was found in only

four cases. These were highly malignant growths (Fig. 499); none of the patients survived the five-year period.

Although it is possible for squamous-cell cancers to occur in the skin overlying the breast, it is extremely rare in the author's experience, and is apparently more common in the male than in the female breast. Squamous-cell cancer of the areola has been observed but once. This was in a woman, 50 years old, in whom a small ulcer 1 cm. from the nipple was excised and proved to be a typical epidermoid carcinoma. A few days later, radical mastectomy was performed, but careful study failed to reveal any evidence of cancer in either the breast or axillary nodes.

Prognosis

The prognosis of epidermoid mammary cancer is variable. The epidermoid tumors forming cancerous cysts and developing in benign cysts of this type have a good prognosis. Epidermoid carcinomas occurring in fibro-adenomas undergoing a malignant change or in neomammary cancer are highly malignant.

Treatment

Squamous-cell carcinomas of the breast should be treated by radical mastectomy. The more highly differentiated cancers arising in epidermal cysts are radioresistant. There is insufficient information on the response of the other forms of intramammary squamous-cell cancers to warrant a statement in regard to this form of therapy.

BASAL-CELL CANCER

Although basal cells may predominate in one or more portions of comedo or gelatinous carcinomas, the tendency is for these tumors to form either mammary tubules or alveoli. Two types of true basal-cell cancer have been described in the breast. One of these is rodent ulcer or basal-cell epithelioma which may be found on the nipple or on the areola. A case of rodent ulcer in the female nipple has been described by Robinson, and one in the male breast has been reported by Wainwright. The intramammary basal-cell cancers are of the adenocystic type. One of these has been illustrated by Lee, Pack and Scharnagel as a form of sweat-gland cancer. Three have been previously reported by the author. A fourth case has been recently observed.

Rodent Ulcer

Rodent ulcers on the surface of the breast are nonmetastasizing lesions similar to those found elsewhere on the skin which may be

treated by roentgen-ray therapy. The treatment consists of intermediate voltage x-ray therapy, administered in doses of 2,000 roentgens once weekly for a total of three doses. The physical factors are 140 kv. 25 ma., 35 cm. skin distance and filtration equivalent to 4 to 6 mm. of aluminum.

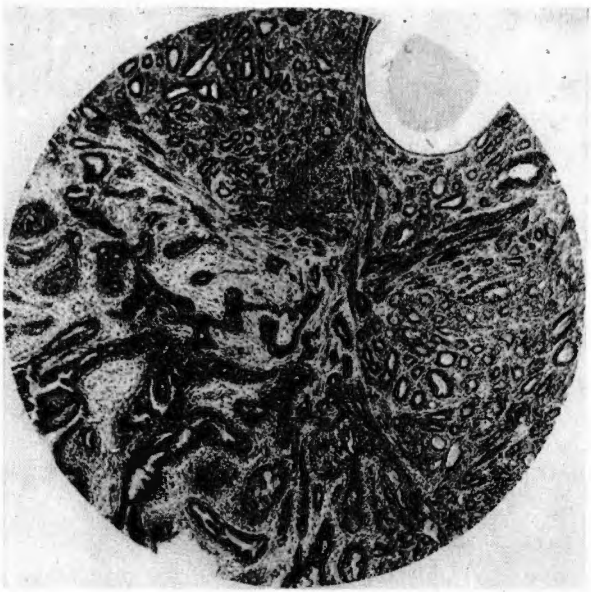


FIG. 500. Adenocystic basal-cell cancer arising in sweat-gland adenoma.

Adenocystic Basal-Cell Cancer

The basal-cell cancers of the skin which are adenocystic in type are subepidermal lesions arising from appendages of the skin such as the sudoriferous or salivary glands or the pilosebaceous apparatus. It is, therefore, not unlikely that the rare intramammary basal-cell cancers are of sweat-gland origin.

The adenocystic basal-cell cancers studied by the author have all been in patients in their middle forties. The tumors were sharply circumscribed, varying from 2.5 to 6.0 cm. in diameter and contained micro- or macroscopic cysts. Involvement of the regional lymph nodes did not occur, and so far, none of these cases has had a fatal termination. Three were treated by wide excisions and the other by radical mastectomy. The latter is the preferred method of treatment.

The histories of the four cases of intramammary basal-cell cancer in our series (see Figs. 500-502) follow.

Case 1. Patient referred by Dr. C. E. McLeod, Middletown, Conn. A

FIG. 501

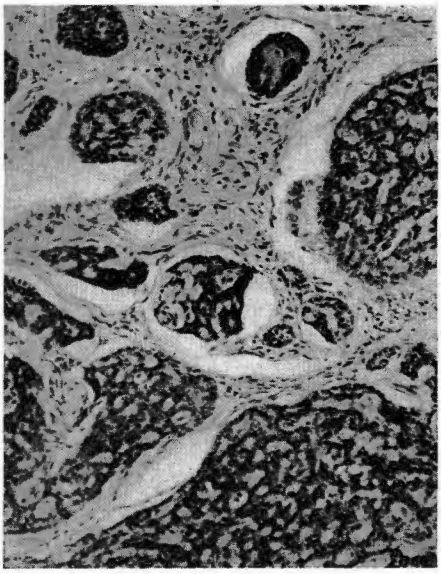


FIG. 502

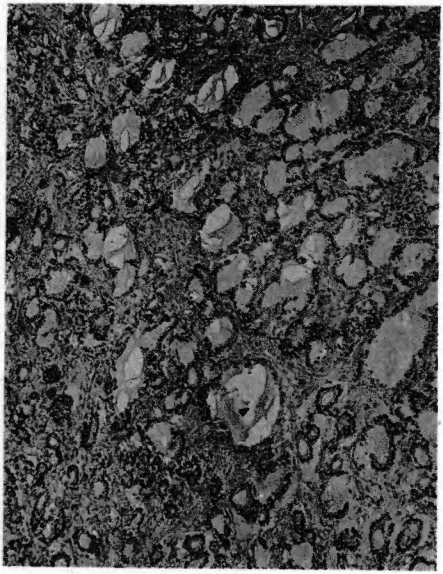


FIG. 501. Intramammary adenocystic basal-cell cancer. Photomicrograph of a tumor treated by excision and postoperative irradiation. The patient was reported well 6 years later.

FIG. 502. Photomicrograph of a basal-cell mammary tumor treated by simple excision. The histology suggests an adenoma of the parotid gland.

FIG. 503

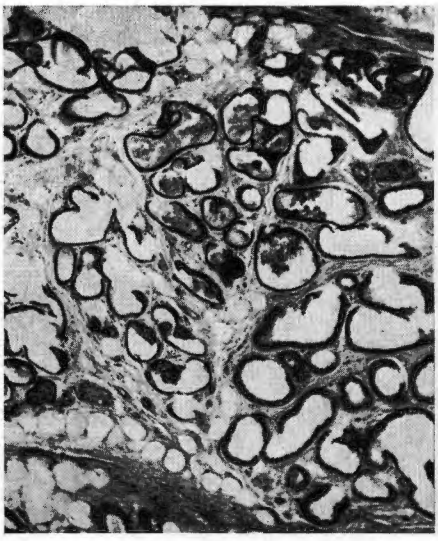
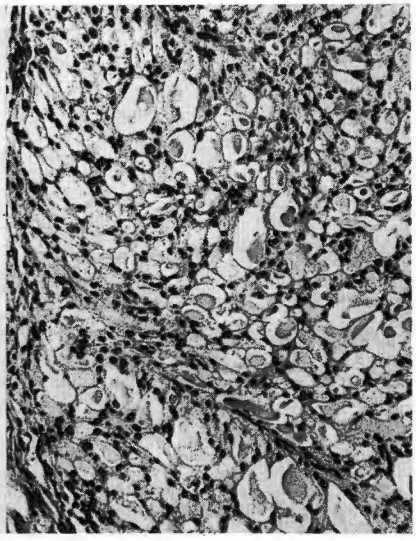


FIG. 504



Sweat-Gland Tumors of the Axilla.
FIG. 503. Photomicrograph of a cystadenoma of the eccrine or exocrine type.
FIG. 504. Photomicrograph of low-grade adenocarcinoma of the apocrine type.

FIG. 505

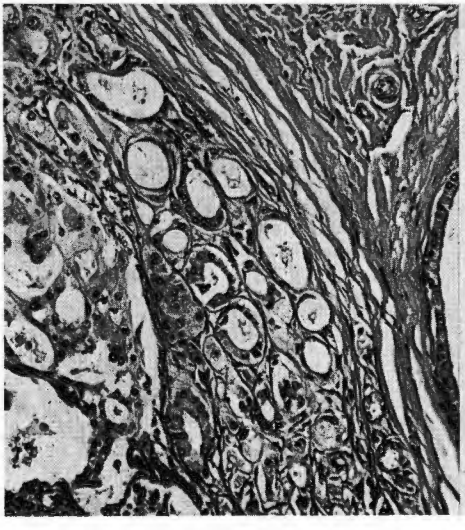


FIG. 506

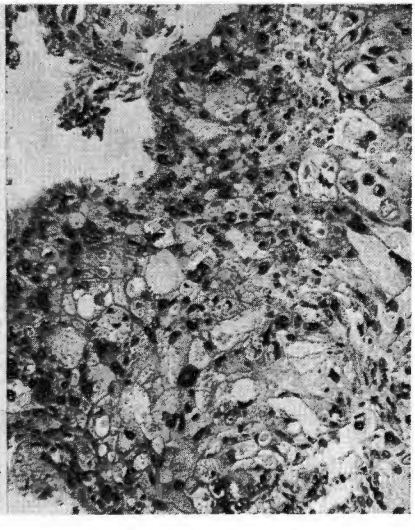


FIG. 505. Photomicrograph of sweat-gland metaplasia in the epithelium of a benign fibro-adenoma.
FIG. 506. Photomicrograph of a sweat-gland cancer showing the large pale eosinophilic cells characteristic of these tumors.

woman, 46 years old, had a freely movable mass 6.0 cm. in diameter of 11 years' duration in the lower outer quadrant of the left breast. Simple excision was performed in October, 1940. The excised tumor was completely encapsulated and lobulated. Further treatment was refused. The section showed a typical adenocystic basal-cell cancer.

Case 2. No. 56134—Patient referred by Dr. L. A. Keasby, Lancaster, Pa. A woman, 46 years old, had a lump, 3.5 cm. in diameter, of one year's duration deep in the central zone of the right breast. Biopsy and radical mastectomy were performed in February, 1935. The tumor was circumscribed and contained one small cyst. Microscopically, it was a typical adenocystic basal-cell cancer. The patient was well in 1940.

Case 3. No. 39095—A woman, 46 years old, had a tumor excised from her breast elsewhere. The specimen contained an encapsulated tumor mass 5.0 cm. in diameter. The tumor was soft and spongy, and on section was of a slaty black color. The gross diagnosis suggested hemangioma. The microscopic preparations showed an adenocystic basal cell cancer. No follow-up report was available.

Case 4. No. 35154—A woman, 44 years old, had a mass 2.0 cm. in diameter in the upper outer quadrant of the left breast. It was freely movable. A wide excision was done in April, 1924. Postoperative irradiation was given. The microscopic structure showed a typical adenocystic basal-cell cancer. The patient was well in 1930.

SWEAT-GLAND CANCERS

As previously pointed out in Chap. 15, both eccrine and apocrine sweat-gland tumors may be found in the breast. Adenomas of the eccrine gland occur superficially in the region of the areola and cystic tumors or intracystic papillomas of the apocrine types are found beneath the nipple or areola. Both types of tumors, however, in the author's experience are more common in the axilla without relation to mammary tissue. (Figs. 503, 504.) Malignant tumors of the eccrine sweat glands are of the basal-cell type. The adenocystic basal-cell cancers just described probably arise from these structures. Sweat-gland cancers arising in the apocrine glands are composed of large eosinophilic or pale cells often associated with large droplets of coagulated secretion. Some of these cancers arise in pre-existing sweat glands which are found in a superficial location in the breast in the region of the nipple, in the submammary fold or in the axillary prolongation of the gland. Other cancers histologically resembling this group are neomammary cancers with a tendency to differentiate sweat-gland structures. (See Chap. 24.)

There were but three sweat-gland cancers in our series which were microscopically identical with extramammary cancers of the apocrine glands. Two of these occurred in the lower hemisphere and the third was near the axillary border. These are cases, numbers 60118,

TABLE LXXXI
INTRAMAMMARY SWEAT-GLAND CANCERS

PATH NO.	AGE	DURATION	SIZE	LOCATION	OPERATION	PATHOLOGY	RESULT
57549	40	9 mos.	8.0 cm.	U.O.Q.[1]	C.C.[2], 1934 Recurrence, irradiated 1936	Fibro-adenomatous reaction	Well 5 yrs.
48918	50	3 mos.	3.0 cm.	Central	C.C., 1932	Glandular	Dead, metastasis to liver 5 yrs. later
46277	61	1 mo.	3.0 cm.	U.I.Q.	C.C., 1929 Recurrence, 1930, radium	Glandular	Dead after 2 yrs.
40422	55	5 mos.	3.0 cm.	Submammary fold	C.C., 1928	Glandular, invading sweat glands	Well 7 yrs.
60118	51	2 mos.	2.0 cm.	Submammary fold. 2 lumps, bilateral	C.C., 1939 Other breast amputated 2 yrs. previously	Glandular, vascular, invading sweat glands	Well 2 yrs. later
39261	51	1 yr.	5.0 cm.	U.O.Q.	C.C., 1926	Secretory type	Well 7 yrs.
37342	61	4 yrs.	5.0 cm.	Central	C.C., 1925 Recurrence, 1927	Fibro-adenomatous reaction	Dead 2 yrs. later
36677	42	2 mos.	5.0 cm.	Submammary fold	C.C., 1925	Circumscribed, translucent in appearance	Well 6 yrs.
31280	37	1 yr.	0.5 cm.	Lower hemisphere, 2 lumps	Excision, 1920. C.C., 1922	Fibro-adenomatous reaction	Dead 2 yrs. later
27575	60	10 mos.	5.0 cm.	Central	C.C., 1921	Hard, circumscribed adenomatous arrangement	Well 5 yrs.
24175	38	14 mos.	3.0 cm.	Submammary fold	C.C., 1919 Excision 2 yrs. previous	Dermoid cyst, also present	Well 13 yrs.
22509	53	2 mos.	3.0 cm.	U.O.Q.	C.C., 1917	Cystic type	Well 8 yrs.
16474	36	5 mos.	5.0 cm.	Central	C.C., 1914	Glandular	Well 6 yrs.
14805	35	2 mos.	6.0 cm.	U.O.Q.	C.C., 1913	Cystic, papillary	Lost

[1] U.O.Q. = upper outer quadrant.
[2] C.C. = radical mastectomy.

40422 and 14805 in Table LXXXI. The remaining cases were selected from the neomammary cancers described in Chap. 24, and showed histologic gradations relating them unmistakably to that group of tumors. As a subgroup, however, they have certain pecu-

FIG. 507 FIG. 508

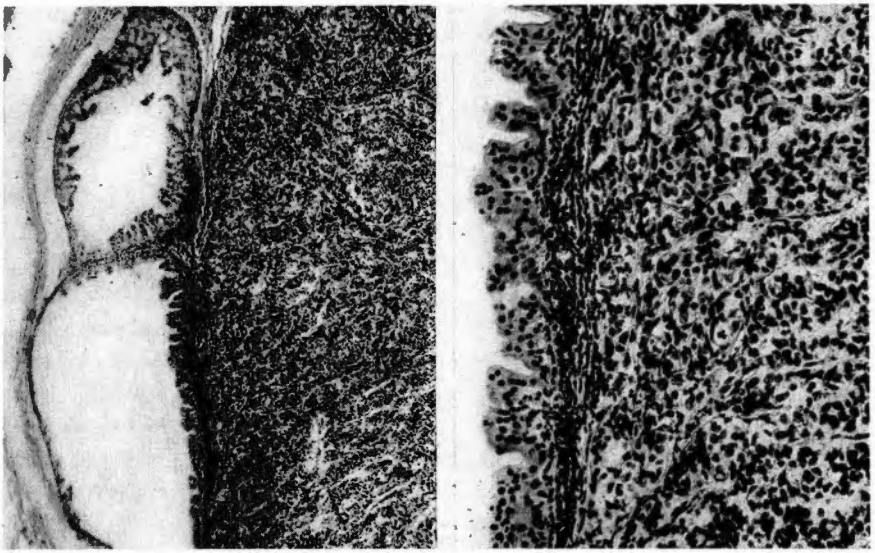


FIG. 507. Intramammary sweat gland cancer. Low power photomicrograph.
FIG. 508. High power photomicrograph. A portion of the persisting sweat gland is shown in the upper portion of both photomicrographs.

liarities which warrant a description of them in connection with tumors of the sweat-gland group.

Pathology

The peculiarities of the 14 cases of sweat-gland cancer in our series were: the variable age distribution (35 to 61 years); the number of cases found in the lower hemisphere or submammary fold; the soft or cystic character of some of these growths; and the good prognosis despite the malignant microscopic features (there were 67 per cent of five-year survivals). Two patients had several discrete lumps, and in one both breasts were affected.

With one exception, the tumors were located in the central zone, the axillary tail of the breast, or the lower hemisphere. The duration of symptoms did not differ from ordinary mammary cancer. The tumors were circumscribed but not encapsulated and had either a

yellowish or translucent appearance on section. Three were cystic and another was associated with a dermoid cyst.

The tumors in this group were selected on the basis of their microscopic features. Three cases showed characteristics identical with sweat-gland tumors found in the axilla or elsewhere in the skin of the body. These features included: (1) invasion of preformed sweat glands; (2) a vascular or cystic arrangement in which small cells formed papillary projections into the fluid or vascular filled cavities after the manner of sweat-gland tumors; (3) hydropic degeneration of

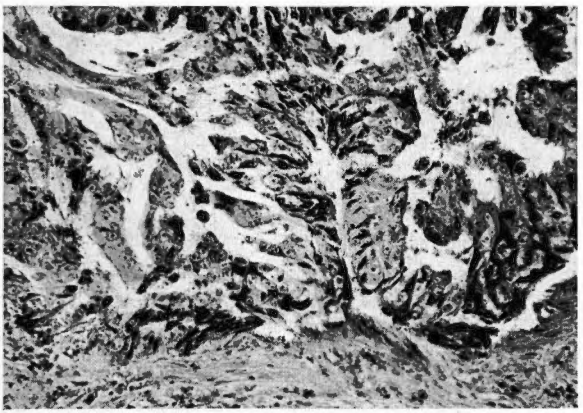


FIG. 509. Neomammary (medullary) cancer with sweat gland features. The photomicrograph shows characteristic alveoli composed of large eosinophilic cells. Note the myofibrils in the stroma of the tumor at the bottom of the picture.

cells with secretory droplets; (4) the formation of alveolar glandular structures lined by several layers of large pale cells with pleomorphic nuclei resting on a basement membrane of smooth muscle. The remaining 12 cases show distinct glandular arrangements with the characteristic large, pale cells but show transitional features toward neomammary cancer. Some of these growths showed a peculiar fibromyxomatous reaction in the adjacent mammary lobules. (Fig. 500.)

Treatment

All of our patients were treated by radical mastectomy which is the treatment of choice since there is no data regarding the radiosensitivity of these growths. The axillary lymph nodes were involved in the majority of the cases. Eight patients remained well beyond the five-year period. One died from metastasis five years after operation, three were dead from the disease within two years, and the other two cases have been insufficiently followed.

TUMOR FORMATION IN SUPERNUMERARY BREASTS

It is customary to draw a distinction between supernumerary breasts, which have either nipple and areola (or both) in combination with persistent or atrophic gland tissue, and aberrant breast tissue which is without nipple or areola. The frequency and distribution of supernumerary breasts and the variable structure of these accessory organs have been discussed in Chap. 1. Speert, in his recent review of the subject, questions the statement found in the older literature that tumor formation is relatively more common in the supernumerary breast than in the normal organ. De Cholnoky also states that "there is no evidence that carcinoma develops more frequently in these formations than in normal breasts." Recent studies corroborate the observation of Matti that aberrant axillary mammary tissue but not supernumerary breasts are more prone to malignant change than the normal. Tumor formation may be found in the supernumerary breasts when glandular tissue is present but is more frequent in aberrant mammary tissue.

The cases of tumor formation in accessory breasts and mammary tissue reported in the literature were collected in 1929 by Razemon and Bizard. These authors list 43 cases of carcinoma, 28 of which were in the axilla and 23 cases of benign tumor of which 19 also had an axillary location. Biancheri, in 1932, was able to collect only 31 cases of cancer. He considered some of the reported cases unproved since a connection between the normal breast and the axillary tissue was not eliminated with certainty.

Pathology

The most common tumors found in aberrant or accessory breasts are fibro-adenoma and carcinoma. In the author's material there is one case of fibro-adenoma occurring in a supernumerary breast in the groin. This was in a woman, 42 years old, who was operated upon under the clinical impression of fibrosarcoma. White reported a fibro-adenoma excised from one of two supernumerary breasts located beneath the normal breast. Pattarin removed a myxomatous fibro-adenoma from an accessory breast over the left seventh chondrosternal articulation. The tumor had grown to the size of a large nut in four months. A tumor of similar histology was excised from the axilla by Palumbo. Similar cases were excised from the vulva by Friedel and also by Roth. Noronha has reported cystic disease in axillary breast tissue, and Searcy and Pack reported an adenofibroma

developing in a paramammary lobule below, but not connected with, the right breast.

Carcinoma is more frequent than benign tumor formation in aberrant mammary tissue. It is usually found only in proximity to the normal breast, that is, in the axilla, sternal or clavicular regions. Patel and others, however, have reported a carcinoma of the vulva developing in a supernumerary breast in that location. Supernumerary breasts are more than twice as frequent in women as in

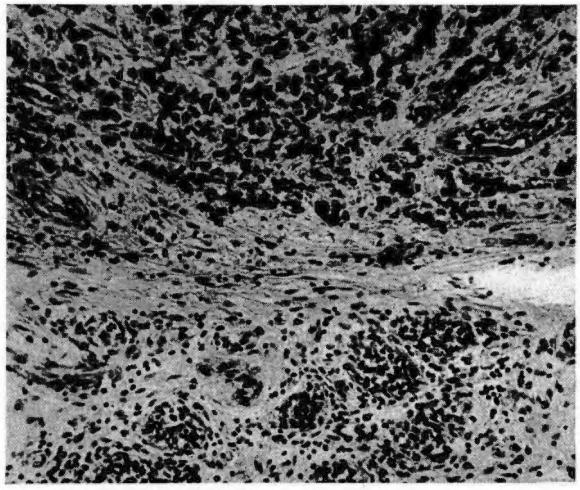


FIG. 510. Cancer arising in aberrant axillary mammary tissue. The photomicrograph shows the margin of an infiltrating lobular cancer.

men, and neoplasms in such formations are far more common in women than in men.

In the author's series there were seven cases of cancer in aberrant breast tissue. (Table LXXXII.) All of them occurred in the axilla of women. The youngest patient was 39 and the eldest 67 years old. With one exception, the duration of symptoms was between four and 24 months. A swelling, tenderness, and pain or discomfort in using the arm were the chief symptoms noted. The tumors varied between 2 and 8 cm. in diameter and occupied a zone of fat or thickening in the axilla with or without adjoining swellings produced by enlarged and indurated axillary lymph nodes. The initial treatment in four of the seven patients was simple excision. This was followed by irradiation in two patients who refused the radical operation. In the other patients radical mastectomy was performed with dissection of the axilla, but in one instance not until the tumor had recurred. The four adequately followed died from the disease.

TABLE LXXXII
CANCER IN AXILLARY BREASTS

PATH NO.	AGE	DURATION	SIZE	OPERATION	MICROSCOPIC	REMARKS	RESULT
32885	60	1 yr.	2.5 cm.	Exploration. Radium. Radical mastectomy, 5–2–23	Scirrhous	Breast negative	Signs of metastasis, 1–17–24
29712	67	2 yrs.	2.0 cm.	15 years ago excision of benign tumor, left breast 3–2–22, excision axillary tumor. C.C.[1] advised, but refused	Scirrhous	Breast negative	
25390	55	8 mos.	8.0 cm.	C.C. 10–10–19	Medullary	Breast negative. Supraclavicular glands positive	Dead, metastasis 3–26–20
22504	42	6 wks.	6.0 cm.	7–10–17, excision. C.C. 11–30–17	Schirrhous	Breast negative. Axillary glands positive	
22316	42	4 mos.	3.0 cm.	2–1–15, excision. P.O.[2] irradiation	Adenocarcinoma	Breast negative. Axillary glands positive	Dead, metastasis 4–4–20
20022	39	16 mos.	3.0 cm.	10–10–15, excision. Recurrence in scar. C.C., 5–6–16	Medullary	Breast negative. Axillary glands positive	Recurrence and death, 12–6–16
16282	46			1–15–14 C.C.	Medullary	Breast negative	

Mass, tenderness, pain on use of arm; axillary or supraclavicular nodes are involved, the breasts are rarely involved. There are none in our series. Tumor may be on axillary vessels but no edema of arms occurred.

[1] C.C. = radical mastectomy.
[2] P.O. = post operative.

one slightly beyond the five-year period, the others within a period of about a year. Three of the cases were classed as infiltrating scirrhous cancer (Fig. 510), three as medullary or neomammary cancer, and one as adenocarcinoma or sweat-gland cancer. The interesting pathologic feature is the relative frequency with which the primitive form of neomammary cancer is found in the section. In all the cases submitted to the complete operation, the tumor had infiltrated the axilla, but the breast was negative.

Treatment

Excision is indicated when tumor formation is present in supernumerary breasts. When the diagnosis of cancer is made in aberrant axillary breast tissue, the radical mastectomy should be performed. Experience has shown that primary axillary cancer may extend into the mammary gland or a minute primary tumor which escapes clinical observation may be responsible for the axillary growth. (See Part VI.)

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27

Carcinoma and Other Tumors of the Male Breast

Tumors of the male breast are far more infrequent than those in the female gland, but the variety found is nearly as great. The exceptional conditions not found in the male breast are mammary dysplasia, which is related to ovarian dysfunction, and the abnormalities arising during lactation. The two most common conditions are fibro-adenomatous hypertrophy, or gynecomastia, and carcinoma. Menville, in 1933, reviewed gynecomastia in the male breast, and Wainwright, in 1927, collected the cases of carcinoma reported to that date. A more recent study was contributed by Gilbert, in 1933. In 1930, Neal and Simpson reviewed a large variety of benign and malignant conditions, and in 1934, a similar study was published by Moore. In 1941 Sachs, through a questionnaire sent to the physicians of United States and Canada, collected 205 cases of cancer in the male breast with pathologic data on 178, and also found 172 cases reported in the literature excluding those of Wainwright and the series of Gilbert. Sachs found mammary cancer to constitute 0.38 per cent of malignancies in men and estimated its frequency to be 1.32 per cent of the incidence of mammary cancer in women. In the

entire series the average age was 57.17 years and the average duration of symptoms was 1.14 years. Axillary nodes were present at the initial examination in 48.3 per cent. The predominant pathology was adenocarcinoma (40.7 per cent) and the per cent of five-year survivals for 205 followed cases was 47.8 per cent.

In our records there are 150 cases of benign and malignant lesions of the male breast as compared with 5,855 cases in the female gland; a ratio of approximately 1:40. There are 108 cases of fibro-adenomatous hypertrophy or gynecomastia, 30 cases of mammary cancer and 3 sarcomas. The 9 remaining cases were: infections including chancre 5, lipoma 2, papilloma 1, and dermoid cyst 1. The incidence of diseases of the male breast in our series corresponds with that reported by Neal and Simpson. These authors studied a series of 152 cases involving the male breast in a total series of 5,314 cases of diseases of the breast; for distribution see Table LXXXIII.

In a larger series reported in 1933, Neal found that 30 per cent of tumors of the male breast were carcinomatous; 6 per cent, sarcomatous; and the remainder, benign.

TABLE LXXXIII

LESIONS IN THE MALE BREAST REPORTED BY NEAL AND SIMPSON

Pyogenic mastitis	4
Cysts	3
Hypertrophic mastitis (gynecomastia)	46
Fibro-adenoma	51
Lipoma	6
Benign papilloma	1
Sebaceous adenoma	1
Lymphangioma	1
Mammary carcinoma	25
Skin cancer	3
Mammary sarcoma	7

BENIGN CONDITIONS OF THE MALE BREAST

Chronic Mastitis and Fibro-Adenoma

Fibro-adenomatous hypertrophy is the most common lesion of the male breast. The 108 cases in our series have been discussed under the heading Gynecomastia in Chap. 4. When enlargement results in a diffuse, tender swelling, the condition is often regarded as mastitis, which is incorrect from the standpoint of pathologic and endocrine studies. Hence, the 46 cases reported by Neal and Simpson have been listed as gynecomastia in the above tabulation although they were originally tabulated as chronic mastitis. Neal and Simpson were aware of the unsatisfactory diagnostic terms used for this condition

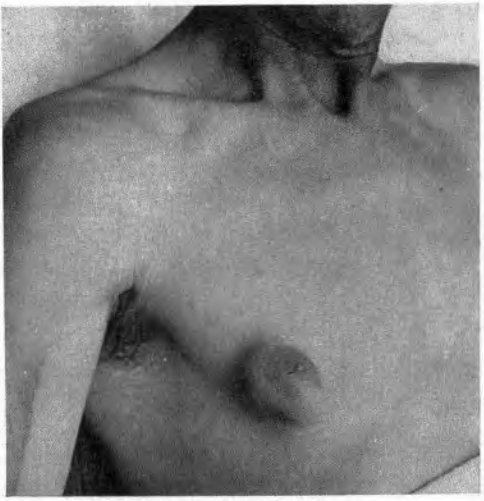

FIG. 511. So-called fibro-adenoma of the male breast. The photograph shows a circumscribed discrete swelling in a man of 48 years. The patient has remained well 8 years following excision.

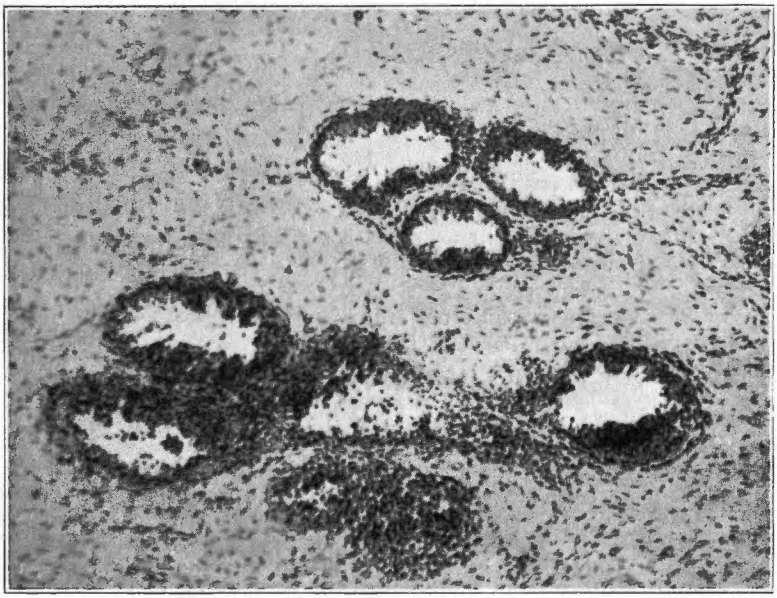

FIG. 512. Photomicrograph showing the histology of the lesion in Figure 511.

which included "chronic mastitis," "chronic interstitial mastitis," "chronic lobular mastitis," "chronic proliferative mastitis," "chronic productive mastitis," "chronic hypertrophic mastitis," "chronic indurative mastitis," "chronic sclerosing mastitis," "chronic diffuse interstitial mastitis," and "chronic induration of the breast." When occurring at puberty the condition is often incorrectly referred to as adolescent mastitis. On the other hand, when fibro-adenomatous hypertrophy of the male breast results in a discrete nodular swelling, the lesion is usually classed as benign fibroma or fibro-adenoma. In the author's series of 108 cases of gynecomastia, a discrete mass was palpated in 82 of the patients. Since on microscopic examination such a mass is made up of a growth of ducts and periductal fibrous tissue, classification of the lesion as fibro-adenoma is not without justification. (Figs. 285, 511, 512.) Thus, Neal and Simpson grouped 45 of their cases as fibro-adenomas and 6 as fibromas although the fibromas contained "rudiments of epithelial elements" microscopically. Our 82 cases of fibro-adenomatous hypertrophy which gave a discrete mass on palpation have been grouped with the cases of more diffuse hypertrophy, under gynecomastia (Chap. 4).

Infectious Mastitis and Cysts

Infectious mastitis or abscess in the male breast is rare, but may result from trauma or complicate systemic infectious diseases such as typhoid fever, mumps, septicemia, syphilis or tuberculosis. Neal and Simpson report 4 cases of pyogenic abscess with necrosis and suppuration. Only one case with acute abscess formation following a blow to the breast was recorded in our series. The four remaining cases were chronic infections, one a chancre in a man of 75, another a periductal mastitis associated with gynecomastia in a boy of 14, and the other two were infections of undetermined origin in adults. Moore reports a case of tuberculous mastitis occurring in a man of 33 years who had pulmonary involvement. Smith and Mason reported a similar case and reviewed the literature. Infections in the male breast, unless accompanied by abscess formation, cannot be distinguished clinically from early carcinoma or from gynecomastia. Surgical excision, therefore, is the treatment of choice, since by this means both diagnosis and cure may be established.

Cysts of the male breast are extremely rare. Neal and Simpson who list three cases within the breast proper state that they may be the result of involutional changes in a fibro-adenomatous hypertrophy or the end stages of chronic infection which has stenosed the ducts. There is one case of epidermoid cyst in our series, and Neal and Simpson report a case in which such a cyst was attached to the skin. These cysts may be adequately treated by simple excision.

Papilloma

In cases of gynecomastia, minute intracystic papillomas may be found in the large ducts. (Fig. 513.) Larger growths may give rise to papillary carcinoma. Benign intracystic papillomas of a palpable size are extremely rare, however. The author has observed but a single case in a man of 42 years. Angerer has reported a similar case.

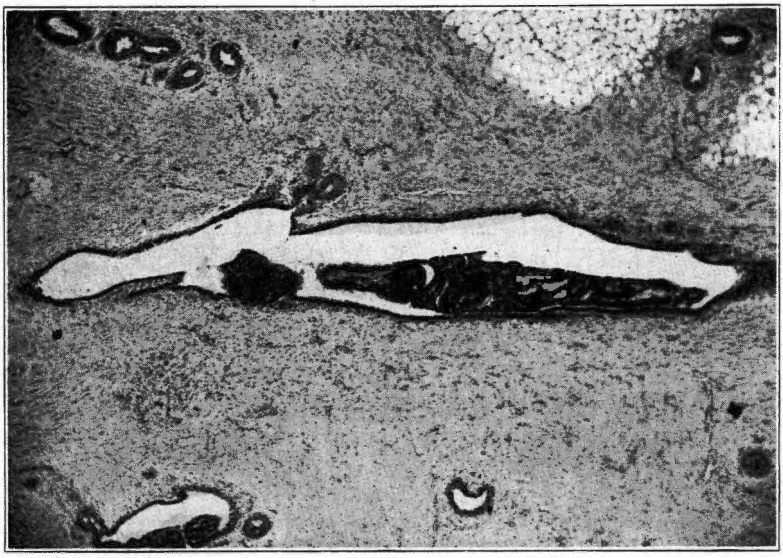

FIG. 513. Minute intraductal papilloma occurring in gynecomastia. This lesion was excised from a colored man of 33 years who had a nodular mass in the left breast of 3 years' duration.

A large papilloma of the nipple the size of a tongue, which was successfully excised, has been reported by Duncker. The tumor was of four years' duration and had a slight ulceration on its surface but was histologically benign.

Lipoma

If the fibro-adenomatous nodules resulting from gynecomastia are excluded, the lipoma is the most common benign tumor of the male breast. Neal and Simpson record 6 cases, one of them complicated by fat necrosis. White has reported a case, and there are two such cases in our records. In both, discrete tumors were palpated. In one instance, two distinct tumor masses were found. (Fig. 514.)

Hemangioma and Lymphangioma

Both hemangioma and lymphangioma of the male breast have been described. Neal and Simpson report a lymphangioma, and

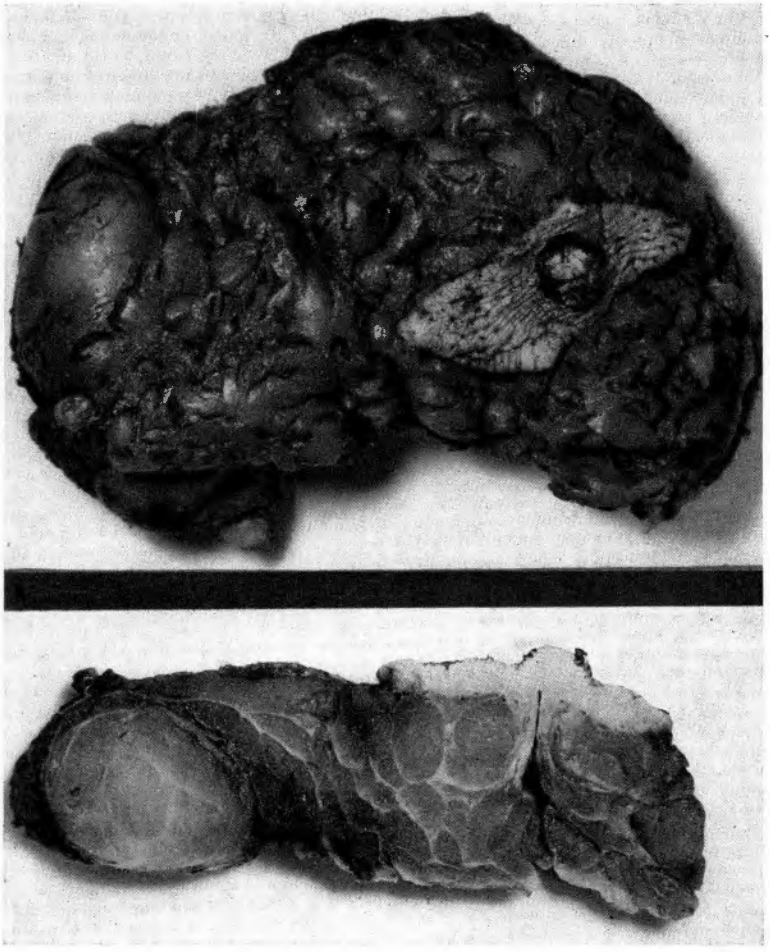

FIG. 514. Lipoma of the male breast. Because of the keratotic changes in the nipple shown in upper photograph the clinical diagnosis was Paget's disease. The benign encapsulated lipoma is distinctly shown in the lower photograph. The patient was 45 years of age at the time of the excision, and was well 13 years later.

Johnston has recorded a capillary hemangioma 4 cm. in diameter which was excised from a man of 51 years. These patients remained well following excision.

Treatment

The treatment of gynecomastia has been discussed in Chap. 4. Simple excision is indicated for other benign lesions of the male breast.

CARCINOMA OF THE MALE BREAST

Carcinoma of the male breast is a rare disease and comprises about 0.1 per cent of all malignancy. Only 30 cases were recorded in our series during the time that 2,524 cancers of the female breast were observed. Wainwright, in 1927, collected 418 cases. In addition to isolated case reports, a series of patients have been reported since by Neal and Simpson, by Gilbert, by Moore and by Sachs. In the large group of cases reviewed by Wainwright, the average age of the patients was 54.2 years which is approximately 4 years later than for female mammary cancer. The youngest patient was 22, the oldest 91 years. The duration of symptoms averaged 29 months (the average is 11 months in women). Involvement of the axillary lymph nodes was recorded in 69 per cent of these cases.

Because of the smaller amount of fatty stroma and glandular tissue in the male, ulceration of skin and symptoms referable to the nipple were more frequent. (Figs. 515, 517.) Ulceration occurred in 38 per cent of the cases reviewed by Wainwright. A bloody discharge from the nipple was relatively more common and a higher percentage of cases were reported as Paget's disease because of involvement of the nipple. Pain and trauma were more often given as symptoms of onset, probably because men are prone to disregard the significance of early changes in this organ. The pathologic varieties of mammary cancer corresponded to those found in the female breast. Infiltrating lobular cancer (scirrhous carcinoma) was the most common form, but the percentage of the circumscribed forms of adenocarcinoma (21 per cent) was approximately twice as high as in the female breast, and squamous-cell cancers (related to primitive structures of the nipple pouch) were relatively more common (approximately 9 per cent).

Despite the greater number of circumscribed cancers of a low degree of malignancy, the prognosis was poorer in men than in women, the five-year survivals comprising only 19 per cent of the 163 cases followed. This is not true of the recently treated cases. Sachs reports 47.8 per cent survivals.

FIG. 515

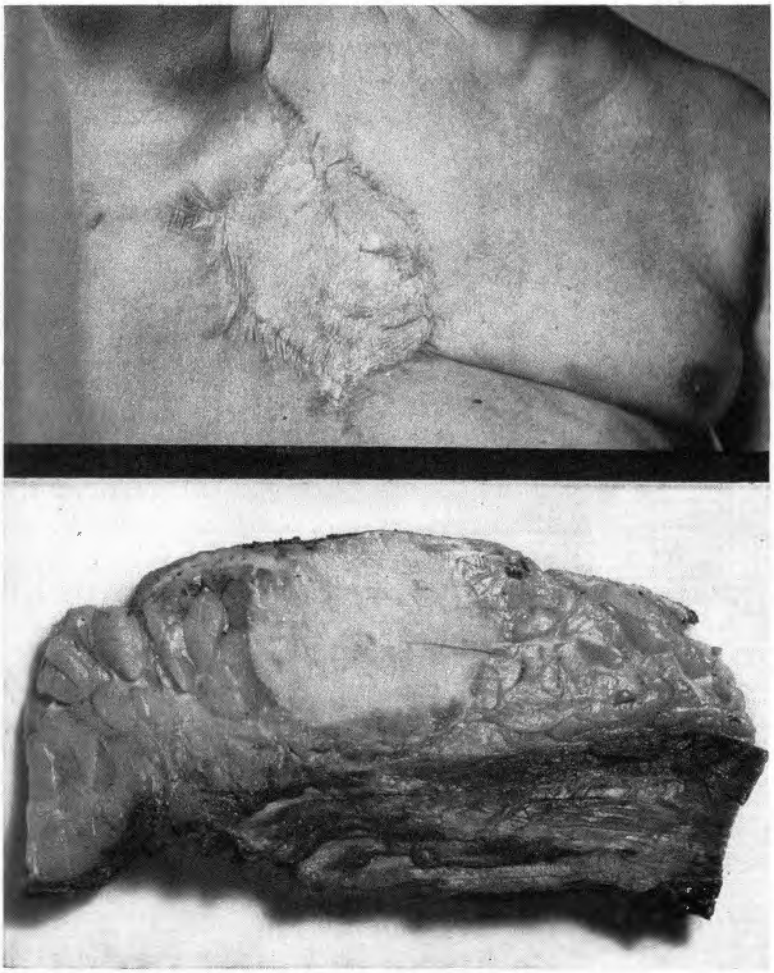

FIG. 516

Infiltrating Lobular (Scirrhous) Cancer in a Colored Man Aged 56.

FIG. 515. The patient had a pre-existing, bilateral gynecomastia. The scar following operation is shown.

FIG. 516. Gross specimen showing the infiltrating character of the cancer. The patient died 6 years after the radical mastectomy from metastasis.

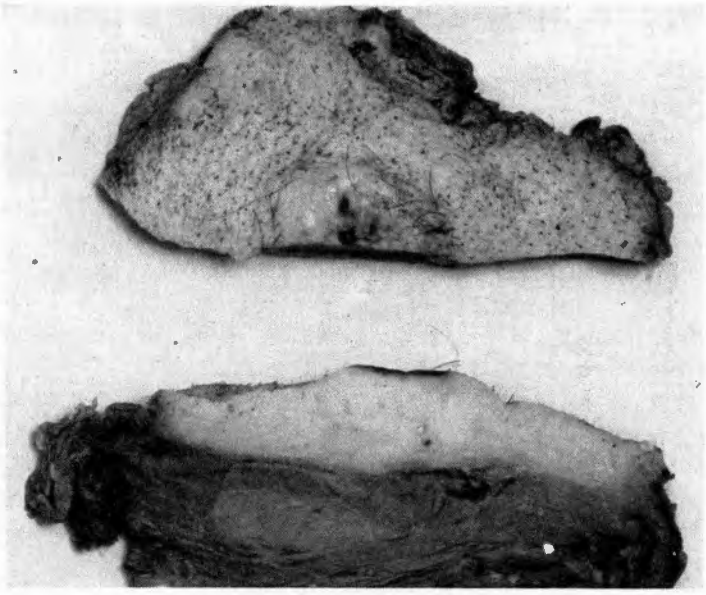

FIG. 517. Duct cancer of the male breast. The gross specimen shows the infiltrating character of the lesion which has produced ulceration of the nipple.

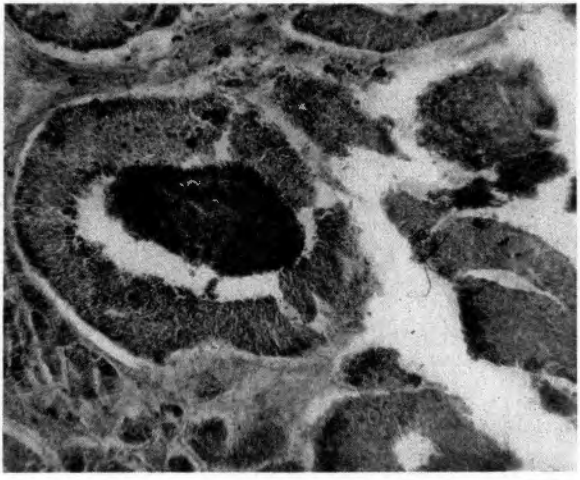

FIG. 518. Photomicrograph of the duct cancer of the male breast shown in Figure 517.

The observations of Wainwright are corroborated by a study of the 30 cases in the author's series. Sixty per cent of the patients were between 50 and 70 years, 20 per cent under 50, and 20 per cent over 70 years. In 18 patients the duration of symptoms was one year or less, in 12, more than a year, and in one-half of the latter group the duration was 3 or more years. The patients were evenly divided between those in which a mass was the symptom of onset and those in which changes in the nipple were first noted. The nipple changes included retraction, scaling and soreness, discharge (usually bloody), and ulceration in the order of frequency given. (Figs. 517, 518.)

The findings on examination in mammary cancer in the male are similar to those in cancer of the female breast. Because of the smaller size of the gland the mass is usually near the nipple. Although frequently movable on the deeper structures, it often is attached to the overlying skin which is usually dimpled, thin and shiny, discolored or ulcerated. The size of the growth varied between 1.5 and 7.0 cm.

Differential Diagnosis

Mammary cancer of the male must be differentiated from gynecomastia, from benign tumors such as lipoma, dermoid cysts and papilloma and from chancre of the nipple.

From Gynecomastia. Gynecomastia in our experience is three times as common as cancer of the male breast. When the swelling is diffuse and when it is bilateral, or when it occurs in adolescent boys under 21 years, the clinical diagnosis is relatively certain and biopsy is rarely necessary. In men in middle life and beyond, the hypertrophy or gynecomastia may give rise to a discrete nodule often classed as fibro-adenoma. The tumor in such cases does not have the hardness of cancer and is not attached to the overlying skin. It does not produce dimpling or retraction of the nipple which occurs relatively early in cancers of the male breast. Nevertheless, it is a safe rule to excise such discrete nodules, since this is the most effective treatment for discrete gynecomastia and permits accurate diagnosis. In all cases of mammary enlargement in the male, the testes must be carefully examined to rule out the possibility of teratoma which is at times responsible for an endocrine disturbance resulting in gynecomastia.

From Benign Neoplasms. Benign neoplasms which give rise to a discrete nodule in the male breast are excessively rare. Intracystic papilloma, lipoma, and benign epidermoid cysts may occur. Any such discrete nodule should be treated by excision and the diagnosis established by pathologic study. Ulceration of the nipple with the clinical picture of Paget's disease may result from invasion of the nipple by

mammary cancer in the male breast. Operation should not be performed without waiting for a serologic report to rule out syphilis.

From Sarcoma. Sarcoma of the male breast produces a hard infiltrating mass similar to that found in mammary cancer. Usually, younger individuals are affected. Sarcoma is far rarer than mammary

FIG. 519 FIG. 520

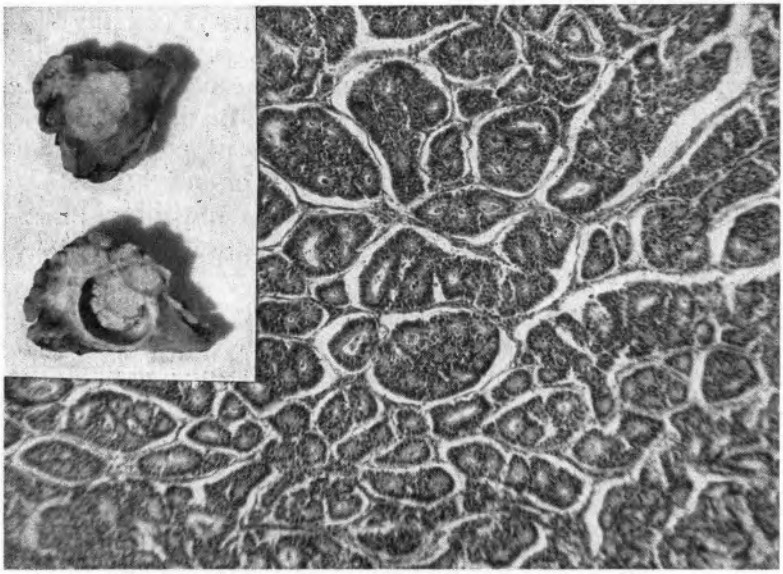

FIG. 519. Papillary adenocarcinoma of the male breast. Gross specimen showing the intracystic character of the growth.
FIG. 520. Photomicrograph showing the adenomatous character of the tumor.

cancer; only four cases are recorded in our series. The differential diagnosis can be made only under the microscope.

Pathology

The majority of cancers in the male breast like those in the female are hard, infiltrating growths, with attachment to the skin and invasion of the neighboring fat and subcutaneous tissue. Two-thirds of the cases in the present series were described as infiltrating. Some of these, microscopically classed as infiltrating lobular cancers, resembled Paget's disease in the gross because of the proximity to and invasion of the nipple, but no case of typical Paget's disease was reported. Typical Paget's cancers of the male breast have been reported by Rubenstein, by Handley, and by Archibald, however.

Several of the infiltrative growths produced plugging and distention of the large ducts and on microscopic examination were duct cancers. One-third of the growths were circumscribed. A few of these were

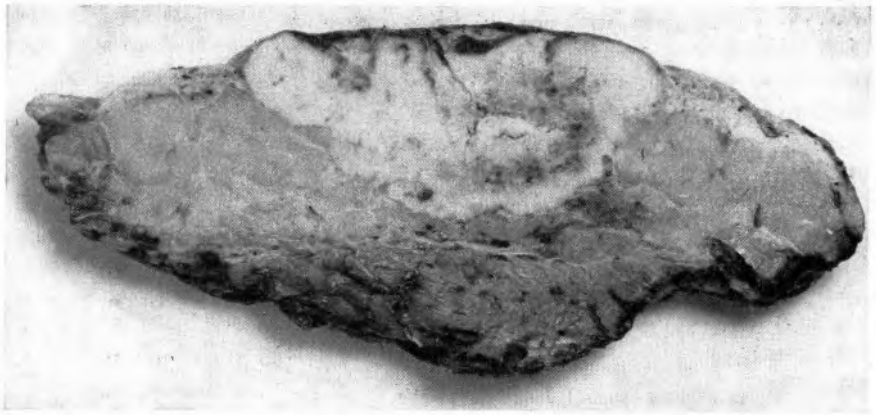

FIG. 521. Gross specimen of neomammary cancer of the male breast.

intracystic papillary tumors. (Figs. 519, 520.) Others were typical comedo carcinoma. Two were solid, circumscribed, medullary tumors (neomammary cancers). (Figs. 521, 522.)

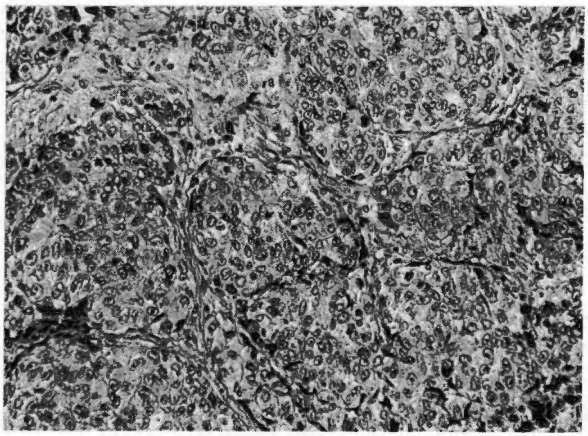

FIG. 522. Photomicrograph of the neomammary cancer shown in Figure 521.

Microscopic study of the cancers in our series indicates that infiltrating lobular cancers which comprise 70 per cent in the female comprise only 50 per cent of cancers in the male breast. Comedo cancer, papillary adenocarcinoma, duct cancer composed of transitional cells and neomammary cancer are relatively more frequent

as shown in the following table. This is to be expected, since under normal conditions the male breast is practically devoid of lobular elements and the nipple and the large ducts (which are partially derived from the primitive nipple pouch) constitute the major epithelial structures.

TABLE LXXXIV

PATHOLOGIC VARIETIES OF CANCER OF THE MALE BREAST

Infiltrating lobular cancer	14 cases[1]
Comedo adenocarcinoma	5 "
Papillary adenocarcinoma	4 "
Transitional cell duct cancers	3 "
Neomammary (Medullary cancer)	2 "
Adenocarcinoma (sweat-gland type)	2 "
Total	30 "

[1] Two of these showed a marked alveolar arrangement, and were of a low degree of malignancy.

The pathologic forms of carcinoma of the male breast described by Wainwright in 78 cases, microscopically studied, correspond closely to those found in our material. The pathologic types, other than scirrhous cancer or carcinoma simplex, constituted 47 per cent. The additional types of cancer in Wainwright's series not represented in our cases, were gelatinous carcinoma, squamous-cell cancer and typical basal-cell epithelioma.

The Relation of Cancer to Pre-existing Benign Tumors of the Male Breast. The long duration of symptoms and slow growth of some of the cancers of the male breast suggest that the disease may arise in a pre-existing benign growth. Since gynecomastia with or without a discrete fibro-adenomatous nodule is the most common benign affection in the male breast, it is logical to assume that this condition may predispose to cancer. Malignancy was not found in the follow-up reports in our series of gynecomastia. Menville, however, found two reports of malignant change in gynecomastia. One of these was reported by Berns and another by Erdheim. In three of our 30 cases of carcinoma in the male breast, there was an associated gynecomastia. (Figs. 515, 516.) Gilbert, in 47 cases studied at the Memorial Hospital, found that cancer was associated with hypertrophied mammary glands in nine patients. Ewing believes that unusual development in the male breast regardless of its inciting cause may predispose to cancer. Circumscribed adenocarcinomas may arise from benign cystic papillomas. Wainwright has illustrated such a case and another is shown in Figs. 519, 520. It is interesting to note that papillary growths of microscopic size are frequently found in

gynecomastia. It is also probable that some of the squamous-cell carcinomas described in the male breast arose from benign epidermoid cysts.

Histogenesis of Cancer of the Male Breast. Experimental and clinical studies indicate that the rarity of cancer in the male breast, the advanced age at which it arises, the relatively slow growth of many of these tumors, and the relative frequency of unusual pathologic forms are all related to the absence of intense endocrine stimulation by the ovarian hormones. In male mice and rats, whether castrated or noncastrated, mammary cancer arises in the same frequency as in the female if intense estrogenic stimulation is applied (see Chaps. 33, 34). The author has been able to show in the rat, when daily doses of estrogen at the upper physiologic levels are administered for periods of 10 to 20 months, that mammary cancer appears more quickly in response to cancerogenic dosage. It is apparent, therefore, that whether or not the ovarian hormones play a role in precipitating the cancers that arise in the female breast after the menopause, they are nevertheless responsible for the increased susceptibility to cancer of the female mammary gland as compared with that of the male.

The adult male breast is practically devoid of lobular structures. As previously stated this accounts for the relative frequency of cancer arising in the ducts (comedo and intraductal papillary adenocarcinoma). It also accounts for the relatively high percentage of cancers related to derivatives of the primitive nipple pouch (transitional cell duct cancers, neomammary or so-called medullary cancers and cancers of the sweat-gland type). However, the terminal tubules in the male as well as the female breast contain undifferentiated epithelium which under appropriate stimulation will produce a further ramification of ducts and at times lobular structures. This is readily demonstrated in animals by stimulation of the gland with estrogenic and luteal hormones (see Chapter 2). For this reason lobular cancers may arise from the terminal tubules of the mammary gland in the male.

Prognosis

In 1927, Wainwright was able to report follow-up data on 163 cases of which 19 per cent survived the five-year period. In our own series there are 25 cases adequately followed. Of these 17, or 68 per cent, were dead within a period of three years, two of them postoperatively. Eight, or 32 per cent, survived the five-year period. Three were well more than 10 years and five died of recurrence 6 or 7 years after radical mastectomy. In 205 cases followed by Sachs 47.8 per cent survived the 5-year period.

Treatment

A study of the methods of treatment and follow-ups in conjunction with the pathologic specimens indicates that cancer of the male breast is inherently a more favorable disease than cancer of the female breast although in the past the results of treatment have been poorer. Circumscribed neomammary cancers and low-grade adenocarcinomas are relatively more common in the male than in the female breast; the tumor is more readily accessible to palpation and more easily noticed on inspection. The results in the past have suffered from delay and from inadequate surgery. The average duration of cancer in the male at the time of treatment was more than two and one-half times that in the female. Apparently, the patient and the family physician had not been sufficiently informed in regard to the importance of early diagnosis and treatment in conditions of the male breast. In many of our cases the initial treatment was administered late and was simple excision or mastectomy without an axillary dissection. The higher percentage of local recurrences, even among those cases surviving the five-year period, indicates that insufficient amounts of skin overlying the tumor were excised.

As in cancer of the female breast, cancer in the male requires prompt and accurate diagnosis and any discrete nodule should be excised and subjected to microscopic study. If carcinoma is found, the radical mastectomy with careful axillary dissection and adequate removal of the pectoral muscles and sufficient skin should be performed. Postoperative irradiation should be given in accordance with the technic described in cancer of the female breast. If these rules are followed, the percentage of five-year survivals should surpass that obtained in cancer of the female breast. Post-operative irradiation in cancer of the male breast is indicated because of the difficulty in removing sufficient skin.

SARCOMA OF THE MALE BREAST

A variety of sarcomas of the male breast have been reported, the majority of them fibrospindle-cell and lymphosarcomas. The number of cases in the literature is difficult to estimate since cellular fibroadenomas and myxomas and anaplastic carcinomas may have been erroneously included as sarcomas in the early reports. Thus, Lee and Pack report three cases of giant myxoma of the breast in men, a form of tumor previously classified as fibrosarcoma or cystosarcoma phyllodes. Deaver and McFarland report two fibrosarcomas, both in men

60 years of age and tabulate the age incidence of 30 collected cases. In 1926, Caylor and Shugrue, described a mammary fibrosarcoma in a man of 52 which developed in a pre-existing fibro-adenomatous hypertrophy. Neal and Simpson in 1930 reported 4 fibrosarcomas, 1 lymphosarcoma, 1 liposarcoma, and 1 chondromyxosarcoma in the male breast. The more recent reports of Hemenway, Angerer, and of Despaigne and Bolanos were all fibrosarcomas in men over 50 years of age. There are 4 sarcomas of the male breast in our series, 3 of these are lymphosarcomas, and 1 is a fibrosarcoma. (Fig. 523.)

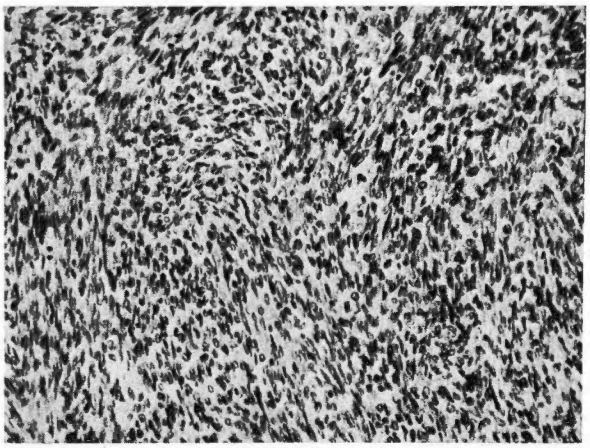

FIG. 523. Photomicrograph of fibrosarcoma of the male breast.

Sarcoma of the male breast occurs, as a rule, in patients past middle life. According to Despaigne and Bolanos, the average age is 45.6 years or nearly 10 years younger than the average age for cancer in the male breast. The relatively late age of these patients is explained by the predominance of fibrospindle-cell and lymphosarcomas which are usually diseases of adults regardless of the organ affected. While these sarcomas are rapidly growing tumors with attachment to the overlying skin, the fibrospindle-cell forms may be preceded by a mass of relatively stationary size, which has persisted for years, before the rapid growth develops.

The size of the mass at the time of operation in the reported cases varies from 2 to 7 cm. in diameter although in one case cited by Deaver and McFarland the mass was as large as an adult head. Multiple and bilateral mammary sarcomas in the male have been described. Usually, there is no axillary involvement in fibrosarcomas, but lymphosarcoma and liposarcoma are prone to involve the axillary nodes. Lymphosarcoma of the male breast is a rapidly fatal

disease in our experience, and I have been unable to find a report of a cured case in the literature. Spindle-cell sarcomas arising in the subcutaneous connective tissue in the region of the breast are also highly malignant growths.

Apparently, fibrosarcomas arising within the gland proper on the basis of a pre-existing fibro-adenoma or fibro-adenomatous hypertrophy have a lower degree of malignancy and some of these cases are probably cellular giant myxomas rather than sarcoma. Our case of fibrosarcoma was living 17 years after radical mastectomy, and 11 of the 34 cases of sarcoma in the early literature reviewed by Connell in 1907 were cured.

Treatment

Simple mastectomy with dissection of the pectoral fascia is the treatment of choice for sarcoma of the male breast. If pathologic examination reveals lymphosarcoma or liposarcoma, postoperative irradiation is indicated because of the radiosensitivity of these growths. The fibrospindle-cell tumors are radioresistant.

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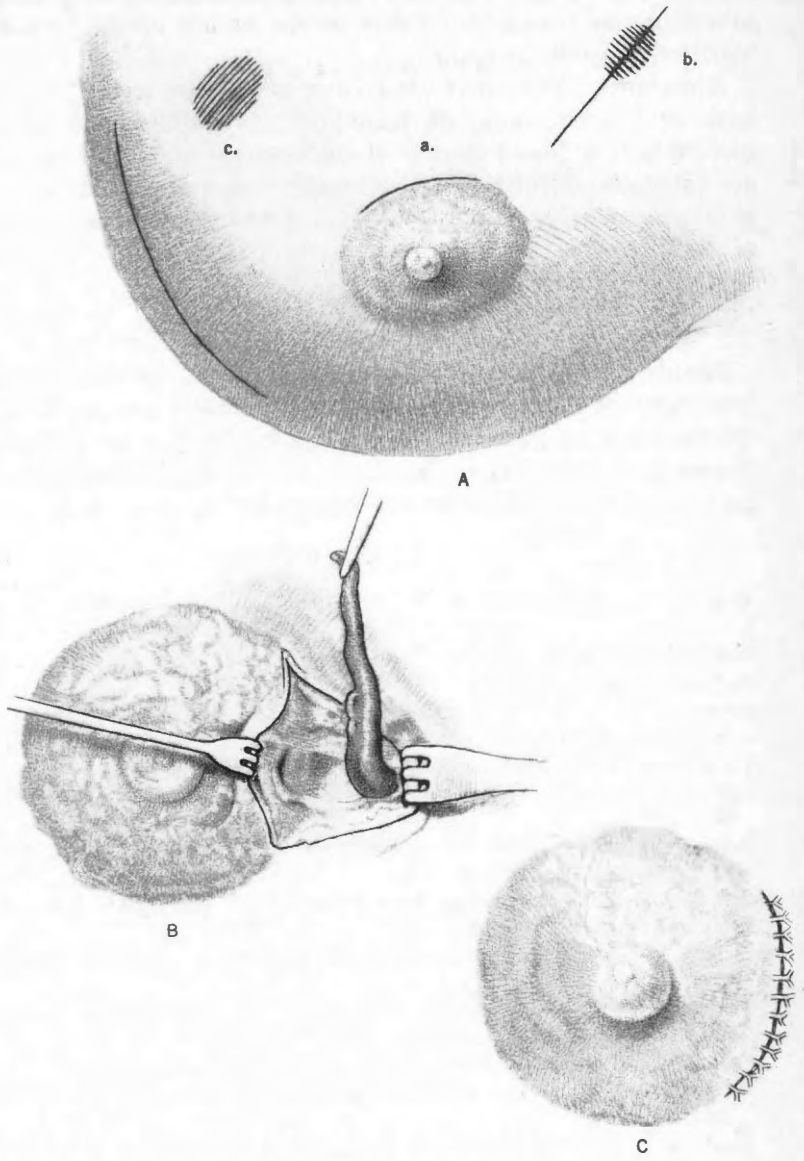
PLATE I

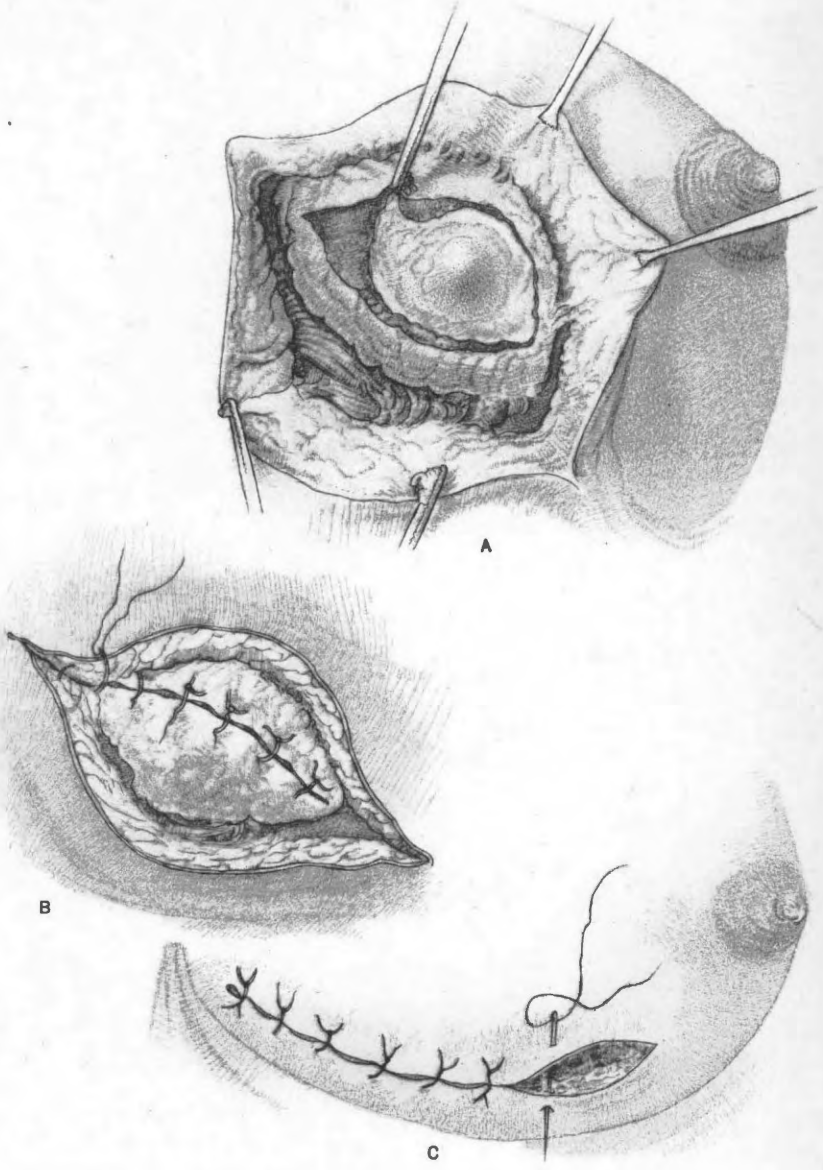


PROCEDURES FOR THE REMOVAL OF BENIGN TUMORS.

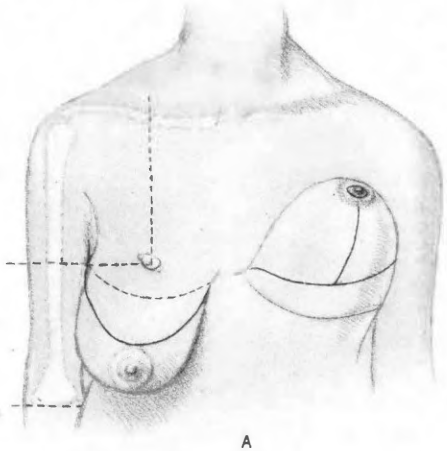
A. Incisions for the removal of benign breast tumors.
   a. Curved areolar incision
   b. Radial incision
   c. Curved marginal incision of Warren

B. Excision of duct papilloma through curved areolar incision. (Babcock's operation.) The duct is excised with a minimum amount of surrounding tissue.

C. Closure of the areolar incision following the removal of duct papilloma.



EXCISION OF BENIGN MAMMARY TUMOR THROUGH THE WARREN INCISION.
A. Exposure and dissection of the tumor through a curved incision at the lower border of the outer mammary fold.
B. Closure of the wound by layers with interrupted catgut sutures.
C. Approximation of the skin edges with interrupted sutures of fine silk.



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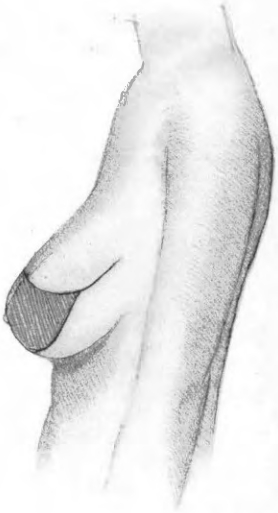

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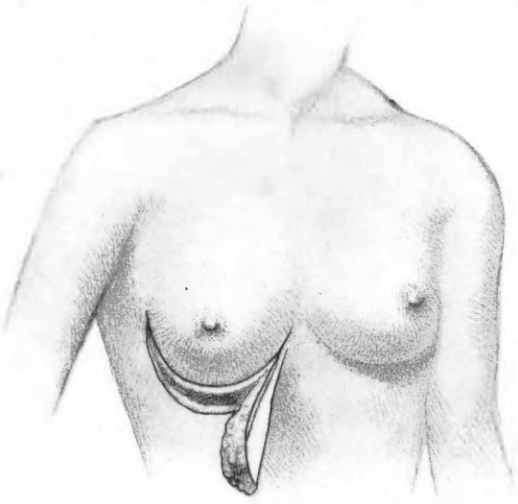
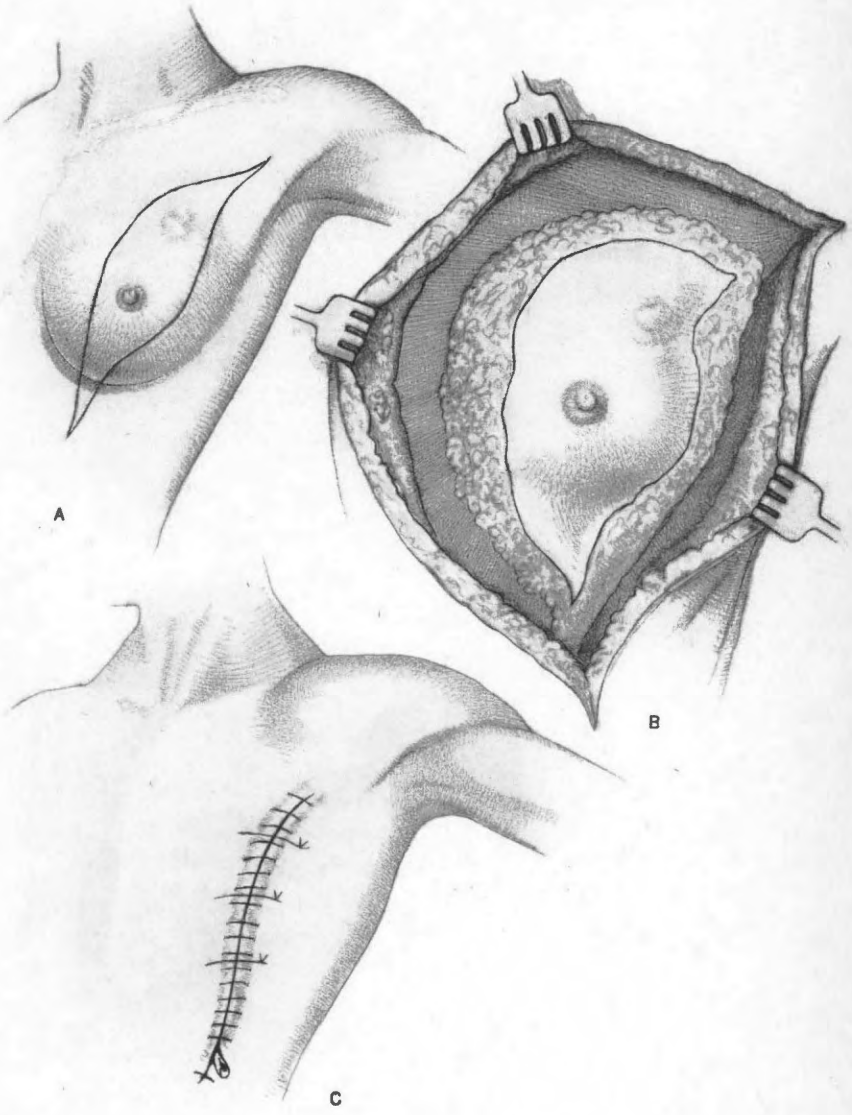


C

PLASTIC REPAIR OF THE HYPERTROPHIED BREAST.

A. Outlines of the anterior and posterior flaps and for incision for transposition of the nipple at the intersection of lines from the mid-humerus and mid-clavicle.
B. Lateral view showing the amount of tissue to be removed.
C. Removal of a semilunar segment at a second stage. (Maliniak's operation.)

PLATE IV



SIMPLE MASTECTOMY.

A. Incision.
B. Dissection of the breast from the fascia overlying the pectoral muscles.
C. Closure of the wound with interrupted sutures and drainage.

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PART VI

THERAPY

ORIENTATION

Conditions of the breast are equally divided into cases which need adequate examination and reassurance only, benign lesions for which treatment is indicated, and those of a malignant nature. Under all conditions, the physician must determine without delay the benign or malignant nature of the lesion and no therapeutic procedure is justified which does not rest upon an accurate diagnosis.

Endocrine therapy with corpus luteum hormone (progesterone injections) is indicated in mastodynia, in selected cases of adenosis and may prevent recurrence in cystic disease. Estrogen therapy relieves painful engorgement of the breast in the puerperium. No form of endocrine therapy (progesterone, testosterone or lactogenic hormone) whether by mouth, injection or pellet implantation has proved notably beneficial for recurrent or metastatic mammary carcinoma in the author's experience. Testosterone preparations are harmful if there are bony metastases, and estrogen preparations are contra-indicated in all forms of mammary carcinoma.

Aspiration is valuable in the diagnosis of a suspected blue-dome cyst and will suffice for treatment in one-third to one-half the cases. It is not the preferred method of diagnosis for solid tumors. Excision for benign tumors assures accurate histopathologic diagnosis and usually suffices for cure; and is, therefore, the recommended mode of treatment. Simple mastectomy is inadequate for malignant conditions and too radical for benign lesions. It may be used in cases with multiple papillomas invading the ducts in more than one quadrant of the breast and in selected cases of recurrent adenosis. In mammary fibrosarcoma and in giant myxomas mastectomy with removal of the pectoral fascia should be performed.

Radical mastectomy is the treatment of choice for mammary carcinoma unless there are definite contra-indications to the procedure. If the lesion is operable, mastectomy without pre-operative irradiation is performed and if at operation the disease is found to be confined to the breast routine post-operative irradiation is not given. When the axillary nodes are involved routine post-operative irradiation is employed. If the tumor is clinically at the borderline of operability and inoperability pre-operative irradiation is given. For clinically inoperable carcinomas, whether primary, recurrent or metastatic, irradiation is the treatment of choice. Irradiation with low voltage therapy is of value in infectious mastitis, particularly of the periductal or tuberculous variety.

28

Treatment of Benign Tumors of the Breast

The majority of benign tumors of the breast are best treated by simple excision. This applies to fibro-adenoma, intracystic papilloma, lipoma, solitary blue-dome cyst and localized nodularity in other forms of mammary dysplasia. Excision has the outstanding advantage of assuring accurate diagnosis by pathologic study and will usually suffice to cure. A carefully made incision assures a good cosmetic result since a deposition of fat soon replaces the excised tissue restoring the original form of the breast.

Aspiration, simple mastectomy, endocrine therapy and irradiation are other forms of treatment which merit consideration in special circumstances. When treating benign lesions of the breast, the preservation of normal function during the childbearing period must

be considered as well as the importance of establishing accurate diagnosis and obtaining good cosmetic results.

ASPIRATION

Cystic tumors of appreciable size may be readily aspirated. If the dome of the cyst be superficial, aspiration may be performed quickly

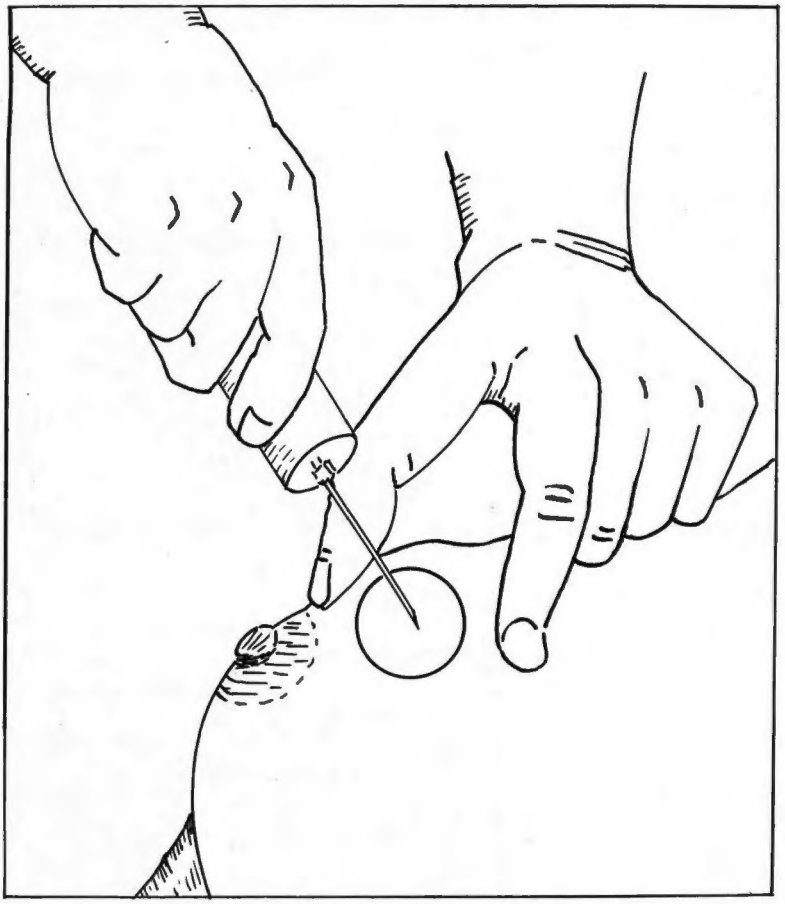

FIG. 524. Procedure to aspirate blue-dome cysts.

and without local anesthesia. The overlying skin is cleaned with iodine and alcohol, and a 22-gauge needle on a 10 or 20 cc. locked-barrel syringe inserted into the cyst at right angles to the skin. (Fig. 524.) As the needle is pushed forward with the right hand, the cyst is

stabilized by grasping the surrounding tissue between the left thumb and forefinger. Little or no suction is required to aspirate the straw-colored or smoky fluid. The cyst may refill and require aspiration several times, but in one-third of our cases a single aspiration has sufficed.

If dark-brown or bloody fluid is aspirated, the presence of intracystic papilloma or papillary carcinoma is probable and surgical excision is indicated. It has been our practice to examine cyst fluid microscopically. A few red blood cells in fluid which is not grossly a bloody color is not regarded as significant.

If the cyst is deeply located and gives the impression of having a thick wall, a larger needle should be used. Under such conditions, the sterilized skin is injected with a small wheal of novocain at the site chosen for aspiration, and a minute opening is made with a bistoury before inserting the needle for aspiration. The needle must be sharp or the cyst will be turned aside rather than penetrated.

Multilocular or multiple blue-dome cysts are usually not successfully treated by aspiration.

EXCISION

Three incisions are in common use to excise benign tumors of the breast: (1) the radial incision, (2) the curved marginal incision of Warren placed at the outer or lower border of the breast, and (3) the curved incision at the areola border. (Plate I.)

The choice of the incision depends upon the location of the tumor, the age of the patient and whether local or general anesthesia is to be used.

In young girls with benign fibro-adenoma of appreciable size located in the outer or lower hemisphere of the breast, the tumor is best removed through the Warren incision since this gives the best cosmetic results. A general anesthetic is preferable for such an incision, since the dissection is carried down to the pectoral muscle and the tumor is approached from behind, a procedure which is somewhat tedious under local anesthesia.

Radial Incision

For benign tumors in the upper inner quadrant and for palpable intracystic papillomas which are usually in the central zone, and for tumors in the upper outer hemisphere in women at or beyond the menopause, the radial incision is the simplest method of approach. Local anesthesia is employed and since the incision is made directly over the tumor, the amount of dissection is minimized. After the

field has been properly sterilized and draped, the skin and subcutaneous tissues in the region of the incision are anesthetized by the injection of 1 per cent novocain. The incision is made in the skin immediately over the tumor and is prolonged toward the nipple rather than toward the upper portion of the breast, so that the scar resulting may be concealed by clothing. (Figs. 525, 526.)

FIG. 525 FIG. 526

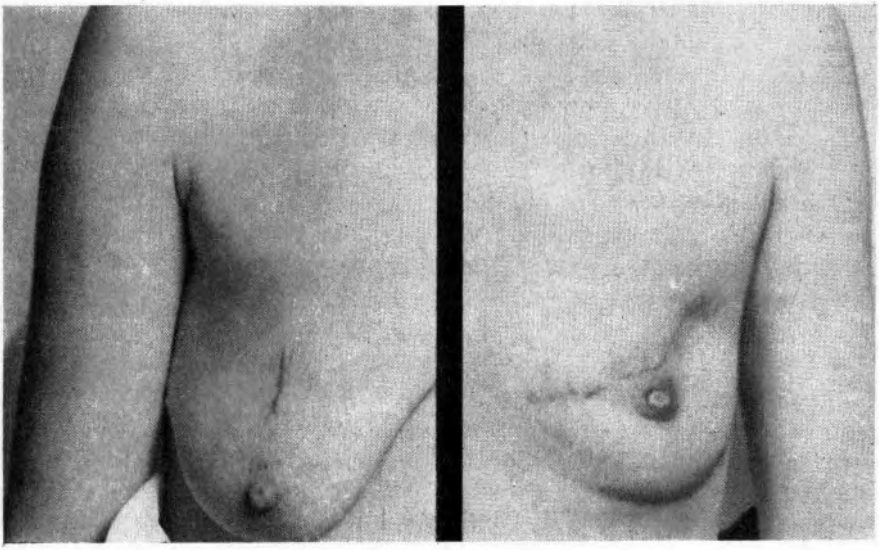

FIG. 525. Correct incision for removal of benign breast tumor. Scar of the radial incision properly placed.

FIG. 526. Incorrect incision for removal of benign breast tumor. Unsightly scar of transverse incision used for a large blue-dome cyst.

The incision is carried through the skin and subcutaneous fat, bleeding points are ligated, and the tumor is again located by palpation. The overlying tissue is then grasped by an Allis clamp which remains in place as a marker, and the surrounding glandular tissue (which is more sensitive than fat) is injected with the local anesthetic. The tumor and the surrounding breast tissue are now excised. Careful hemostasis is employed, the clamps being left in place for a few minutes to control small bleeders without ligatures. The mammary tissues are approximated with several catgut sutures and the subcutaneous tissues are similarly treated. The skin incision is closed with interrupted fine silk sutures, without drainage. Delayed healing and the accumulation of serum in the wound may be avoided by thorough hemostasis and by limiting to an essential minimum the number of ligatures and sutures buried in the wound.

The Warren Incision

The Warren incision gives excellent cosmetic results for benign tumors located in the outer or lower hemisphere of the breast. (Figs. 527, 528.)

The incision is placed on the breast side of the outer or submammary folds. When on the outer submammary fold, it should not extend high enough to show with a sleeveless dress. The operation is best performed under general anesthetic but a local anesthetic may

FIG. 527 FIG. 528

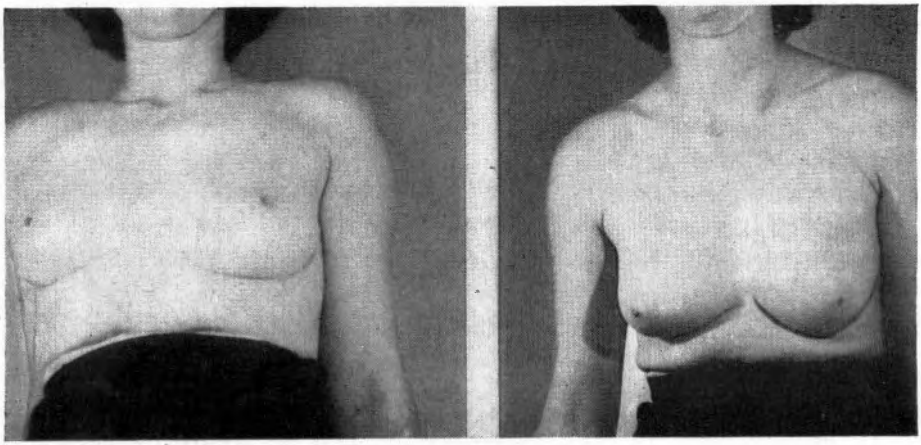

FIG. 527. Removal of fibro-adenoma by the Warren incision. The scar is visible in the submammary fold of the right breast 6 months after the excision.
FIG. 528. The scar is invisible when the patient is in the upright position.

be used. The incision is made at right angles to the skin surface and is carried through the subcutaneous tissues to the pectoralis major muscle. The posterior surface of the breast is then exposed by following the line of cleavage between the breast and muscle; the mammary tissue is then everted through the wound so that the region of the tumor is exposed. The tumor and the surrounding breast tissue are now excised by dissecting through the glandular tissue. No attempt is made to approximate closely the edges of the incised glandular tissue. Bleeding points are ligated and the breast is allowed to fall back to its normal position. The subcutaneous tissues are closed with interrupted sutures of plain fine catgut, and the skin is closed with similar sutures of fine black silk. If there is an unusual amount of fat, a small drain may be inserted; otherwise, none is used. (Plate II.)

Incisions at the Areola Border and the Treatment of Lesions of the Nipple

A curved incision at the areola margin or a small radical incision extending to the nipple may be used to explore dilated ducts beneath the nipple, bleeding from the nipple without palpable tumor, small intracystic papillomas, and other tumors in the central zone. If the lump is easily located by palpation or transillumination, no difficulties need be anticipated in performing the excision. (Plate I.)

If the exploration is performed for a sanguineous discharge without a palpable lump, localization is the chief problem. The discharging duct or ducts should be located by exerting digital pressure along successive radii in the region of the nipple (see Chap. XIV) until the source of the discharge is demonstrated. The affected ducts may be excised by removing a wedge of tissue in the affected quadrant through a radial incision.

Babcock suggests the insertion of the blunt end of a small needle through the orifice of the affected duct using a hand lens if necessary. The opening is enlarged by inserting progressively larger needles. A probe or large needle is then inserted into the duct, well beyond the areola, to function as a guide. A curved incision is made at the border of the areola and the duct containing the probe or needle is dissected out with a minimum amount of surrounding mammary tissue.

The curved incision may also be used in gynecomastia, for the removal of excess mammary tissue. The incision should sweep half way around the circumference of the areola. The nipple and the larger ducts beneath are then dissected free from the deeper structures and pulled forward and the fat and glandular tissue behind excised down to the pectoral fascia. The wound is closed without drainage.

PLASTIC OPERATIONS ON THE BREAST

Plastic reconstruction of the mammary gland may be used for hypertrophied or pendulous breasts. The patient should be cautioned against the expectation of perfect form and function and warned that some visible scarring or irregularity of contour may result. (Plate III.) Although numerous operations have been devised (Kraske, Joseph, May, et al.) that described by Maliniak has been most satisfactory in our experience. As stated by Maliniak, the requirements for successful repair are:

1. The blood supply of the breast must be preserved to prevent partial necrosis.
2. Extensive injury to the galactophorous ducts should be avoided in order to preserve partial mammary function when possible.
3. The gland must be firmly affixed in its new location to prevent recurrence.
4. There should be no conspicuous scarring.
5. All the diameters of the breast must be reduced proportionately to insure an esthetic end-result.

Technic

Position and Incision. The patient is placed in the dorsal position with a sandbag between the shoulders. At this time, an accurate determination of the new position of the nipples must be made and the area marked with a suitable dye (brilliant green). The location is determined by the intersection of two lines; the horizontal one drawn halfway between the clavicle and the elbow, and the vertical through the middle of the clavicle. After the proper aseptic preparation of the operative field, the nipple and areola are circumscribed by an incision passing through the full thickness of skin leaving at least 2 cm. of areolar tissue about the nipple. An elliptical transverse incision is then made in the skin of the breast with the lower portion of the curve at the upper margin of the areolar incision. Another elliptical incision is then made more or less parallel to this one, but situated at a point beneath the lower border of the areolar incision. The skin between these two incisions is completely removed, and all bleeding points ligated. The superior flap is next dissected. At the predetermined point on the superior flap a small circular incision is made. The diameter of this button-hole incision into which the nipple is to be inserted should be 1 cm. smaller than the areola circumscribed by the first incision.

Dissection and Excision. The lower portion of the breast is dissected from the pectoral fascia. The excess fat and parenchyma are then removed from the inferior portion, and the breast tissue is drawn toward the midline by means of numerous sutures joining the breast to the upper rectus and pectoral fascia.

Closing. The nipple and areola are brought up through the new circular opening in the superior flap, and held in place by small sutures. The skin around the areola is approximated to the superior flap with properly selected suture material, care being taken not to

tie the sutures so tight as to produce ischemia of the flap margins. The lower transverse incision is then closed with interrupted silk sutures. Before closure, two penrose drains are placed at either end of the incision to be removed within 48 hours. Zeroform gauze is used as dressing material and a pressure bandage is applied.

Two-Stage Technic. In cases where it is necessary to remove considerable breast parenchyma, this is best done in two stages, to diminish the danger of necrosis in the transplantation of the nipple. In the first stage, the nipple and the partially diminished breast are transposed to the new position without disturbing the blood supply in the nipple region. The reduction of the breast is limited to the lower pole, and the branches of the internal mammary artery on the medial aspect of the breast are not disturbed.

The second stage is performed 4 to 6 weeks later, and at this time excess fat, skin and glandular tissue are removed through a crescent-shaped incision through the submammary and lateral mammary folds.

OPERATIONS ON THE NIPPLE

Various operations have been used for inverted or umbilicated nipples (so-called mammilliplasty). The operations described in the literature prior to 1917 have been discussed by Deaver and McFarland. These procedures are no longer practiced since the cosmetic results are rarely permanent and, if the deformity interferes with nursing, it is a more certain and simpler procedure to put the baby on a formula.

Removal of the nipple and an underlying core of tissue including the large ducts through an incision encircling the areola is indicated for cases of suspected Paget's disease. If the lesion of the nipple has failed to respond to simple hygienic measures for a period of several weeks, and if the Wassermann reaction is negative, this is the most satisfactory method of biopsy for adequate pathologic study. These patients are usually past the childbearing period and the resultant deformity is not a serious one.

This operation may also be used for bleeding nipple resulting from intracystic papilloma within the ampullae of the nipple itself. It is not, however, used by the authors for bleeding nipple without a palpable tumor or for papillomas outside of the ampullae. For this purpose a radial incision or the procedure of Babcock, as described, is preferable.

SIMPLE MASTECTOMY

As Bloodgood had stated, simple mastectomy is inadequate for malignant conditions and too radical for benign lesions. In some clinics it is frequently performed for bleeding nipple without a palpable tumor and for various forms of chronic cystic mastitis. The authors' practice, however, is to use more conservative measures and

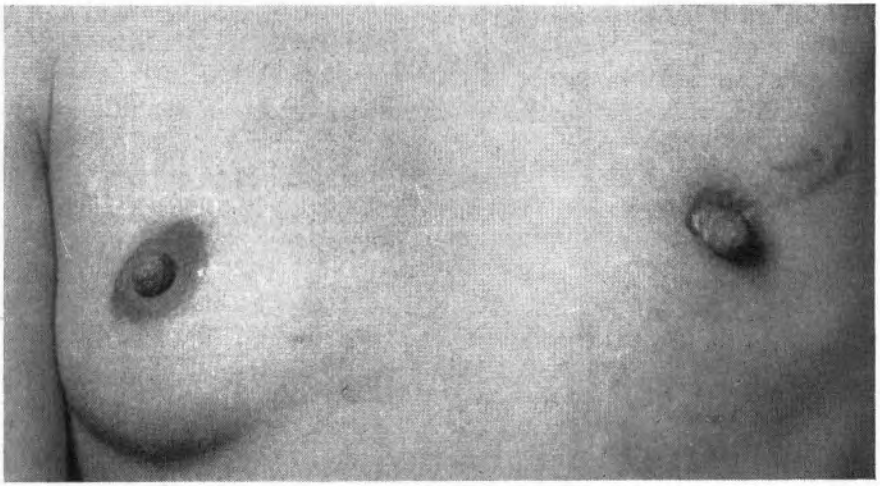

FIG. 529. Simple mastectomy with preservation of the nipple. The breast in this case was removed for adenosis.

to limit the use of mastectomy in benign conditions to cases of virginal hypertrophy where plastic operation is unsuitable, and to cases with multiple papillomas invading the ducts in more than one quadrant of the breast and for recurrent nodules other than cysts in adenosis. In such cases, the mastectomy is performed without preservation of the nipple. (Plate IV.)

Technic

Mastectomy Without Removal of Pectoral Fascia. The incision encloses an elliptical area of skin with its widest portion at the areola margin and proceeds transversely from one mammary fold to the other. (Similar to Fig. 530 E.) The skin is undermined along the superior and inferior flaps and the subcutaneous fat and the glandular tissue are removed down to the pectoral fascia. Thorough hemostasis is carried out using ligatures of fine chromic catgut. After removal of the breast, it may be necessary to excise additional

skin in order satisfactorily to approximate the edges. The wound is closed with interrupted sutures of fine black silk and a single drain is inserted. If preservation of the nipple and areola is desired, the upper incision sweeps around the lower margin of the areola, so that these structures are retained on the upper flap (Fig. 529).

Mastectomy with removal of the pectoral fascia, but without dissection of the axilla, is indicated in cases of mammary sarcoma and in giant myxomas of the breast which are of doubtful malignancy. In such cases, the excision is usually performed through an elliptical incision with its long axis parallel to the anterior axillary fold. The ellipse enclosed by the incision is similarly placed, but is smaller than the one used for radical mastectomy. (See Chap. 29.) The advantage of this incision is that it permits examination of the axillary lymph nodes. If metastases are found the incision can be prolonged to permit an axillary dissection. The dissection is carried down through skin and superficial connective tissues to the pectoral muscle along the upper line of the ellipse. The breast and subcutaneous tissues are then drawn away from the thoracic wall by the assistant, and the dissection of the pectoral fascia from the muscle is begun along the upper and medial portion of the muscle. The dissection of the fascia is carried well beyond the limit of the breast laterally. The connective tissue of the pectoral fascia is now severed toward its axillary aspect together with the vascular connections. The breast is now freed from the chest. All vessels are ligated, and the pectoralis major muscle is left bare. (Plate IV.)

The index finger is now passed into the axilla through the upper end of the wound, and the axillary nodes are palpated. If none is found, the axilla is not entered surgically, but if enlarged nodes are felt, these should be excised and examined by frozen section, for occasionally sarcoma of the breast will metastasize to this region. If the nodes are negative, the wound is closed with interrupted deep catgut sutures and interrupted skin sutures of black silk. A drain is inserted at the lower angle of the wound. If axillary lymph nodes are involved, the operation may be extended to this region.

IRRADIATION

Irradiation of the breast for benign tumors has been advocated from time to time. Cutler proposed this procedure for bleeding nipple associated with nonpalpable intracystic papilloma, and Taylor has practiced it for chronic cystic mastitis.[1] Experience has shown, however, that roentgen therapy applied directly to the breast for such benign conditions is rarely satisfactory. Small doses of roentgen

[1] Menville reported the results of roentgen-ray therapy in gynecomastia.

rays are without the desired effect and when repeated large doses are given, atrophy and fibrosis of the mammary tissue result. This is accompanied by changes in the size and shape of the gland and by pigmentation of the skin. In young women, such treatment may interfere with subsequent lactation and, in rare instances, mammary carcinoma has developed at the site of a roentgen-ray dermatitis when repeated courses of therapy have been given. Furthermore, irradiation for benign lesions of the breast does not permit pathologic verification of the diagnosis which is always an important consideration in treating such conditions. The author does not use irradiation for benign tumors of the breast, except when a painful keloid scar has followed a previous excision.

Roentgen-ray therapy is practiced for a variety of mammary infections such as acute puerperal mastitis, plasma-cell mastitis and tuberculosis. The indications for such treatment have been discussed in Chap. 6. If suppuration is to be prevented in acute puerperal mastitis, roentgen-ray therapy should be instituted immediately after the onset of symptoms. If begun within 24 to 48 hours after the onset of symptoms, less than 10 per cent of the cases go on to suppuration.

Dosage

We prefer either low voltage or intermediate voltage therapy, maximum 140 kilovolts, with not more than 6 mm. of aluminum filtration. The treatments are given in divided doses of approximately 200 roentgens repeated at intervals of several days; not more than 700 roentgens are used. High voltage roentgen-ray therapy (200 Kv.) for a total of 1,000 to 1,200 roentgens has been advocated by Nicolson and Gillespie for involvement of the axillary nodes in cases of tuberculous mastitis. The authors, however, have had no experience with this treatment. It has been our practice to excise the axillary nodes.

After roentgen therapy given directly to the breast in chronic cystic mastitis, Taylor and Brown noted improvement in 50 per cent of the cases. A total of 1,200 roentgens in three equal doses on alternate days was used. The physical factors were 200 Kv., 30 ma., 50 skin-target distance through a 10 × 10 cm. field, with a filter of 0.5 mm. copper. Taylor and Brown have practiced roentgen-ray castration for chronic cystic mastitis in women near the menopause. Its use may be indicated in cases where simple excision or endocrine therapy does not yield satisfactory results. It has the disadvantage, however, of producing menopausal symptoms in about 50 per cent of the cases. The technic for sterilization with roentgen-ray therapy is given in Chapter 30 (see page 694).

ENDOCRINE THERAPY

Endocrine therapy for benign conditions of the breast has received increasing attention in recent years. In order to decide whether endocrine therapy is indicated for benign lesions of the breast, the clinician must familiarize himself with the various types of endocrine preparations available, their dosage, and their physiologic effects. Changes in the mammary gland may be produced by administering the steroid sex hormones including estrogens, testosterone and progesterone, and by using pituitary preparations such as the lactogenic hormone. The steroid hormones just mentioned can be given by intramuscular injection, orally or may be applied as an ointment to the breast. They are sometimes implanted in the form of pellets. The effective dosage is usually in the range of one to several milligrams. The pituitary hormones are available for intramuscular injection in aqueous solution and are not effective by mouth or by inunction. Hormone therapy is not given during the days of menstruation.

Estrogen Therapy

The estrogens are most frequently used and have the widest range of application in benign lesions of the breast. The preparations which are available, their relative potency by parenteral and oral administration, and whether or not they have a prolonged action are listed in the accompanying table. The benign mammary conditions which may be treated by estrogen therapy include: painful engorgement; acute mastitis and engorged accessory mammary tissue in the puerperal breast; anachronistic secretion including galactorrhea and nonhemorrhagic discharges associated with dilated ducts; underdevelopment of the breast or hypomastia; and chronic cystic mastitis.

Inhibition of Mammary Secretion. High doses of estrogen continuously maintained for a period of days inhibit mammary secretory activity and the increased vascularity of the breast which accompanies this functional activity. The treatment of mammary engorgement and secretion demands relatively high doses of estrogen or the direct application of estrogenic ointment. In the prevention of painful engorgement, the patient is fitted with an uplift binder and the estrogen is given by mouth in the form of stilbestrol, or its derivative monomestrol. Five milligrams in the morning and 5 mg. in the evening are given on the first day, and 5 mg. daily thereafter for four days, a total of 30 milligrams. (Abarbanel obtained good results with a total dose of 50 mg. Mendel, Goldman and Cane obtained satisfactory results with total doses of 20 to 30 mg. in 55 cases.) The same

dosage plus inunction with 1 gram of estrogenic ointment (stilbestrol, 0.5 mg. per gram) twice daily should be applied to prevent puerperal mastitis, and the inunction alone to inhibit engorgement of accessory breasts in the puerperium. Large doses of stilbestrol preparations are well tolerated in the puerperium, but must be used with caution at other times. To inhibit anachronistic mammary secretion, the injections of stilbestrol or estradiol compounds in doses of 1 to 2 mg. twice weekly plus the application of estrogenic ointment twice daily is preferred. Treatment should be discontinued in one month regardless of whether or not good results are achieved.

Hypomastia. The application of estrogenic ointment is indicated

TABLE LXXXV

POTENCY IN RAT UNITS PER MILLIGRAM OF VARIOUS ESTROGENIC COMPOUNDS

COMPOUND	PARTIAL LIST OF TRADE NAMES	AUTHOR'S ASSAYS: BY INJECTION[1]	AUTHOR'S ASSAYS: BY INJECTION	AUTHOR'S ASSAYS: ORAL ADMINISTRATION	PROLONGED ACTION ON INJECTION[2]	DOSAGE
Estradiol[3] (alpha)	Dimenformon Estradiol Ovocylin Progynon-DH	12000	3300	330	No	.2–1 mg.
Estradiol Benzoate	Benovocylin Dimenformon-benzoate Progynon-B	6000	1700	170	Yes	.2–5 mg.
Estradiol Dipropionate	Diovocylin	5000	2500	250	Yes	1–5 mg.
Diethyl Stilbestrol	Stilbestrol Stilrone	3000	3300	1650	No	0.5–5 mg.
Stilbestrol Monoethyl Ether	Monomestrol		500	400	Yes	0.5–5 mg.
Estrone[3] +	Estrone Theelin Amniotin Estrogenic hormone Estrolin Estromone Folestrin Menformon Theelestrin	1000	1000	133	No	1–2 mg.

[1] The data in this column were obtained from the following sources: For estradiol (alpha benzoate) and estrone: Whitmen, et al: Jour. Biol. Chem., 118: 789, 1937.
For estradiol propionate: Miescher, et al.: Biochem. Jour., 32: 725, 1938.
For stilbestrol: Dodds, et al.: Nature, 142: 34, 1938.
All other data are based on the author's assays.
One rat unit is the equivalent of 10 international units.

[2] None of the estrogens has prolonged action by mouth.

[3] Ointments contain 0.125 to 0.2 mg. per Gm. of estradiol (alpha) and 0.2 to 0.5 mg. per Gm. of estrone.

for hypomastia. The author has used estrone ointment (0.5 mg. per gram Menformon Dosules "Roche Organon"). One gram is applied nightly for several months to both breasts. The mammary development thus stimulated, however, is not permanent. It is dependent upon the growth of young edematous connective tissue which increases in density and correspondingly decreases in volume after a period of several months. The results are improved if during this treatment the patient is given injections once weekly of progesterone (5 mg. in oil).

Chronic Cystic Mastitis. Estrogen therapy has been used in various forms of chronic cystic mastitis, and is most effective in moderate doses in mastodynia or painful breasts. The details of this form of therapy in the treatment of chronic cystic mastitis have been discussed in Chap. 12. The action of estrogen in these cases is not definitely known. It may have an effect on the state of engorgement of the painful breasts, or bring on a relatively atrophic resting stage (see Chap. 33), or it may act indirectly through prolonging corpus luteum function. Large doses or long continued estrogenic therapy in chronic cystic mastitis are contraindicated. Doses equivalent to 1 mg. estrone twice weekly over a period of one month, or stilbestrol preparations by mouth and reduction of therapy in the second month and discontinuation of all therapy within three to six months are safe and usually successful procedures.

TABLE LXXXVI
CORPUS LUTEUM HORMONES

COMPOUND	PARTIAL LIST OF TRADE NAMES	INTRAMUSCULAR INJECTION	ORAL ADMINISTRATION	DOSAGE
Progesterone (synthetic)	Proluton, Progestin, Lutocylin, Progestone	Yes	No	5–10 mg.
Progestin (natural)	Lipo-Lutin, Progestin	Yes	No	1– 5 mg. (1 rabbit unit = 1 mg.)
Anhydrohydroxy-progesterone	Lutocylol, Pranone, Progesterol	No	Yes	5–10 mg.
	MALE SEX HORMONES			
Testosterone propionate	Perandren, Neo-Hombreol, Oreton	Yes	No	10–25 mg.
Methyl-testosterone	Neo-Hombreol (M), Metandren, Oreton-M	No	Yes	10 mg.

Testosterone Therapy

Testosterone therapy has been recommended for the treatment of painful engorgement in puerperal patients, for gynecomastia, for inhibition of galactorrhea and for the treatment of chronic cystic mastitis. Effective preparations are available for injection, for oral administration and for inunction. The 10 mg. dose is most convenient whether injections or oral administration is used. The ointment contains 4 mg. per 2 grams. If testosterone propionate therapy is used for gynecomastia, the treatment should be continued for six weeks giving injections of 10 mg. twice weekly (Peranden, Ciba). For additional therapy, testosterone ointment may be applied directly to the breasts. Similar therapy is used for chronic cystic mastitis.

Abarbanel reports prompt relief of painful engorgement following a single injection of 10 mg. of testosterone propionate. The author has not been successful in controlling galactorrhea with testosterone therapy.

Progesterone Therapy

Injections of progesterone (5 mg. in oil) are administered twice weekly for the last two weeks of one, two or three consecutive menstrual cycles in patients with chronic cystic mastitis, including the subvarieties of mastodynia, adenosis and cystic disease. Relief of symptoms in cases of mastodynia and adenosis lasting 12 to 18 months are observed in most cases. In cystic disease the treatment is of doubtful value but may prevent recurrence following surgery or aspiration. Following treatment by injection, orally active progesterone (anhydrohydroxy-progesterone) may be given for one month in doses of 5 mg. every other night.

Pituitary Hormones

The anterior pituitary preparations available that have occasionally proved useful in treating benign mammary conditions are two: lactogenic hormone and anterior lobe extract (or a similar preparation from pregnant mare's serum). Lactogenic hormone stimulates mammary secretion, increases the vascularity of the stroma, and decreases the bulk of the fibrous tissue. It has been administered, with indifferent results, to increase the amount of milk in nursing mothers. The author has used it following estrogen therapy in cases of chronic cystic mastitis. A stable preparation of 100 I.U. in dry form for dilution in 1 cc. of sterile water for intramuscular injection is available (Prolactin, Schering). The injections should be given daily or every other day for a total of 7 to 10 injections.

Anterior lobe pituitary extract combining gonadotropic and thyrotropic factors is available and equine from pregnant mare's serum. The international unit is 0.25 mg. of a standard powder. These preparations may be given intramuscularly in doses of 10 to 25 I.U. in cases of hypogonadism and sexual development may be accompanied by mammary enlargement. There is no direct effect on the breast.

CHEMOTHERAPY

Sulfanilamide and Sulfathiazole

Experience with sulfathiazole (2-sulfanilamidothiazole) in cases of acute puerperal mastitis, in chronic suppurative mastitis, or in plasma-cell mastitis is still meager. Its use, however, is justified on the basis of experience with other infections. In acute puerperal mastitis treatment should be begun with the first symptoms. The initial dose is usually 2 or 3 grams by mouth and 1 gram every four hours thereafter for several days, the blood level being maintained between 3 and 7 mg. per 100 cc. Urine analysis and blood counts should be repeated daily to guard against toxic effects. The chemotherapeutic effects of the newer drug, sulfadiazine (2-sulfanilamidopyrimidine) have not been tested by the author on mammary infections. Experience has shown that it is unwise to give irradiation during the period when the sulfonamide drugs are being administered.

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Rules of Procedure in Treatment of Mammary Cancer

While much depends on the individual judgment of the clinician and the experience gained by following his own cases over a period of years, there are a few main principles concerning the treatment of mammary cancer which seem well established.

1. No definite nodule in the breast should be treated without microscopic evidence which will establish its benign or malignant nature. If the mass is cystic or large, aspiration biopsy will usually suffice. If this is inconclusive surgical biopsy with or without the use of cauterization is indicated. Patients with bleeding nipple should have a biopsy to determine the pathology of this condition.

2. Every patient with mammary cancer should have the benefit of radical mastectomy unless there are definite contraindications to the procedure.

3. The decision to operate should not be made until the extent as well as the malignant nature of the disease is established to the best of the clinician's ability. This at times will necessitate careful examination of the breast, roentgen-ray films of the chest and of the spine, pelvis and other bones.

4. If the lesion is definitely inoperable, irradiation to the limits of tolerance should be given.

5. If the lesion is termed operable, it is our practice to proceed with the radical procedure following microscopic confirmation of the diagnosis without preoperative irradiation. If the disease is confined to the breast, routine postoperative irradiation is not given.

6. If the extent of the tumor appears to be at the borderline of operability and inoperability, preoperative irradiation is given followed by the radical mastectomy within a period of from six to eight weeks. Preoperative irradiation is particularly effective in large circumscribed adenocarcinomas (exclusive of the gelatinous variety).

7. If a clinically operable cancer is found at the operation to involve the axillary nodes or extending to or beyond the limits of the dissection, the routine postoperative irradiation is given.

8. Recurrent and metastatic cancer are treated by irradiation without routine roentgen-ray castration.

9. Roentgen-ray castration is used in young women to avoid the complication of pregnancy and for the occasional benefits observed

10. Throughout the management of cases of mammary cancer complications and manifestations of recurrence and metastases must be treated on their merits. The fact that the malignant nature of the disease has been established or the inability permanently to cure the patient should not be allowed to lead to half-hearted, palliative procedures.

29

Surgical Treatment of Mammary Cancer

While the radical mastectomy as devised by Halsted and Meyer is no longer the sole method by which to treat mammary cancer and is now frequently supplemented by irradiation, it is still the major means to combat the disease. This procedure still accounts for the largest percentage of five-year survivals. The operation attempts to remove in one mass all of the structures which are liable to immediate invasion by the tumor, and is based on the assumption that spread of the disease from its original focus proceeds by continuous permeation in all directions. For this reason, a wide en bloc excision of the structures surrounding the primary tumor is attempted, and any separation or tearing of tissues within the operative field, which might result in structures invaded by the tumor being left behind, is scrupulously avoided.

The original basis for the operation was empirical, and antedated Handley's theory of lymphatic permeation by cancer cells. However, experience with the localization of recurrences and metastatic foci

following less extensive types of mastectomy was ample reason to attempt the widest possible excision. It is now known that in a certain number of cases the extension of the cancer occurs by way of the blood stream, and that tumor emboli may result in metastasis to the lungs, brain and bones in cases where the axillary lymph nodes and the neighboring tissues have been proved to be uninvolved by microscopic examination of the specimen following radical mastectomy. The fact that the five-year survivals do not exceed 75 to 80 per cent even in early cases where the disease is found only in the breast demonstrates that there is a fundamental limitation to the operation originally conceived by Halsted and Meyer. Nevertheless, it remains true that the standard procedure for radical mastectomy rests upon sound pathologic principles and is applicable to the majority of cases where clinical evidence fails to indicate that the disease has already passed beyond the scope of the operation.

FUNDAMENTAL PRINCIPLES OF RADICAL MASTECTOMY

The plan of operation for radical removal of the breast is to excise in one piece a safe margin of normal tissues together with the cancer, to include the adjoining pathways (lymph nodes and lymphatics) along which the cancer spreads, and to guard against the transplantation of malignant cells during the operation by the careful manipulation of the affected tissues. The proximity of the cancer to vital structures and its extent at the time of operation determine the success of treatment.

The palpable tumor is taken as a center of the skin to be encircled and removed by the incision, while the apex of the axilla is taken as the upper limit of dissection.

Dissection of the deep fascia is carried out medially to the sternal attachments of the pectoral muscles, laterally to the border of the latissimus dorsi, and inferiorly to the sheath of the rectus abdominis muscle.

The incision should permit the removal of a maximum amount of skin in the region overlying the tumor (at least 5 cm. beyond the margins of the cancer) and an adequate exposure for the dissection of the axilla. To obtain the widest possible margin on the body side of the new growth, both the major and minor pectoral muscles are removed.

After cutting through the skin, subcutaneous tissues and muscular attachments, the dissection is begun in the apex of the axilla to avoid mechanical and traumatic dissemination of cancer along this pathway during the operation. Cutting across vessels and lymphatics is to be

avoided as much as possible, and hence the structures are removed in one mass.

The closure of the wound should be left out of mind until the end of the dissection, the defect being closed by grafting if necessary. These are fundamental principles of the operation devised by Halsted and Meyer.

RADICAL MASTECTOMY

Preoperative Preparation

The patient should be prepared for the operation both physically and psychically. Palliative treatment only should be given to patients with hypertension, cardiac involvement, of an age making operation hazardous, or those in whom the extent of the disease is such as to preclude cure.

The patient should be told that there is a possibility that the breast will have to be sacrificed. It is well to state that the nature of the tumor will decide the extent of the operation. For some tumors, the growth is removed and the breast saved; for others, the breast is removed and the patient saved.

The radical procedure can usually be justified to the patient by stating that unusual tissue observed necessitated the complete operation to prevent more serious complications. Some responsible member of the family should be fully informed, of course.

Preoperative measures include adequate sedation the evening before operation and a preliminary basal analgesic 45 minutes before the operation. A general anesthetic is the routine preferred in our clinic. It is to be noted that there is more bleeding with the closed systems of anesthesia than with the open drop ether method. Facilities for the use of intravenous fluid including glucose, blood plasma and transfusion should be available.

Position. The patient is placed in the supine position with the arm abducted at right angles on an arm board with a slight elevation of the shoulder on the affected side (a sandbag is convenient).

The preparation of the skin should include the affected breast, the chest wall on that side, the shoulder and axilla, and the arm down to the elbow. A satisfactory clean-up is one utilizing the following solutions in the order given:

1. Alcohol—70 per cent
2. Ether
3. Any adequate skin antiseptic which has proved satisfactory to the operator.

4. Alcohol—70 per cent to follow iodine if used.
   Where preoperative irradiation has been used recently, iodine preparations are contraindicated.

In draping the patient, care should be taken to allow sufficient exposure and to prevent contamination of the operative field.

Pathologic Diagnosis

An adequate pathologic diagnosis is prerequisite to radical mastectomy. This may be carried out in one of the following ways:

1. **Aspiration Biopsy.** An area of skin over the tumor is prepared and anaesthetized. A nick is made in the skin with a bistoury scalpel An 18-gauge needle, tightly fitted to a 20-cc. syringe, is introduced into the tumor through the skin nick. Negative pressure is constantly exerted through the needle by partial withdrawal of the syringe barrel. The needle is passed deeply into the tumor once or twice and the negative pressure is gently released. The syringe is disconnected from the needle; the needle is then withdrawn and the contents are forced on a glass slide. Smears are made; the tissue is fixed, stained and cover slips mounted. This method is especially useful where preoperative irradiation is considered desirable or in clinically inoperable cases. This technic is easily carried out in the office.

2. **Surgical Biopsy.** This procedure is usually performed in the operating room, followed immediately by radical mastectomy should carcinoma be identified. A small exploratory incision is made over the tumor. The tumor together with the margin of surrounding normal tissue is excised, providing the growth is less than 5 cm. in diameter. Should the mass be large and closely attached to skin, removal of a small piece of tumor may be the better choice of procedure. The tumor should not be unduly manipulated by instruments during its excision. The operator himself should bisect the tumor, after its removal, for gross inspection. Having formed an opinion of the gross pathology, a suitable portion is selected for biopsy and the portion considered significant is then turned over to the pathologist for frozen section. A sponge moistened in saline is then packed into the wound to control bleeding. THE OPERATOR SHOULD NOT EVIDENCE IMPATIENCE DURING THE INTERIM BETWEEN THE EXCISION AND THE REPORT OF THE PATHOLOGIST. Where possible, the operator should view the microscopic tissue along with the pathologist and arrive at the working diagnosis in consultation with him. Where malignant change is found, the operative defect is immediately swabbed out with carbolic acid followed by 70 per cent alcohol. A dry sponge is packed into the defect and retained in place

by a few skin sutures. Instruments and gloves should be discarded for fresh sterile preparations. The breast and surrounding tissue having been previously prepared for the complete operation, this procedure may be performed without further delay. If there is disagreement as to the pathologic diagnosis, it is the wiser policy to close the incision and await more adequate study of the tissue.

Incision

A variety of skin incisions may be used for radical mastectomy. The important points are to remove sufficient skin to get an adequate ex-

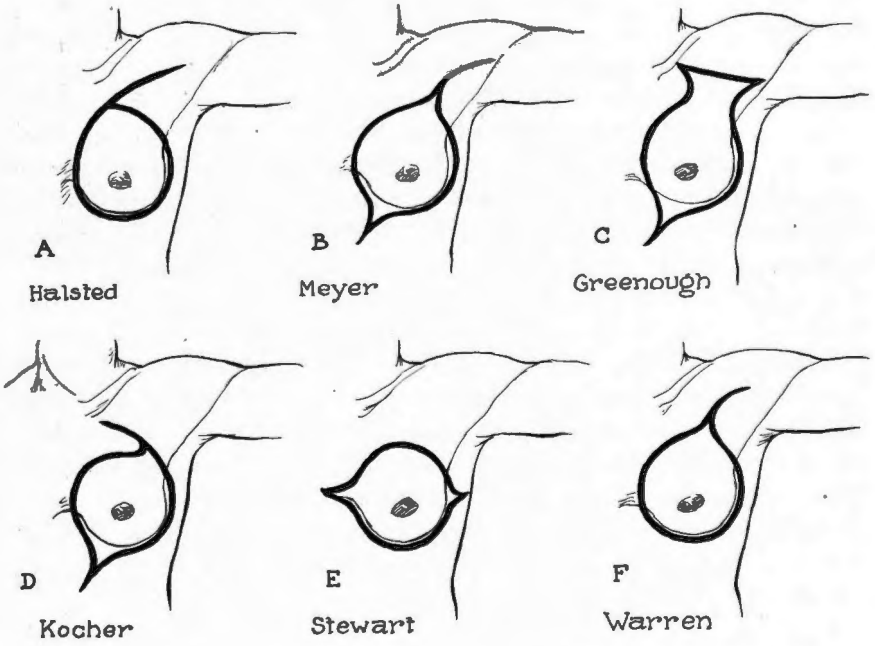

FIG. 530. Some of the incisions used for radical mastectomy.

posure, yet to avoid carrying the incision onto the arm or into the axilla itself which may interfere with the subsequent mobility of the extremity. (Fig. 530.) The original Halsted and Meyer incisions with modifications are still favorites. Adequate exposure is also obtained by the incisions of Greenough, Rodman, Stewart, etc. The authors' preference is for the Finney modification of the Meyer-Halsted incisions. The procedure is to determine by palpation the location and circumference of the growth. The medial portion of the incision which sweeps around a safe distance to the inside of the circumference

is carried from a point near the insertion of the pectoralis major down to the level of the origin of the abdominal rectus muscle. The lateral incision is begun at a point on the medial incision determined by the location of the growth, carried sufficiently lateralward to permit a safe margin beyond the border of the tumor, and joined to the medial incision below the breast. (Fig. 531.) Medially and laterally, skin flaps are dissected to limits which permit complete removal of the pectoral muscles and a thorough dissection of the axilla. The flaps should be undermined fairly close to the skin to prevent local recurrences from cancerous deposits in the superficial lymphatics.

The extent of the skin margins, given the tumor and the degree to which the undermining of the flaps approximates the skin varies with different operators. The Halsted school advocates a wide excision of skin which may necessitate grafting, and which requires less undermining of the remaining flaps. The Handley School, with adequate but less removal of skin, undermines extensively close to the skin (which frequently causes sloughing of portions of the flaps). The Finney operation utilizes a modification of the Handley method and a primary closure of the defect is done where possible.

Dissection

After the flaps have been prepared, the dissection is carried through fat and subcutaneous tissues until the following land marks are identified:

1. Medially, the fascia at the junction of the sternum and the origin of the pectoralis major muscle.
2. Superiorly, the cephalic vein or the clavicle.
3. Laterally, the edge of the latissimus dorsi muscle and near the insertion of the pectoralis muscle in the humerus.
4. Inferiorly, the fascia overlying the rectus abdominis.

Dissection beyond the limits given above has been shown by previous experience not to add to the number of cases cured. (Fig. 531.)

The pectoralis major having been exposed, the fibers near the clavicle are separated, the index finger is passed beneath the muscle near the tendinous insertion raising the muscle over the finger. The muscle is divided near its attachment to the humerus. Bleeding points are clamped and tied individually. The major portion of the pectoral muscle is then further separated from its clavicular fibers (the operator being careful of the cephalic vein) and the upper portion of the sternum by sharp and blunt dissection. Bleeding points en-

countered are clamped and tied. The pectoralis major is then reflected downward. The brachial fascia below the coracoid process and the costocoracoid membrane together with the pectoralis minor tendon near its insertion are next divided and the muscle reflected downward. The subclavian vein, artery, a portion of the brachial plexus and many branches of these major structures are exposed next. (Fig. 532.)

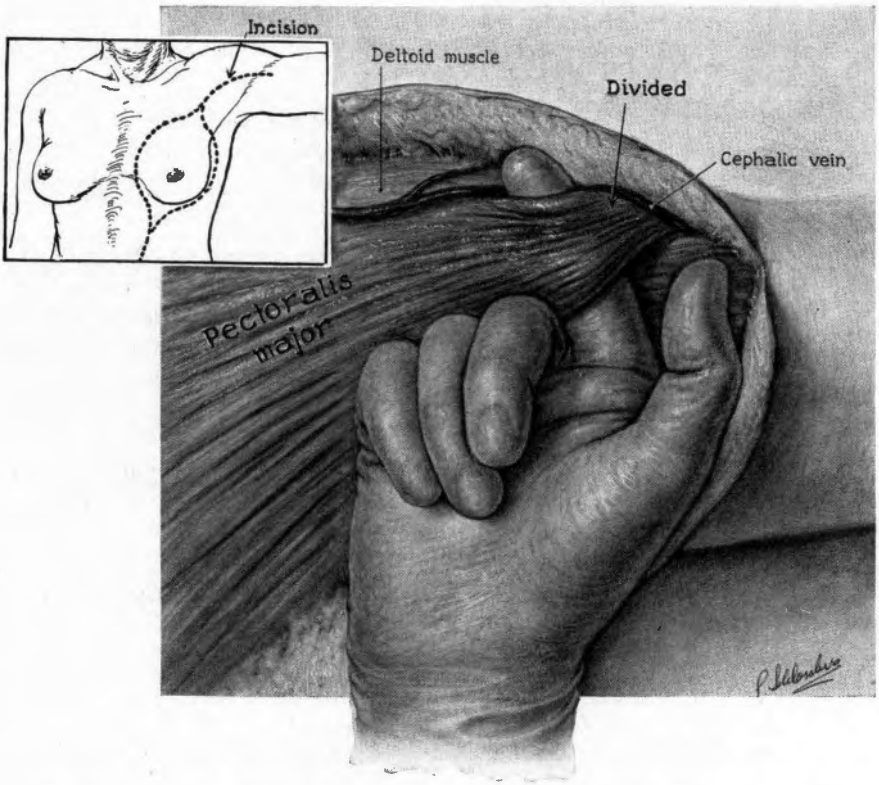

FIG. 531. Operative stages in radical mastectomy. Incision and preparation of flaps (insert, upper left). Isolation of the fibers of the pectoralis major prior to division. The cephalic vein acts as a guide in separating the pectoral from the deltoid fibers.

Axillary Dissection. The axillary dissection is begun at the apex, at the proximal end of the axillary vessels. The structures encountered from the apex of the axilla laterally are: the superior thoracics, the thoracic branches of the acromiothoracic and the subscapular arteries, their accompanying veins, the short thoracic nerves, the long thoracic nerve. The dissection proceeds from the proximal end of the axillary vessels and progresses distally, each branch of artery and vein being traced close to the main vessels, cleanly dissected, clamped,

divided and ligated individually. The clamping or ligating of large sections of tissue, as to include a venous and arterial branch at the same time, is avoided.

The dissection should be thorough, removing all possible fatty tissue. lymph glands and areolar tissue. The long thoracic nerve

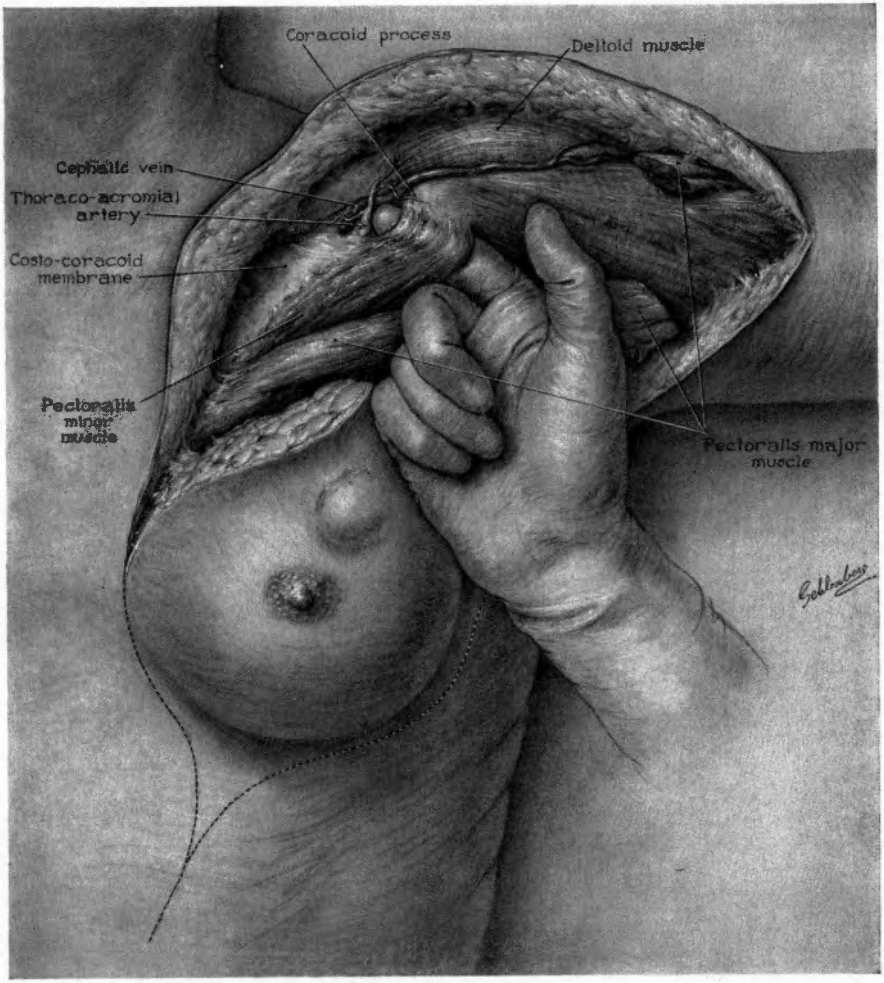

FIG. 532. Operative stages in radical mastectomy. Division and reflection of the pectoralis minor muscle and beginning of the axillary dissection.

should be preserved unless involved by the tumor. The subscapular vessels may be divided, if necessary, to remove the surrounding tissue. Rarely, the wall of the axillary vein is invaded by metastatic growth. In this case, the vein should be resected. Experience has shown that

this does not produce postoperative edema of the arm or other complications.

Completion of Chest Wall Dissection, Removal of Breast. The medial chest-wall dissection is now completed, freeing the pectoral muscles from the sternum and chest wall. Next, the serratus fascia is dissected away from the chest wall back to the posterior border of the scapula. A plexus of veins is frequently encountered in this area which may be quite troublesome. Inferiorly, a portion of the anterior sheath of the rectus muscle may be removed to advantage in certain cases. The axillary contents, the breast and the muscles are removed en masse.

Hemostasis should be thorough. The vessels near the axillary vein and artery should be ligated with silk. Bleeding points over the chest wall may be either ligated with fine silk or the vessels may be sealed by electrocoagulation. We have observed the collection of an increased amount of serum in the wound after electrocoagulation, but the method has the advantage of reducing the time required for operation. (Fig. 533.)

Closure and Drainage

A stab wound is made in the skin of the axilla, and through it a cigarette drain is inserted to the apex of this space. Another drain (a Penrose drain) is placed beneath the medial flap; this extends toward the clavicle and presents at the lower end of the incision as shown in Fig. 534.

The incision is now closed. In accordance with the practice of some surgeons no effort is made to exert tension to approximate the flaps, any remaining defect being covered with Ollier-Thiersch grafts. In many cases, however, the skin edges can be approximated by the use of tension sutures. A more sightly scar and a shorter period of hospitalization is thus assured. Where the skin flaps are readily approximated, subcutaneous sutures of fine black silk are used in addition to the skin stitches.

A pressure dressing is applied, using an excess of Dakin's gauze or a sea sponge in the axilla. All dead space is obliterated and air, accumulated serum, and blood are expelled from the wound before the dressing is applied.

SKIN GRAFTING FOR INCOMPLETE FLAP CLOSURE

The skin of the anterior thigh is shaved and prepared in a similar fashion to that of the breast operative field. An Ollier-Thiersch graft is then taken from this area. The graft is obtained by the method de-

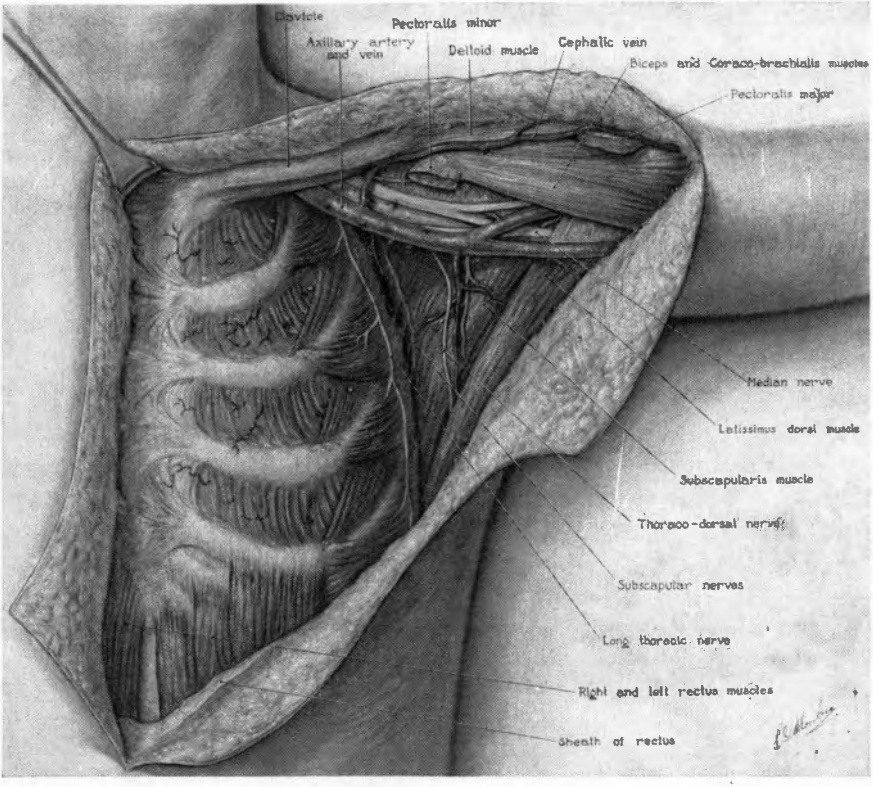

FIG. 533. Operative stages in radical mastectomy. The completed dissection showing the anatomy of the operative field. (By courtesy of Surgery, Gynecology, and Obstetrics.)

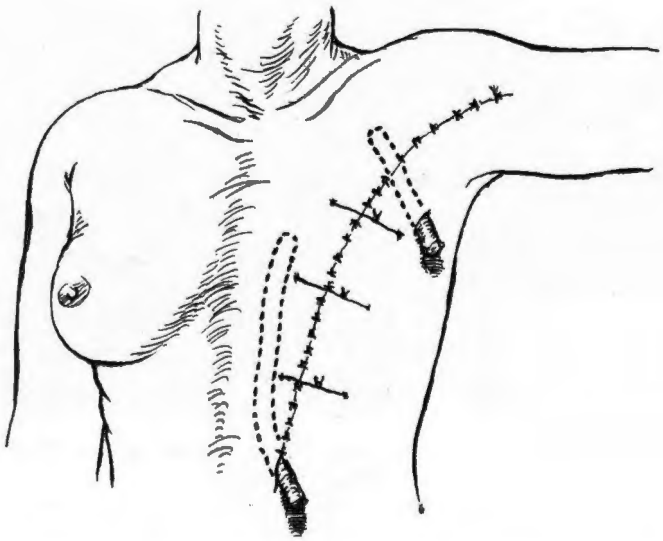

FIG. 534. The wound at the completion of the operation showing the line of suture and the insertion of drains.

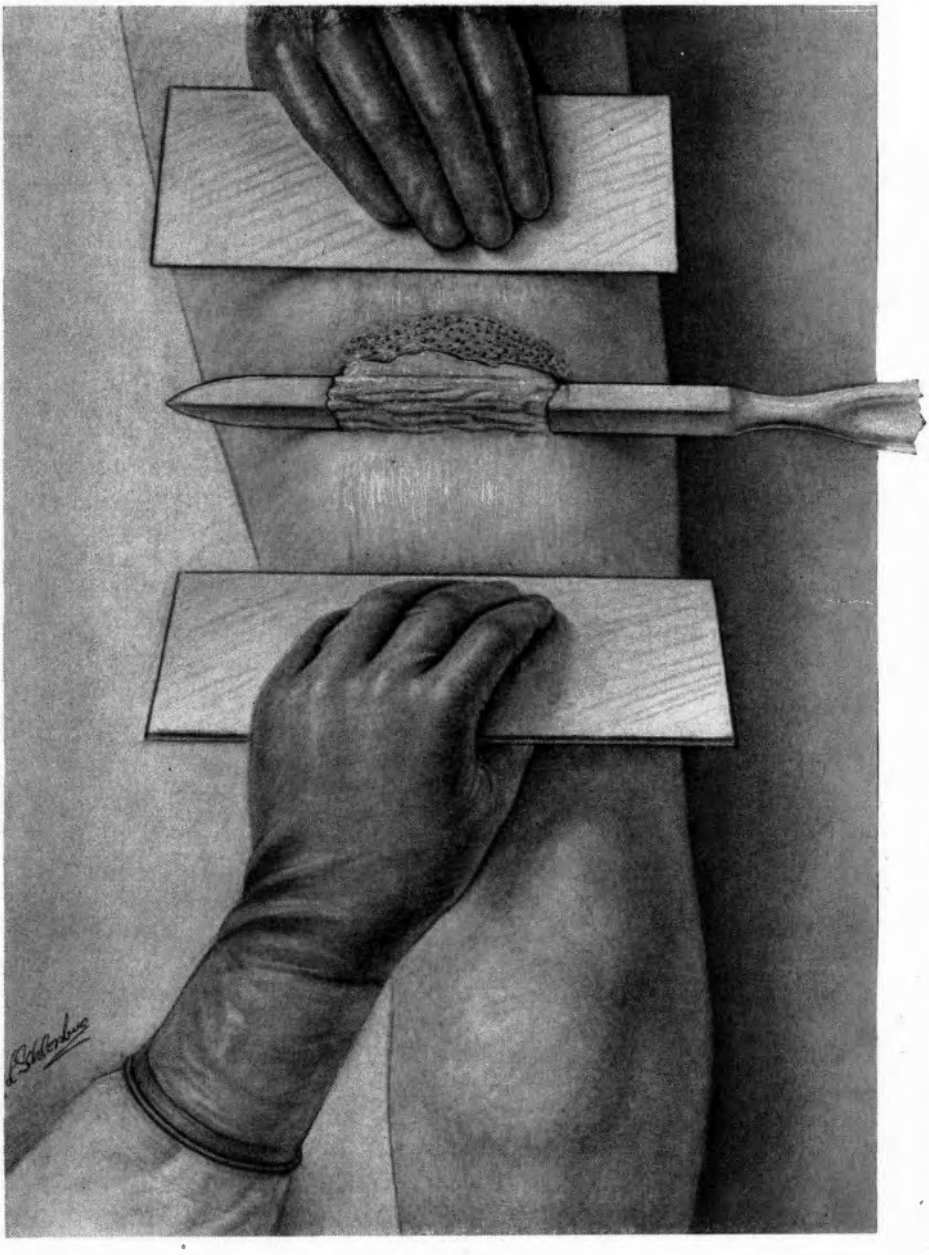

FIG. 535. Removal of skin graft from thigh. (By courtesy of Surgery, Gynecology, and Obstetrics.)

scribed by Davis. The skin is made taut by the use of narrow wooden boards. (Fig. 535.) A sharp knife with a sufficiently long blade is used to cut a satisfactory width of skin. The knife blade is held flat against the skin and then passed with a sawing motion through the derma but not the full thickness of the skin. The graft should be the thick-

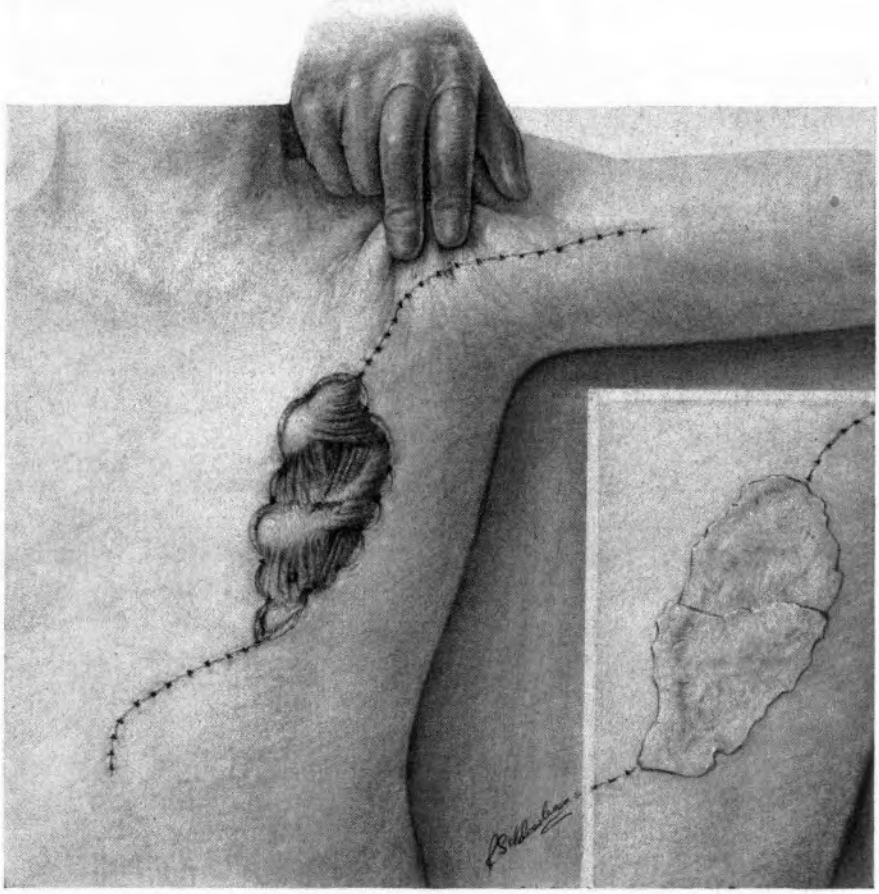

FIG. 536. Area to be grafted and application of skin graft (lower right). (Figures 533, 535 and 536 reproduced by the courtesy of Surgery, Gynecology and Obstetrics from I. Ridgeway Trimble. Cancer of the Breast. Surg., Gynec., and Obst., January, 1940, 72:82-92).

ness of tissue paper. (Fig. 535.) When a sufficient amount has been obtained, it is spread out on a sheet of gutta percha with the raw surface up, using saline solution freely, to keep it moist. The graft is evenly distributed over the gutta percha.

The denuded area at the site of the breast amputation must be

dry. The raw surface of the graft is then applied over the denuded area and pressed firmly down upon it by means of warm saline sponges. A few small V-shaped slits are cut into the graft to permit the escape of air and serum from beneath. This prevents lack of approximation. (Fig. 536.) A special pressure dressing is then applied. This consists of zeroform gauze placed immediately over the graft, a thin layer of dry gauze, followed by a sufficient amount of sea sponge for transmitting even pressure to the graft. This dressing is strapped firmly in place by means of adhesive before the remaining dressings are applied over the operative site. The dressing over the graft is changed in 72 hours. Pressure is maintained for 5 to 6 days.

POSTOPERATIVE CARE

The arm on the affected side is to be extended at right angles to the chest when patient is placed in bed, and supported on a pillow. Use of the arm is encouraged after the second postoperative day.

The first dressing is usually performed on the second postoperative day at which time the drains are shortened; these are removed on the third day.

No patient should be finally discharged following a radical mastectomy until satisfactory function of the arm on the affected side has been regained, nor without proper instructions as to cosmetic appliances (a padded brassiere). A prosthesis of sponge rubber or latex modeled from the remaining breast is available for patients who are particularly sensitive to the cosmetic defect (Brown). The patient should be encouraged to return for periodic examinations twice yearly for the first two years and once yearly thereafter.

1. Incision and undercutting of the skin.
2. Dissection of fascia and division of muscular attachments of pectoralis major and minor.
3. Exposure of axilla, isolation of the axillary vessels.
4. Removal of apical fat and lymph glands between the axillary vessels, brachial plexus, chest wall, and subscapular muscle. Preservation of the long thoracic nerve unless involved by tumor.
5. Removal of breast, pectoral muscles, and axillary tissue en masse from the chest wall.
6. Ligation or coagulation of vessels over the chest wall.
7. Closure of skin incision (or grafting) and insertion of drains.

8. Application of pressure bandages, obliterating dead space.
9. Rehabilitation of the patient.

ALTERNATIVE PROCEDURES IN PERFORMING RADICAL MASTECTOMY

The numerous modifications proposed in the early part of the present century for the performance of the radical mastectomy have fallen into disuse. Most of the proposed variations for outlining the incision are without significance or offer no advantages over the standard Halsted-Meyer operation. There are, however, a few alternative procedures which are in use and which merit mention.

Incisions

In using the standard elliptical incision which parallels the anterior axillary fold, the operator may follow either the Halsted or Handley school of thought. The Halsted technic requires the removal of a wide margin of skin about the circumference of the growth and frequently necessitates grafting. The Handley technic requires less removal of skin but extensive undermining of the flaps close to the skin which may result in sloughing. The wound may usually be closed without grafting, but postoperative irradiation of the chest wall is advisable for the larger growths if the Handley technic has been followed.

The Stewart mastectomy which employs an elliptical incision running transversely has certain advantages. If the breast is large and pendulous or if the tumor is located in the outer segment of the breast, this technic is preferred by some operators. This incision permits the removal of large amounts of skin and closure without grafting. Since it does not extend upward toward the arm, it has certain cosmetic advantages. In using the Stewart incision it is important that the axillary portion of the ellipse be well rounded and not carried so far into the axilla as to threaten cutting across the lymphatic pathways of the arm.

Dissections

In performing the muscular dissection, the so-called muscular tour may be completed before beginning the axillary dissection. After cutting through the insertion of the pectoralis muscle near the humerus, the dissection is carried through the clavicular fibers and continued down over the sternum cutting away the slips of origin of the pectoral muscles. By performing the medial portion of the muscular dissection before proceeding to the axilla, the lymphatics

perforating the anterior intercostal spaces are severed, thus interrupting the potential pathway of mediastinal involvement before disturbing the breast.

Skin Removal

There are several schools of thought in regard to the amount of skin to be removed at the time of mastectomy. It has been pointed out in Chapter 20 (p. 468) that recurrence following operation is most frequent in the skin and subcutaneous tissues of the chest wall, and all observers are agreed that the handling of such tissues and the underlying fascia in this region has a direct bearing on the incidence of local recurrence. Rodman in reporting the results of mastectomies performed in accordance with the operative procedure devised by his father advocates the use of the Rodman technic which insures wide skin and fascial removal with avoidance of skin grafting. In this operation the diameter of the sacrificed skin overlying the tumor is not less than 15 centimeters and the skin flaps are carefully undermined as advocated by Handley. Rodman reported the percentage of local recurrences in his 132 cases as 2.2 per cent, in comparison with the following percentages recorded by others:

White	22.6 per cent local recurrences.
Lewis and Rienhoff	19.2 per cent local recurrences.
Haagensen and Stout	22.8 per cent local recurrences.

The followers of Halsted likewise advocate adequate skin removal but do not stress primary closure of the flaps but resort to skin grafting.

In the British school of thought the removal of large portions of the skin and extensive undercutting of the flaps are deemed unnecessary and reliance against recurrence is placed upon irradiation.

Since radical mastectomy is still the major means by which to combat mammary carcinoma, any curtailment of the thoroughness of the procedure, as originally practiced by the Halsted-Meyer School, must be looked upon with misgivings, since all of the accumulated evidence is in favor of the soundness of the fundamental principles outlined for this operation in the preceding pages.

OPERATIVE MORTALITY

The operative mortality for radical mastectomy in the hands of experienced surgeons is close to 1 per cent. Higher figures are usually given by teaching hospitals where the operative results of surgical residents are included. The following tabulation was compiled by Pack and Livingston.

TABLE LXXXVII[1]

OPERATIVE MORTALITY IN MAMMARY CANCER

SURGEON	HOSPITAL	NO. OF CASES	PERCENTAGE
Lee, B. J.	Memorial Hospital, New York	217	0.9
Mathews, F. S.	St. Luke's Hospital, New York	218	1.3
White, W. C.	Roosevelt Hospital, New York	157	2.9
Pack, G. T., and E. M. Livingston	Memorial Hospital and New York City Cancer Institute	130	0.7
Smith, G. Van S., and M. K. Bartlett	Free Hospital for Women, Boston	164	1.3
Lane-Claypon	British Health Ministry	2006	3.0
McClure, R. D.	Henry Ford Hospital, Detroit	150	4.0
Lewis, D., and W. F. Rienhoff, Jr.	Johns Hopkins Hospital, Baltimore	950	6.4

[1] From Pack, G. T. and E. M. Livingston: Treatment of Cancer and Allied Diseases, New York. Paul B. Hoeber, 1940. Vol. 1, p. 712.

Operative risk is diminished by meticulous attention to the following precautions:

1. Rigid criteria for operability.
2. Careful preoperative preparations.
3. A competently administered and suitable anesthesia.
4. Complete control of hemorrhage.
5. The avoidance of shock.
6. The avoidance of infection.

The criteria of operability, in addition to taking into consideration the general condition of the patient, must include the feasibility of establishing a cure. The radical mastectomy as outlined in the above discussion represents the modern limits of the operation. The dissection is no longer extended above the clavicle for supraclavicular metastasis, portions of the chest wall are not removed when involved by the disease, and heroic measures such as shoulder-girdle amputations are no longer attempted to control the disease. For such advanced cases, reliance is placed upon irradiation.

The prevention of hemorrhage, shock and infection in radical mastectomy requires the same rigid technic used in other major operations. The extent of the operation requires careful hemostasis, the gentle handling of tissues, and a carefully administered anesthetic, if shock is to be avoided.

PATHOLOGIC RECORD

As an aid to prognosis and as a guide to further therapeutic procedures which may be necessary in cases which suffer recurrence.

the extent of the disease at the time of operation, the pathologic form and the grade of the cancer should be established by proper pathologic study. The surgeon should record in his operative note his impressions of these fundamental facts from gross examination, and at a later time he should compare them with the pathologic report. In this way, much valuable information will be obtained. The skill of the surgeon in recognizing the characteristics of the disease from its gross appearance also will be improved by such studies.

FIVE-YEAR SURVIVAL RATES FOLLOWING RADICAL MASTECTOMY

Although approximately 50 years have elapsed since the standard procedure for radical mastectomy was described by Halsted and Meyer, it is still difficult to make unqualified statements in regard to end-results. There are a variety of factors other than the technic of the operation itself which influence the results reported from different clinics. Among these are: (1) different pathologic standards for the diagnosis of cancer; (2) differences in classifying the stage of cancer treated; (3) variations in the standard of operability; (4) variations in the statistical method for calculating five-year survivals.

1. In any series of cases treated by radical mastectomy, a certain number of so-called borderline but benign cases are inevitably included even after the specimen has been subjected to competent pathologic study. These include benign intracystic papilloma, forms of adenosis, and atypical adenofibromas. Some of the large clinics at the present time classify nonmetastasizing intracystic papilloma as Grade-I cancer. Among the cases operated upon by Halsted and originally classified as adenocarcinoma, some were subsequently reclassified as adenosis or Schimmelbusch's disease on restudy. Atypical fibro-adenomas, particularly those found in pregnancy, are difficult to classify with assurance and are an additional source of error.

2. It has become customary to speak of five-year cures in groups according to the stage of cancer treated. In discussing the end-results, Halsted drew a distinction between the cases in which the cancer was confined to the breast and those in which the regional lymph nodes were involved. Numerous objections and refinements of this grouping have been suggested because nodes thought to be positive prior to operation were found to be negative on pathologic study, and on the other hand, nodes not palpated clinically were found involved on microscopic study. A further subdivision for late cases of cancer was introduced by Steinthal, since cases considered inoperable

by modern standards were included in the early operative statistics. In cases studied pathologically there has been a further tendency to subdivide the cancers treated according to the pathologic grade, or the pathologic form. These various methods of classification have rendered the comparison of results in the different clinics exceedingly difficult.

3. The question of operability or inoperability in cases of advanced cancer remains a matter for clinical judgment. Obviously with increased experience a number of cases formerly subjected to radical mastectomy are excluded from the operable group. This must be borne in mind in comparing results which include cases treated in the early part of the present century. In the more recent decades cases with erysipeloid involvement of the skin, skin metastasis beyond the area immediately adjacent to the tumor, extensive involvement of the axilla, and involvement of the supraclavicular nodes have been excluded from the operable group. Difference of opinion still persists in regard to the influence of age, pregnancy and lactation mastitis upon operability.

Haagensen and Stout consider those cases inoperable in which any of the following findings are present:

1. Edema of more than one-third of the skin over the breast.
2. Satellite tumors of skin over breast.
3. Chest wall tumor nodules (parasternal or intercostal).
4. Edema of arm.
5. Inflammatory carcinoma.
6. Distant metastases.
7. Carcinoma developing in pregnancy or lactation.
8. Any two of the following:
   A. Ulceration of skin.
   B. Edema in less than one-third of skin over breast.
   C. Fixation of tumor to chest wall.
   D. Axillary nodes greater than 2.5 cm. in transverse diameter, if proved by biopsy.
   E. Fixation of involved nodes to skin.

4. There are two principal methods by which to calculate the five-year survival rate. The crude five-year rate (used by the authors) is based upon the number of patients living and free of clinical evidence of carcinoma at the end of 5 years. No deduction is made for those cases dying postoperatively or from natural causes during this five-year period.

The net five-year survival rate is based upon the number of cases living and free from clinical evidence of disease at the end of five years after having eliminated all cases dying from causes other than

mammary cancer during that period. In both of these accepted methods of calculation it is important that consecutive, unselected cases[1] be reported, that the nature of the disease be microscopically verified, that the period of calculation should begin at the time of the radical mastectomy and not with the onset of symptoms and that the patient be free from clinical evidence of the disease at the end of the five-year period. The term "definitive cures" refers to the fact that the patients are clinically without evidence of disease. There is obviously no method of standardizing this since many of the follow-up reports are based upon letters from the patient or family physician and the term "living and well" in such reports is not comparable to a negative examination by the surgeon which includes roentgenograms of the chest and skeleton. Certain authors have stressed the importance of the natural survival rate of untreated cases of carcinoma as a standard of comparison for the results achieved in treated cases. This natural survival rate, however, is calculated from the onset of symptoms as stated by the patient, rather than the date of operation. The patients are never clinically free from the disease and unless autopsied cases only are included, microscopic evidence of the cancer is not available.

A review of the numerous reports in the literature, with these considerations in mind, permits certain generalizations in regard to the surgical curability of mammary carcinoma.

If all cases of mammary carcinoma are considered, regardless of the stage of the disease, and if radical mastectomy is the only method of treatment, approximately one third of the cases will survive the five-year period. In our own material the five-year survival rate in 1,957 followed cases was 34.2 per cent. This series included 75 cases in which no treatment of any kind was given because of the advanced stage of the disease. The over-all five-year survival rate in other large American clinics for a similar period of time (1890-1935) where untreated cases are not included may be broken down, usually into 65 per cent survivals for patients without axillary involvement, and 20 per cent for those with positive axillary nodes; this ratio is two cases with axillary disease to one without. Calculated on such a basis, the over-all five-year survivals are 35 per cent.

The authors believe that the five-year survival rate of 33 1/3 per cent for unselected cases of mammary carcinoma surgically treated represents a fair base line. Taylor, in a review of the literature in 1932, found the five-year survival to be 30.6 per cent in 7,974 cases. We have reviewed the surgical results in American literature since

[1] The term "absolute" survival rate refers to the fact that all cases presenting themselves for treatment are included, whether hopeless or suitable for treatment.

1932 for an equal number of cases (8,585) and have found the five-year survivals to average 36.9 per cent (Table LXXXVIII). Combining the two series of 16,559 cases a five-year survival rate of 33.7 per cent is obtained. In order to emphasize the variable factors that may enter into such calculations, the five-year survival rate of 34.1 per cent for all cases in our series is raised to 38 per cent if we included 101 cases of adenosis and benign intracystic papilloma treated by radical mastectomy through the fear or impression that cancer was present. The figure is further increased to 39 per cent if we exclude those cases that were considered too advanced to have surgical treatment. On the other hand, the figure drops to 33.5 per cent if we exclude patients who report themselves well by letter at the end of five years but who die less than a year thereafter, cases which were not subjected to a competent physical examination, to exclude clinical evidence of the disease.

Since radical mastectomy is no longer the only method by which to treat mammary cancer and since routine pre- and postoperative irradiation has been advocated, it is necessary to estimate the results of surgical treatment in OPERABLE cases. This is a difficult task since rigid standards for operability have not been generally adopted.

TABLE LXXXVIII

COMPARATIVE STATISTICS—FIVE-YEAR SURVIVALS

AUTHOR	YEAR REPORTED	NO. OF CASES	TOTAL CASES PER CENT	WITHOUT AXILLARY INVOLVEMENT PER CENT	WITH AXILLARY INVOLVEMENT PER CENT
Mathews	1932	153	37.8	64	29
Eggers	1932	80	43.8	65.4	33.3
Harrington[1]	1933–34	3740	37.4	63.6	24.3
Klingenstein	1932	42	23	40	17
Eggers, de Cholnoky and Jessup	1941	253	35.5	55.6	21.2
Geschickter	1942	1957	34.1	66	19
Graham	1937	545	29.3	71	12
Brooks and Daniel	1940	72	36.1	91.6	26.7
Simmons, Taylor and Adams	1936	159	43.4	74.8	25
Gordon-Taylor	1938	497	51.9	85.9	35
Jarvis	1936	320	32		
Greenough	1935	352	35.7		
Hawkins	1944	415	41	68.9	28.6
TOTALS	1932–44	8585	36.9	66.7	23

[1] There is an overlap in The Mayo Clinic statistics reported by Sistrunk and McCarty and by Harrington and at various dates—Survival rates of 36.3, 37.4, 43.0 per cent, etc., have been reported. We have chosen 37.4 per cent as representative.

Those clinics where irradiation has always been largely relied upon in the treatment of cancer tend to exclude from the operable group patients who would be considered operable in surgical clinics.

Fortunately, the percentage of involvement of axillary lymph nodes offers a reliable basis to compare groups of cases selected as operable by different clinics. Thus, Adair selected 2,467 cases as primarily operable from among 6,444 cases of mammary cancer. He found that 51 per cent of these had axillary involvement. Adair's operable group included 471 cases treated by radical mastectomy alone, of which 45 per cent survived the five-year period.

From among 2,534 mammary cancers, the author selected 1,664 as primarily operable. The lymph-node involvement in these cases was 50.5 per cent and the five-year survivals 48 per cent. These figures check very closely with those of Adair.

At present, therefore, the five-year survival rate by surgery in *operable* cancer approximates 70 per cent for cases without axillary involvement, and 25 per cent in cases with axillary involvement, and the two groups of cases are about equal in size; the combined curability averages 47 per cent. These figures are given as a maximum theoretic result that can be expected from the Halsted-Meyer operation in the best clinics at the present time. Improvement in results above this figure would represent an increased percentage of cases in the early group without lymph node involvement. This presupposes an effective popular campaign which would actually increase the number of early cases rather than more rigid standards of operability which would exclude late cases from treatment.

Excluded from the operable group are cases with evidence of metastasis to lung or bone, with a palpable enlarged nodular liver, with fixation of the cancer to the chest wall, with the skin changes of inflammatory carcinoma, with ulceration of the skin or other skin changes not in the immediate contact with the tumor, with involvement of the supraclavicular nodes or of nodes high in the axilla, with recurrence following incomplete operation, cases with cancer in pregnancy, or similar tumors at the site of a former lactation abscess, and cases of Paget's cancer with extensive involvement of the breast beneath.

These criteria for inoperability should not influence the clinician to exclude operation for palliative reasons, in cases where irradiation is inadequate or contraindicated. Nor is it assumed that all of these cases are definitely incurable. These criteria are the result of experience which teaches that radical mastectomy in such cases has yielded a percentage of five-year survivals lower than that found in untreated mammary cancer.

Radical mastectomy is unquestionably the treatment of choice in cases which answer the above criteria for operability. This is indicated by Adair's statistics: the five-year survival rate for radical mastectomy in the operable group was 45 per cent and only 18 per cent in a similar group treated by irradiation alone.

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Irradiation of Mammary Carcinoma

A paramount question at present is: to what extent does roentgen-ray or radium therapy supplement or replace radical surgery?

While conflicting ideas prevail in regard to the choice between surgery and irradiation for the individual case of mammary carcinoma, or the use of combinations of both methods, nevertheless, all are agreed that irradiation is necessary for the proper management of certain forms of the disease.

APPLICATION OF RADIOTHERAPEUTICS TO MAMMARY CARCINOMA

There are numerous considerations which must be weighed in applying the principles of radiotherapeutics to a given case of carcinoma of the breast. The most important of these is the extent of the

disease. Small mammary cancers without axillary involvement are best treated by radical surgery, while extensive inoperable mammary cancer is best treated palliatively by irradiation. In between these two extremes lies the greatest number of cases, and here the advantages of surgery, irradiation or a combination of both must be considered. The difficulty in estimating the added value of irradiation to surgical procedures is indicated by the multiplicity of optional technics. No one procedure has been followed for a sufficient period of time fully to establish its worth. Observers vary also in the choice of the time that irradiation is to be employed; i.e., as to whether preoperative or postoperative roentgen-ray therapy best influences five-year survivals.

Further to complicate the picture, adequate pathologic studies are missing from many reports. This makes it difficult to evaluate the effectiveness of irradiation on specific groups of cancers.

Despite these handicaps, a perspective may be obtained by comparing survival rates and contrasting the cures (a) by surgery alone, (b) with the combined methods of treatment, or (c) by treatment with irradiation alone.

In the following discussion of irradiation therapy of the breast, the forms of treatment have been classified in accordance with the following outline:

I. Combined Therapy
   (1) Preoperative Irradiation.
   (2) Postoperative Irradiation.
   (3) Irradiation for Recurrent or Metastatic Carcinoma.
II. Irradiation Therapy Alone
   (1) Roentgen-Ray Therapy Only.
   (2) Interstitial Irradiation.
III. Adjuvant Therapy
   (1) Irradiation Castration.

COMBINED THERAPY

Preoperative Irradiation

It is generally agreed that radical mastectomy affords about 65-70 per cent of five-year survivals when the cancer is confined to the breast and only about 20-25 per cent of such survivals when the disease has spread to the regional lymph nodes. Because the results achieved by surgery are thus limited, irradiation and operative procedures are often combined, and since postoperative irradiation has been somewhat disappointing, there has been a tendency to resort to preoperative irradiation. There are, however, certain disad-

vantages in this procedure. The patient does not always undergo the delay willingly, particularly with the knowledge that a major surgical procedure awaits her at the end of the period of weeks. On the other hand, having passed through such a period, disappearance of the tumor under treatment may give her a false sense of security resulting in refusal to proceed with the operation. Moreover, the treatment adds to the discomfort and the financial burdens of the patient, and either scarring or increased vascularity may add to the labors of the surgeon at operation. The chief drawback, however, is that a positive diagnosis of cancer frequently cannot be made in early cases on clinical grounds. Surgical removal of the growth rather than aspiration biopsy is often necessary to establish the diagnosis. Finally, the statistics on the results achieved by preoperative therapy are still inadequate, and those available do not justify the procedure as a routine (Table LXXXIX).

Indications for Preoperative Irradiation. Preoperative roentgen-ray therapy still should be given further trial in highly anaplastic carcinomas. In large circumscribed adenocarcinomas, in which vascularity is indicated by bleeding from the nipple, it is worthy of trial if radio-resistant gelatinous cancer is ruled out by aspiration biopsy and also in Paget's cancer with involvement of the breast proper. Improvements in technic may bring important results by this method.

Advocates of preoperative irradiation claim the following advantages:

1. A lethal tumor dose may be given in many cases without denying the patient the advantages of operation.
2. If irradiation is to be employed in controlling the tumor, it should be most effective before disturbing the tumor bed with operative procedures.
3. Irradiation decreases the viability of the cancer cells, and correspondingly decreases the dangers of transplanting or disseminating malignant cells into the wound during operation.
4. Since irradiation is necessary in the management of so many cases of mammary cancer, it offers unusual opportunities to study irradiation effects on the tumor and tumor bed which may prove of future value in perfecting the technics of irradiation.

Since adequate preoperative irradiation is a major procedure, it should not be undertaken without a positive diagnosis of cancer.[1]

[1] When preoperative irradiation has been given elsewhere for suspected mammary cancer without confirmation by biopsy, the true pathology of the lesion may be masked by irradiation changes and diagnosis is rendered extremely difficult.

For this reason it is unsuitable in early or borderline cases where diagnosis requires excision of the tumor. Under such conditions the radical operation should be proceeded with at once, following microscopic confirmation of malignancy. When the breast tumor, before operation, is obviously malignant and when metastasis to the axillary nodes is reasonably certain upon clinical examination, preoperative irradiation may be in order, provided the diagnosis has been confirmed by aspiration biopsy (which is, as a rule, readily performed under such conditions).

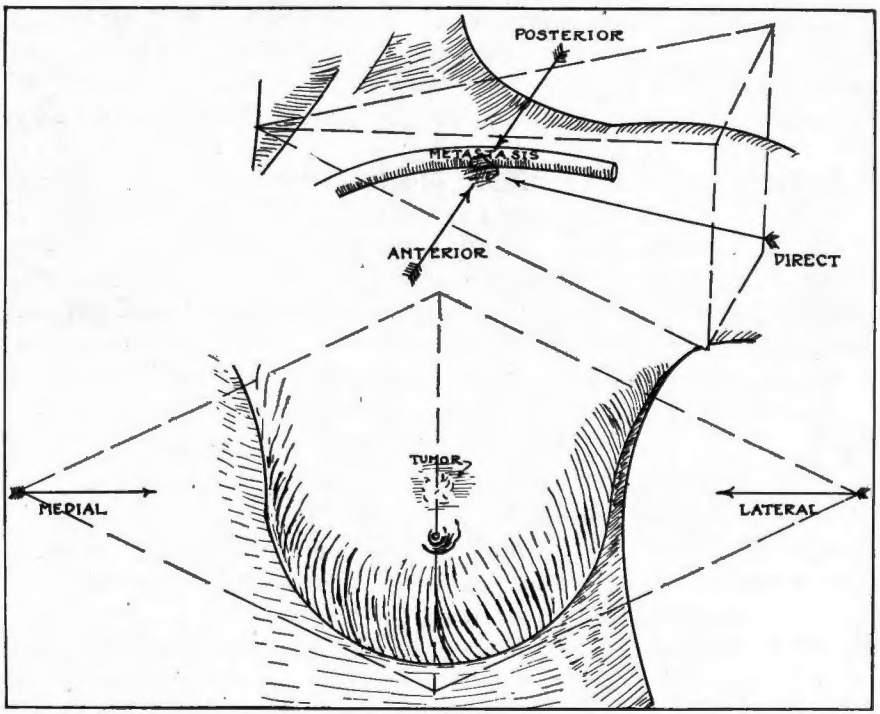


FIG. 537. Diagram indicating the direction of the roentgen-ray beams in irradiating the breast and axilla.

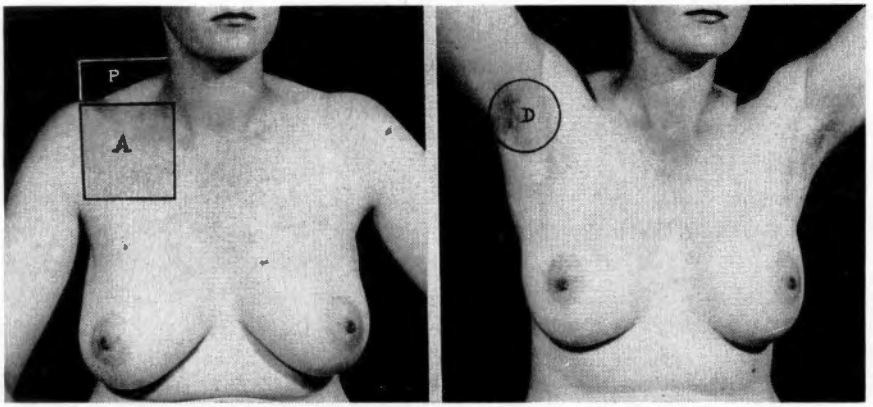
Technic of Preoperative Irradiation. Preoperative irradiation must be given in maximum dosage (between 1,800 and 2,500 roentgens to each port measured in air—see p. 679) and should be given over a period varying from four to six weeks. The patient is then ready for operation within six to eight weeks following the last treatment. Pathologic study of the tissue removed by radical mastectomy following such extensive preoperative irradiation often shows viable cancer, microscopically, in the region where the disease has disappeared clinically.

The skin tolerance varies widely in different patients and is usually less in the axillary fold or the inferior mammary fold because of excessive moisture in these regions.

The technic of irradiation in breast carcinoma has been standardized in our clinic as follows:

THE PHYSICAL FACTORS are 200 Kv., 20 ma., 50 cm. skin-target distance. The average added filtration is equivalent to 0.5 mm. of

FIG. 538 FIG. 539



Routine Fields Used for the Irradiation of Mammary Carcinoma.
(See also Fig. 540.)
FIG. 538. The location of the anterior axillary field is indicated by the square "A," and the posterior axillary field which is only partly visible by the square "P."
FIG. 539. The location of the direct axillary field is indicated by the circle "D."

copper and 1.0 mm. of aluminum. Because of convenience in applying therapy to the axilla, a 6 to 10 cm. cone is used rather than an open port. The remainder of the fields are treated by the open port technic. Five fields are used to give the treatment as designated below. One or two treatments of approximately 200 roentgens each is given per day in rotation over the five fields. The total amount of treatment given to each field varies with the tolerance of the patient. The total dosage per field averages between 1,800 and 2,500 roentgens.[1] The five fields (Figs. 537-540) used are as follows:

1. *A direct axillary field:* the beam is directed through the center of the axilla toward the sternoclavicular joint.
2. *A supra- and infra-clavicular field* (anterior axillary field): the beam is directed at right angles to the skin surface in this region.
3. *A supraspinous or scapular field* (posterior axillary field): the

[1] As used in this chapter the roentgen units given are measured in air.

beam is directed from a posterior direction perpendicular to the skin of this region and towards the axilla.

4. *A medial mammary field:* the beam is directed toward the breast and tangential to the body surface.
5. *A lateral mammary field:* this corresponds to but is opposite in direction to the medial field.

The size of the fields varies with the individual case.

During and following irradiation, one may encounter certain complications such as irradiation sickness, pulmonary fibrosis, skin dam-

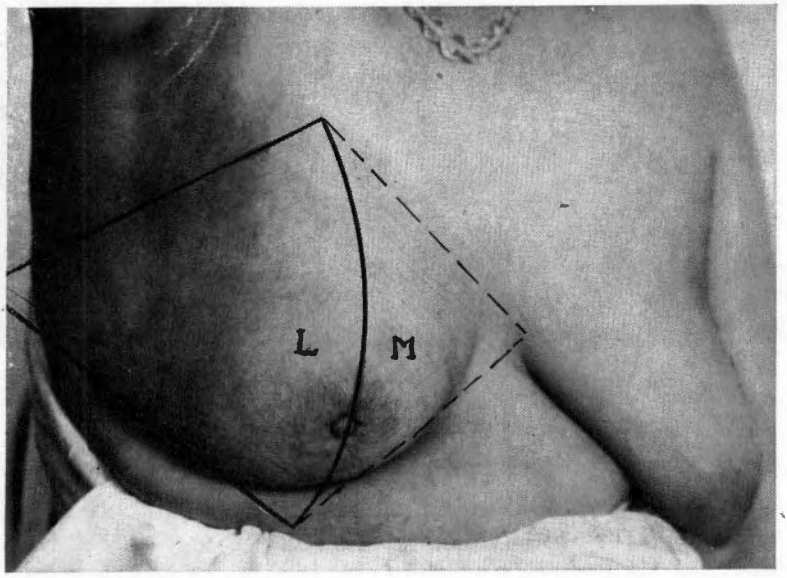


FIG. 540. The triangles "L" and "M" indicate respectively the approximate scope of the lateral and medial mammary fields. This patient shows the condition of the breast at the end of pre-operative irradiation.

age, increased incidence of lymphedema of the arm, and occasionally irradiation neuritis or bone necrosis. While these complications do not contraindicate irradiation, definite advantages should be probable before irradiation treatment is begun.

Postoperative Irradiation

In favorable cases which are controlled by radical mastectomy, routine postoperative irradiation is a debatable procedure. Irradiation may be a needless expense and ordeal. Moreover, when adequately given it is not without untoward effects such as pulmonitis, contractures in the axilla, etc. as noted above. The tolerance of the

Table LXXXIX

PER CENT OF FIVE-YEAR SURVIVALS

1193 CASES OF MAMMARY CANCER (Hawkins)[1]

STAGE OF DISEASE	SIMPLE MASTECTOMY	RADICAL MASTECTOMY	RADICAL MASTECTOMY PRE-OPERATIVE IRRADIATION	RADICAL MASTECTOMY POST-OPERATIVE IRRADIATION 3,500 r, +	RADICAL MASTECTOMY PRE- & POST-OPERATIVE IRRADIATION	X-RAY ONLY	RADIUM ONLY
Operable, limited to breast	48.2 53.6 with P.O. X-ray	68.9	54.5	70.0	69.2	40.0	23.4
Operable, axillary nodes involved	.....	28.6	20.0	35.2	18.2	5.3	14.3
Inoperable						Over 3,500 r 4.8	

[1] This Tabulation is based on a study of patients from the following Institutions:
The State Institute for the Study of Malignant Disease, Buffalo.
Pondville Hospital, Wrentham, Mass.
Palmer Memorial Hospital, Boston, Mass.
Collis P. Huntington Memorial Hospital, Boston, Mass.
Barnard Free Skin and Cancer Hospital, St. Louis.
American Oncologic Hospital, Philadelphia.
Albert Steiner Clinic for Cancer and Allied Diseases, Atlanta, Georgia.
University Hospital, Ann Arbor, Mich.
Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York.

patient for additional irradiation may be unnecessarily lowered by giving treatment to uninvolved areas and thus handicap further treatment should it be administered later for definite recurrence. Roentgen-ray treatment has been most effective when directed specifically to the regions involved by the disease.

Indications for Postoperative Irradiation. Despite minority reports of extremely favorable results achieved by postoperative irradiation (Hutchinson, Pfahler, Wintz) the bulk of evidence indicates

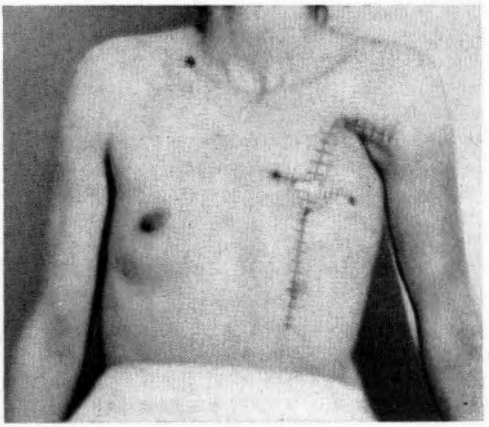


FIG. 541. The condition of the wound prior to post-operative irradiation. The photograph shows the wound ten days following radical mastectomy at the onset of post-operative irradiation.

a more modest improvement of five-year statistics. There is about 5 to 7 per cent increase in the five-year survivals in THOSE PATIENTS WHO HAVE LYMPH NODE INVOLVEMENT, provided the total amount of irradiation is well above 3,500 r (Table LXXXIX). This represents as much as 24 per cent improvement over operation alone in this group. Graham of the Cleveland Clinic is most discouraging in his statement, "In the series of cases of primary cancer of the breast studied there was no general indication that the clinical end-results were better in patients treated by operation and irradiation than in those treated by operation alone." His observations, however, were made before the present technic of divided dosage. A review of those cases more recently treated indicates that postoperative irradiation may be of definite advantage when the disease has spread beyond the limits of the mammary gland itself. Where the likelihood of recurrence in the field of operation can be predicted, postoperative irradiation is unquestionably the logical procedure.

These include cases in which the cancer is operable by clinical standards but where, at the time of operation, it is more extensive than anticipated. Postoperative irradiation is indicated when in undercutting the skin flaps or in performing the axillary dissection the dissection has passed through tissues involved by cancer or dangerously close to disease.

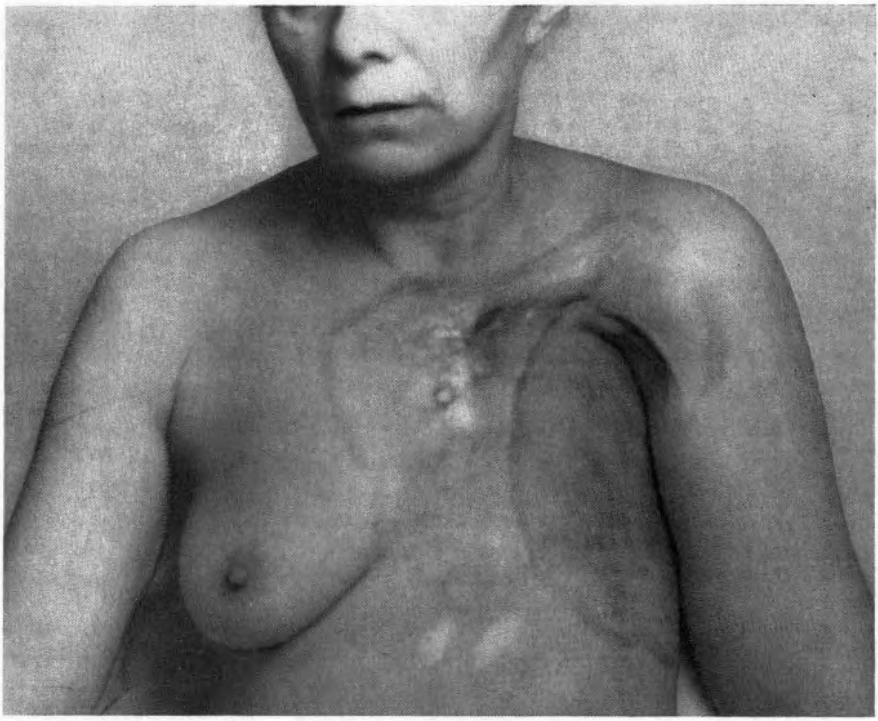


FIG. 542. Irradiation for post-operative recurrence. A standard cycle of post-operative irradiation has been given following recurrence in the parasternal region.

The object of postoperative irradiation is to extend the margin of safety given to the cancerous growth at the time of operation, particularly in the parasternal, axillary and infraclavicular regions, and to prevent or inhibit recurrences resulting from cancer cells that may have been disseminated in the wound. Lewis and Rienhoff have shown that local recurrence takes place in approximately 19.2 cent of the cases subjected to radical mastectomy. Similar figures were reported by White. While the number of cases with recurrent nodules, as shown by more recent studies, is diminished by a more rigid selection for operation, the figure remains relatively high (at least 15 per cent). Where preoperative irradiation has not been used

and where the disease apparently extends to or beyond the limits of operation, postoperative irradiation should be given.

Technic of Postoperative Irradiation. Our technic is as follows. The patient receives irradiation of the chest wall early in the postoperative period (if there have been no complications in the healing of the wound). This is usually 10 days to two weeks after the procedure. Superficial therapy is given with 140 Kv. roentgen-rays to two large ports, 6.0 mm. of aluminum filter is used, and a skin-target distance of 40 cm.

The outlying lymphatic regions receive deep therapy. This is given with the usual physical factors of 200 Kv., 20 ma., 50 cm. skin-target distance, and added filtration of 0.5 mm. of copper and 1.0 mm. of aluminum, using three ports, namely; a supraclavicular-infraclavicular field, a posterior axillary field, and a direct axillary field.[1]

THE PLAN OF TREATMENT is as follows: One superficial treatment is given daily to each of the two chest fields followed by a high voltage cycle of 200 roentgens daily to each of the three axillary fields on successive days. This cycle is repeated until the chest wall has received approximately 1,200 roentgens. Thereafter, the cycle is continued but restricted to the three axillary fields until each of them has received from 1,800 to 2,500 roentgens. This method of treatment which administers intermediate voltage therapy to the chest-wall-fields every fifth day for a total of 1,200 roentgens to each field avoids pleuropulmonitis, and is extremely effective in preventing local recurrence. Permanent skin damage is seldom observed with this technic.

THE RADIUM PACK may be substituted for the x-rays in giving postoperative irradiation. The same five fields described above are used, a single field being treated each day. Each receives 6 to 8 thousand milligram hours at 6 cm. distance at a single treatment; this is repeated until a total dose of from 18,000 to 24,000 milligram hours per field is given. For cancers which have extended widely through the breast, this treatment is not so satisfactory.

IRRADIATION FOR RECURRENT AND METASTATIC CARCINOMA

Recurrent or metastatic deposits of mammary cancer which make their appearance following radical mastectomy are manifestations of

[1] Some clinicians restrict postoperative irradiation to the fields adjoining but beyond the limits of the operation. Thus, Spackman and Hynes treat only a supraclavicular and parasternal field. The supraclavicular field extends from the sternoclavicular articulation laterally to the border of the trapezius. It is usually circular and 8.0 cm. in diameter. The parasternal field extends from the first to the sixth rib, and from the midline 6.0 cm. toward the involved side. Each field receives a total of from 3,600 to 4,000 r. with the usual divided dose technic

an incurable disease. Experience teaches that although life may be prolonged beyond the five-year period and comfort secured by proper palliative measures, the disease cannot be eradicated in this stage by any of the therapeutic measures available at present. In such cases irradiation is preferable to additional surgical measures and if routine pre- or postoperative irradiation has already been given, additional irradiation is still the treatment of choice.

The distinction between recurrent and metastatic cancer is an arbitrary one. The recurrent lesions are those which appear in areas which are accessible to operation; the metastatic ones appear in more distant organs. Recurrence is most frequently seen in the skin and subcutaneous tissues of the chest wall, in the lymph nodes, in the axilla or supraclavicular region on the affected side, and in the opposite breast in the order of frequency given. (See Chap. 20.) The most common sites for metastatic deposits are in the lungs, pleura, liver, bones and brain, in the order of frequency given.

Cutaneous Recurrence

Recurrent nodules in the skin of the chest wall, in the parasternal region, are perhaps the most common type of skin recurrence. Other similar manifestations include recurrence in the scar, isolated nodules elsewhere in the skin, the multiple nodules of carcinoma en curiasse and the carcinomatous dermatitis referred to as inflammatory or erysipeloid cancer.

The circumscribed recurrent nodules in the region of the chest wall are usually superficial and readily accessible to irradiation. The results of treatment are good if an adequate dosage is given, unless the lesion is ulcerated. If ulceration has occurred, the amount of irradiation must be limited because of the danger of producing a defect in the chest wall. The recurrent nodule may involve the bony structure of the sternum. Even in such instances healing may be expected when the irradiation is properly administered.

Treatment. These recurrent nodules may be effectively treated by intermediate voltage x-ray therapy. Treatment is administered to the lesion and a small margin of adjoining tissue through a cone. One thousand roentgens are administered at a single dose which is repeated at weekly intervals for a total of 3000 roentgens. The physical factors are 140 Kv., 25 ma., 6.0 mm. of aluminum filter, 32 cm. skin-target distance. (Treatment with the radium plaque may be substituted, p. 691.)

When the chest wall is more diffusely involved with carcinomatous dermatitis of the erysipeloid or en curiasse form, the size of the field is increased. Under such circumstances, one or two large fields are treated with intermediate voltage therapy in the same

manner as described above. An open port is used for the larger fields and the skin-target distance increased to 40 cm. The total dose recommended above must be reduced when the size of the field is increased.

Solitary recurrent nodules may be treated effectively by various methods: by roentgen-ray therapy, by superficial radium therapy or by interstitial radium therapy. When the skin is involved diffusely by multiple nodules of the erysipeloid or en curiasse form, we have found roentgen-ray therapy to be the most effective treatment. There are isolated cases of diffuse recurrent cancer which seemed to be stimulated rather than controlled by irradiation regardless of the form in which it is given.

Axillary and Supraclavicular Recurrence

Recurrence in the axilla or in the supraclavicular region may consist of solitary or multiple enlarged nodes. If previous irradiation has not been given, a routine cycle of axillary treatments through three ports as described previously should be employed. If routine pre- or postoperative irradiation has been given, it is our practice to treat such recurrences by high voltage roentgen-ray therapy in divided doses (200 r daily) through a single port until the skin tolerance is reached. If the nodules do not disappear, treatment may be repeated at the end of 10 weeks, using reduced dosage because of the decreased skin tolerance. In most of the cases where supraclavicular metastasis occurs roentgenographic evidence of pulmonary metastasis will be found. Under such conditions it is unwise to proceed too energetically with roentgen-ray therapy unless the condition of the patient warrants it. Often the supraclavicular metastasis takes the form of a solitary enlarged node which is readily accessible to excision or interstitial irradiation. Experience has shown that further surgical procedures are rarely justified however, and treatment by interstitial irradiation may be followed by brachial neuritis. We have discontinued both procedures in favor of external irradiation.

Carcinoma in the Opposite Breast

Mammary cancer occurs in the opposite breast in 7.5 per cent of patients who have had mammary cancer. It is difficult to decide by clinical examination whether or not the disease is recurrent and the result of extension across the midline, or whether a second cancer has arisen de novo in the opposite breast. There are three possibilities: (1) bilateral carcinoma at the time of the clinical examination, (2) recurrence and extension in the chest wall to involve the second breast, and (3) carcinoma de novo in the opposite breast.

Radical mastectomy is contraindicated in cases with bilateral mammary cancer at the time of examination. If the disease has not ulcerated or extensively involved the skin, simple bilateral mastectomy may be performed followed by postoperative irradiation. The regular cycle of irradiation may be given to the axillary fields and over the chest wall. It is important, however, to guard against pleuropulmonitis, and, for this reason, in irradiating the chest wall, low voltage therapy should be given through two large ports over each side of the chest, in total doses of 1,500 roentgens to each of the four ports, divided into 500 roentgens per dose alternating with the axillary fields so that one chest port is treated every fifth day. If advanced changes in the skin and axillae are found associated with bilateral mammary cancer, palliative irradiation only should be employed. High voltage (200 Kv.) therapy should be used and the axillary fields treated in the usual manner through three ports. Deep roentgen-ray therapy to the breast should be given tangential to the body wall through lateral and medial ports, but the total dose administered should be kept well within the limits of average tolerance to avoid damage to the lung fields. The general condition of the patient must be carefully watched, and the daily doses should not exceed 200 roentgens.

In patients who have had a previous radical mastectomy and have recurrent disease of the chest wall with involvement of the opposite breast, irradiation is the treatment of choice. In many of these cases pulmonary or mediastinal metastasis will be found on roentgenographic examination and the extent of irradiation given must be governed by the general condition of the patient. It is our plan to treat the chest wall with intermediate voltage therapy as previously described for recurrent cutaneous cancer, and the opposite breast and axilla are treated as described for preoperative irradiation in primary cancer. Under such circumstances, it is important to guard against giving too much irradiation to the lung fields and carefully to watch the blood count and general condition of the patient.

In patients who have had a previous radical mastectomy without obvious recurrence or metastasis but in whom a second carcinoma is found in the opposite breast, radical mastectomy is the treatment of choice providing the second cancer is within the limits of operability as understood for primary carcinoma. Indications for pre- and postoperative irradiation are the same as for cancer of the original breast.

Osseous Metastasis

Bone involvement is a relatively common manifestation in advanced stages of mammary cancer and good, but temporary, results

are usually obtained by roentgen-ray therapy. To obtain optimal results, the treatment should be given before the vertebrae are crushed or pathologic fracture of the long or flat bones occurs. Under such conditions, the region of bone involvement depicted in the roentgenograph is treated through suitable ports with divided doses of deep therapy. If the vertebrae are crushed or pathologic fracture has occurred in the femur or humerus, orthopedic measures should be taken similar to those used for traumatic fractures. Following such treatment, irradiation is carried out. These patients should be put on a high calcium diet. In addition, they should be given dicalcium phosphate and vitamin D. The tablets used by the authors contain 15 grains of dicalcium phosphate and 600 units of vitamin D. These tablets are given three times daily together with a diet rich in milk, cheese and eggs. With such a routine, bony union is obtained more rapidly and pain is relieved more promptly in our experience.

The spine is the most frequent site of osseous metastasis and either solitary or multiple foci may be observed in one or more vertebrae. The lumbosacral region is usually affected. The characteristic symptoms are pain and tenderness over the affected vertebra and radiating pains along the spinal nerves. If the symptoms are characteristic, irradiation may be begun before roentgenographic evidence of the lesions is obtained. If there is evidence of bone destruction in the films, it is important to support the spine. This may be done with a plaster jacket or supporting brace.

Technic. It is our practice to use divided doses of 250 roentgens daily and give a total of from 1,200 to 1,500 roentgens to a single area. The usual physical factors of 200 Kv., 20 ma., 50 cm. skin-target distance, and 0.5 mm. of copper filter are used. If multiple foci exist in the spine, several ports are chosen and these are treated in rotation on successive days. In our experience, moderate doses of irradiation totaling 1,200 to 1,500 roentgens per field suffice to secure healing, although some observers prefer to push irradiation to the point of skin tolerance. It is important to guard against toxic effects and to follow the blood count in treating these patients with osseous involvement. The treatment advised above may be repeated in 6 weeks in lower dosage if indicated.

If osseous lesions are found in the skull, these are treated in a manner similar to that described above, through a single port with the divided dose technic. If the pelvic bones, femur or humerus is involved, these are treated through anterior and posterior ports, as a rule, each port receiving a total of 1,200 roentgens with the divided-dose technic as outlined for treatment of osseous lesions of the spine.

When osseous metastasis has been treated it is important that

normal activity should not be resumed until the roentgenographs reveal adequate healing of bone. After the spine has been treated, adequate support should be continued for three to six months and thereafter it is a good policy to use some type of ambulatory orthopedic appliance such as a Bennett brace or corset. When the pelvis or weight-bearing bones of the lower extremities have been treated, normal activity should not be permitted until films have been made to rule out other foci of bone involvement which might lead to subsequent pathologic fracture.

Visceral Metastasis

In general, metastases to internal organs such as the lungs, liver and abdominal cavity are not successfully treated by irradiation. If mediastinal nodes are involved, deep therapy may be given with good results to anterior and posterior ports in the midline. Cough and pleural effusion may disappear under such treatment. Sometimes with pleural involvement tangential therapy will alleviate cough and effusion. This is particularly true if there is associated rib involvement. Treatment of these complications is discussed later in this chapter. The authors have never seen good results with roentgen-ray therapy given for metastases to the lungs, liver or abdominal regions.

IRRADIATION ONLY

For cancers confined to the mammary gland, the sterilizing effect of irradiation on the tumor growth cannot compete with radical surgery. Uniform irradiation throughout the breast is difficult to achieve and this together with the character of the glandular tissue and the tumor bed makes it difficult to completely eradicate cancer by such means. On the other hand, when the cancer is more extensive irradiation may be effective in regions which are impractical for surgical treatment, such as the supraclavicular area, the sternal region and more distant metastases.

Few clinicians are willing to risk the established percentage of cures obtained by radical surgery in operable cases of mammary cancer for the unproved efficacy of exclusive treatment by irradiation. However, there are some radio-therapeutists who advocate various forms of irradiation as the only means of treatment for the disease in selected cases (Wintz, Keynes, Fitzwilliams, Pfahler and Schriener). A survey of their reports leads to the following conclusions: (1) that small groups of highly selected patients were reported, (2) that pathological diagnoses were frequently missing, (3) that the majority of these authors did not advise against the continued use of surgery.

Most authorities are convinced first, that if the lymph nodes are not involved the results of surgery are superior to those of irradiation, and second, that if the lymph nodes are involved surgery may, but irradiation alone, rarely if ever eradicates the disease.

Indications for Irradiation Without Surgery

The procedure of radical mastectomy has been standardized for a period of approximately fifty years and no significant changes in the technic have been made recently. The choice of cases suitable for surgery, however, has been progressively refined and restricted and irradiation therapy has assumed an increasingly important place in the treatment of extensive or rapidly spreading mammary cancer. RADICAL MASTECTOMY IS NO LONGER CONSIDERED ADVISABLE FOR CANCERS WHICH INVOLVE THE SUPRACLAVICULAR LYMPH NODES AND WHICH HAVE INFILTRATED THE APEX OF THE AXILLA OR WHICH HAVE PRODUCED SKIN METASTASES BEYOND THE AREA IMMEDIATELY IN CONTACT WITH THE TUMOR. By the same token, infiltrating carcinomas, more than 5 cm. in diameter or large fulminant cancers discovered during pregnancy or with erysipeloid involvement of the skin are not suitable for radical mastectomy, since experience has shown that the disease has already passed beyond the region that can be attacked by operation. (See p. 666.) Irradiation, therefore, is the treatment of choice in advanced cancers and should be given to the limits of tolerance.

If, on the grounds of inoperability, rigid criteria have been used in selecting the cases for treatment by irradiation, a favorable response to irradiation does not necessarily alter the fundamental plan of treatment. In many such cases previous experience teaches that the disease has already spread to inaccessible regions and organs. In general, the favorable response to irradiation is local and does not render a previously inoperable cancer, operable. However, there are occasional cases where the response to roentgen-ray therapy is so favorable that radical mastectomy may be warranted.

Technic for Irradiation. When irradiation without surgery is used, the axilla is usually irradiated through three fields—direct, anterior, and posterior fields; and the breast through two fields—medial and lateral, tangential to the body wall. The size of the fields varies with the individual case, and if the breast is large it may be irradiated through a superior field tangential to the body surface. The fields are treated in rotation, one daily, with 200 roentgens to the point of tolerance (usually a total of 1,800 to 2,500 r per field measured in air). The physical factors are 200 Kv., 25 ma., 50 cm. skin-target distance. The average added filtration is equivalent to 0.5 mm. of copper and 1.0 mm. of aluminum.

The radium pack may be substituted for x-rays where sufficient quantities of radium are available. (See page 683.)

If in a period of from six to eight weeks following an adequate course of irradiation, tumor masses or involved nodes remain, additional measures may be indicated. The patient should be observed periodically following such irradiation and, if desirable, further x-ray treatments may be given at selected intervals or new fields may be treated. The behavior of the disease, the general condition of the patient and the tolerance of the skin determine the amount of treatment which may be given.

Where the primary tumor shows signs of being radioresistant or a tendency to ulcerate and fungate, simple mastectomy may be performed. Rarely, lymph nodes or similar outlying masses which have failed to respond may be treated by the implantation of radium needles directly into the mass.

INTERSTITIAL IRRADIATION FOR ISOLATED NODULES

Technic

In treating lymph nodes involved by mammary cancer with interstitial radium, it is important to guard against necrosis of the underlying structures and to place and maintain the needles in position accurately.

As a rule the skin, because of previous irradiation, will not tolerate

TABLE XC

QUANTITIES OF RADIATION NECESSARY TO DELIVER SPECIFIED MINIMUM DOSES IN VARIOUS VOLUMES[1] INTERSTITIAL SOURCES

Filter 0.3–0.5 mm. Gold

	VOLUME OF TUMOR—CUBIC CENTIMETERS						
	10	20	30	40	60	80	100
Threshold Doses[2]	*Millicurie—or Milligram Hours*						
1	275	380	470	530	650	750	845
2	550	760	940	1060	1300	1500	1690
3	825	1140	1410	1590	1950	2250	2535
4	1100	1520	1880	2120	2600	3000	3380
5	1375	1900	2350	2650	3250	3750	4225
7	1925	2660	3290	3710	4550	5250	5915
10	2750	3800	4700	5300	6500	7500	8450

[1] These doses are for use when the needles are to be left in place four days or longer. If they are to be removed in a shorter time, all quantities of radiation should be somewhat smaller. (Quimby, courtesy of the American Journal of Roentgenology and Radium Therapy.)

[2] It is desirable to give about 10 Threshold Doses to metastatic nodes unless previous external irradiation has been given; then 5 or 6 are preferable.

chlorine or iodine antiseptics. After properly sterilizing and draping the region, the area about the nodule is infiltrated with novocain. The radium needles are to be inserted in parallel fashion so that the farthest point between them may receive a lethal dosage of irradiation. They should not be closer than 1.0 cm. apart. The needles are

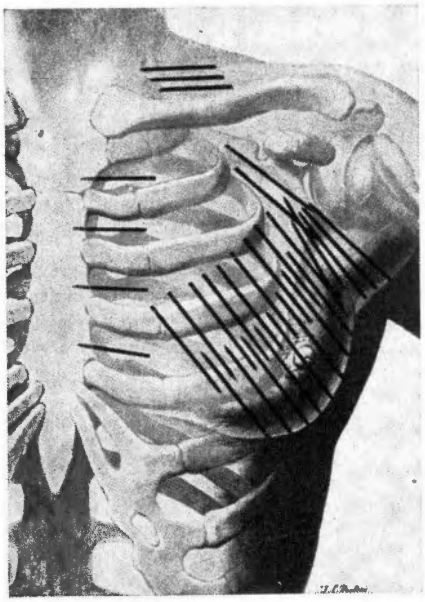


FIG. 543. The treatment of mammary cancer by interstitial radium (Keynes Method). The number and position of the needles used are shown.

grasped by a needle holder or forceps and inserted in the affected tissue after a proper incision has been made. (Fig. 544.) In inserting the needles as much distance as possible should be maintained between them and neighboring bony structures or major vessels and nerves.

The needles should be threaded with strong black silk and the ends of the thread should be securely sutured to the chest wall to aid in maintaining the position of the needles. A dressing should be put over the area and the patient confined to bed and warned that any dressings which are inadvertently removed should be saved.

The dosage required to treat the cancerous lesion depends upon its size as is indicated in Table XC.

In treating superficial skin nodules a radium plaque should be applied directly over the lesion and 1.0 cm. distance from the skin instead of using the interstitial technic. The plaques are small metal containers with a dimension of several centimeters and are square,

rectangular or round. They provide filtration equivalent to 2.0 mm. of brass and may be fastened to a block of wood or bakelite to maintain the desired distance from the skin. If the lesion to be treated

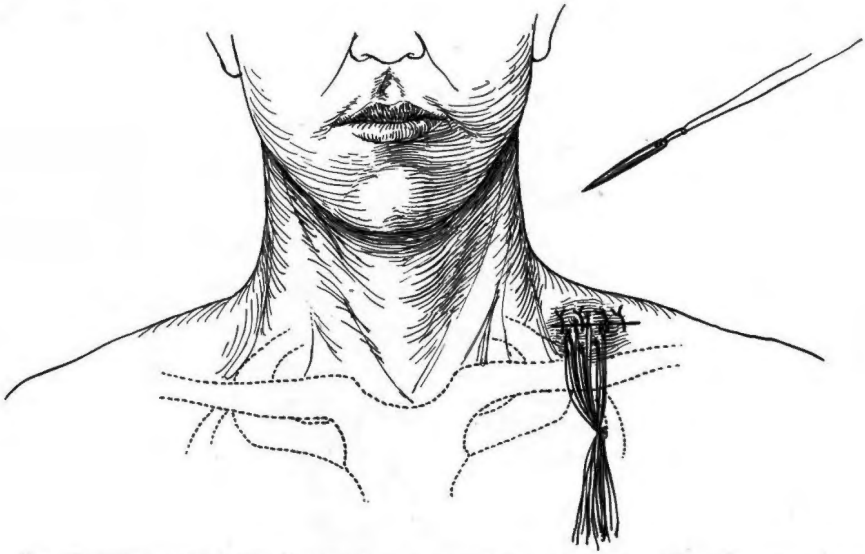


FIG. 544. Interstitial irradiation for postoperative recurrence. The drawing shows the location of 6 radium needles implanted for recurrence in a supraclavicular lymph node following radical mastectomy.

is superficial, the distance from the skin may be 1.0 cm. The radium needles or cells in the plaque should be uniformly spaced, and the amount of dosage required to treat a small lesion is given in the following table.

TABLE XCI

RADIUM APPLICATORS FOR SUPERFICIAL NODULES

TYPE	SIZE	AREA-RADIATING SURFACE	FILTER	DIS-TANCE	DOSAGE MG.	DOSAGE HRS.
Square plaque	1.8 cm. square	2.0 sq.cm.	2 mm. Brass + 0.2 mm. Platinum	1 cm.	700 - 1000	
Rectangular plaque	2.7 x 1.7 cm.	3.75 sq.cm.	"	1 cm.	900 - 1300	
Round plaque	4.0 cm. dia.	7.0 sq.cm.	"	1 cm.	1300 - 1500	

The dosage given in the above table should be about one-half as high if previous external irradiation has been given.

INTERSTITIAL IRRADIATION FOR PRIMARY TUMOR

Interstitial irradiation with radium needles has been advocated (Keynes, Pack and Lee, Teahan and others) for the management of

carcinoma of the breast. Such treatment, however, is not practical in cases with the widespread disease under discussion. This is because a sufficient intensity of irradiation is obtained only a relatively short distance from the needles and the adequately treated tissue is thus localized. Keynes also warns against the use of this method in

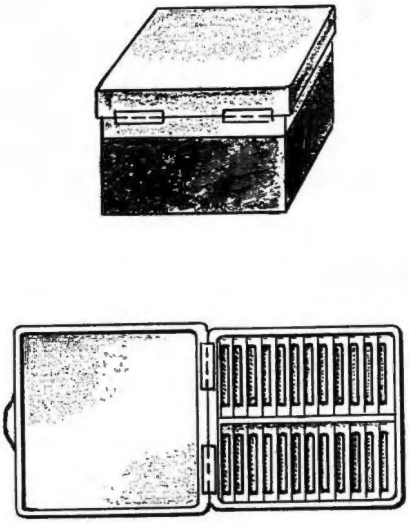


FIG. 545. Radium plaque used for the treatment of superficial recurrence of mammary cancer.

very stout patients because of the difficulty in placing the needles accurately, and also advises against its use for very avascular, ulcerated tumors, since necrosis with delayed healing is apt to result. The technic of Keynes is as follows:

Technic

The amount of radium required is between 75 and 100 mg. Relatively long needles with an active length of 4.8 cm. and 3 mg. of radium are used, filtered with 0.6 or 0.8 mm. of platinum. Approximately 1 mg. is required for each 2.5 sq. cm. of tissue. Each needle is threaded on a strand of thick "salmon" gut which has a single knot about 2 cm. from the eye of the needle. The position of the needles is indicated in Fig. 543. The needles are usually left in position for a period of seven days (168 hours). It has been found empirically that this period of irradiation gives satisfactory results with the dosage employed, and from the point of view of hospital organization a seven-day period is the most convenient arrangement. This exposure should not produce necrosis of the tumor, and al-

though there may be some degree of burning of the skin in a thin patient, this is never excessive.

While the needles are in position the patient should be kept in bed, and the arm on the affected side should be kept at rest on a pillow. Most patients suffer but little pain except on movement, and usually they are able to move about fairly freely after the first 48 hours. Some of them complain of nausea during the second half of the period of irradiation, or may even vomit occasionally. There is no other constitutional effect, and the patients can usually be allowed to get out of bed on the second day after the removal of the needles.

The needles are inserted through skin punctures under gas and oxygen or intravenous anesthesia.

Removal should also be done under anesthesia. After the removal of the needles, the skin should be kept dressed for about 14 days.

Lee and Pack have advocated the use of external irradiation and gold radon seeds in measured tissue dosage implanted into the tumor, in "selected, small well defined carcinomas of the breast." They felt this could not be recommended as a routine preoperative procedure. When the method was used, it was advocated as a substitute for radical surgery.

Teahan recently has published his experiences in the use of interstitial irradiation as an independent method of treating breast carcinoma.

There is little evidence that these methods as an independent form of treatment offer added encouragement in the control of primary operable carcinomas of the breast.

Interstitial irradiation at the time of radical mastectomy has been advocated. (Handley, Moore, Trout.) The radium needles are placed in various locations (intercostal spaces near the mediastinum, supraclavicular region, clavicular portion of the pectoralis major muscle, etc.) under direct vision. This procedure is quite different in method and purpose as compared with intertumoral irradiation.

The limited use of the method and the small number of cases treated to date make its use probational. This method seems to have promise and should be given further trial.

IRRADIATION CASTRATION

Irradiation of the ovaries may be indicated to guard against future pregnancy or to eliminate ovarian function in young women with mammary cancer. Pregnancy is a serious complication and should be prevented by roentgen-ray castration in married women in their twenties or early thirties who have been treated for mammary carci-

noma. Before the menopause, roentgen-ray castration, by eliminating the estrogenic function of the ovaries, may bring about regression of the disease with recurrent or metastatic cancer in women. The benefits, however, are but temporary and are observed in less than one-half of the cases; nevertheless, the treatment is worthy of trial in desperate cases. Some authors (Dresser) advocate routine castration in all women with mammary cancer who are under the menopausal age. In view of the fact that the benefits of such treatment are both temporary and uncertain (Taylor) and that many of the women subjected to such castration are made extremely uncomfortable by the menopausal symptoms, it cannot be advocated as a routine procedure. Farrow concludes that about one-third of the patients in the premenopause will be benefited by castration.

Our technic for castration with roentgen therapy is as follows: The physical factors are 200 Kv., 20 ma., 50 cm. skin-target distance and filtration equivalent to 0.5 mm. of copper and 1 mm. of aluminum. The size of the fields varies with the patient. Four fields are used, 2 anterior and 2 posterior. Four hundred roentgens are given daily over one field. The four fields are treated successively in this order, right posterior, right anterior, left posterior, left anterior. This cycle is repeated one week following the first treatment of the last cycle.

EVALUATION OF RESULTS OBTAINED BY IRRADIATION OF MAMMARY CANCER

To evaluate the results obtained by irradiation in mammary cancer, a number of facts must be given due consideration. First, the modern divided-dose technic utilizing several ports for cross-firing was seldom used prior to 1930. Before that time, about 800 roentgens was given in one or two treatments to three large fields, and the patient returned after a period of months for an additional course of treatment. The divided-dose technic as described here has been generally adopted only during the past 10 years and only recently have data concerning five-year results been accumulated.

Irradiation has been applied most extensively to advanced or hopeless cases and the majority of patients thus treated have been those which were inoperable by modern standards. For this reason, many of the cases surviving the five-year period following irradiation are not clinically free of the disease and cannot be compared with the five-year survivals reported following radical surgery.

Irradiation has been frequently employed following the failure of surgery to eradicate the disease. The combination of surgery and irradiation under such circumstances is quite different from the

routine combination of the two treatments in cases where cure may still be anticipated.

In grouping the cases for comparison, it must be borne in mind that when preoperative irradiation or irradiation alone is given, it is not possible to grade the cancer and to define the extent of the dis-

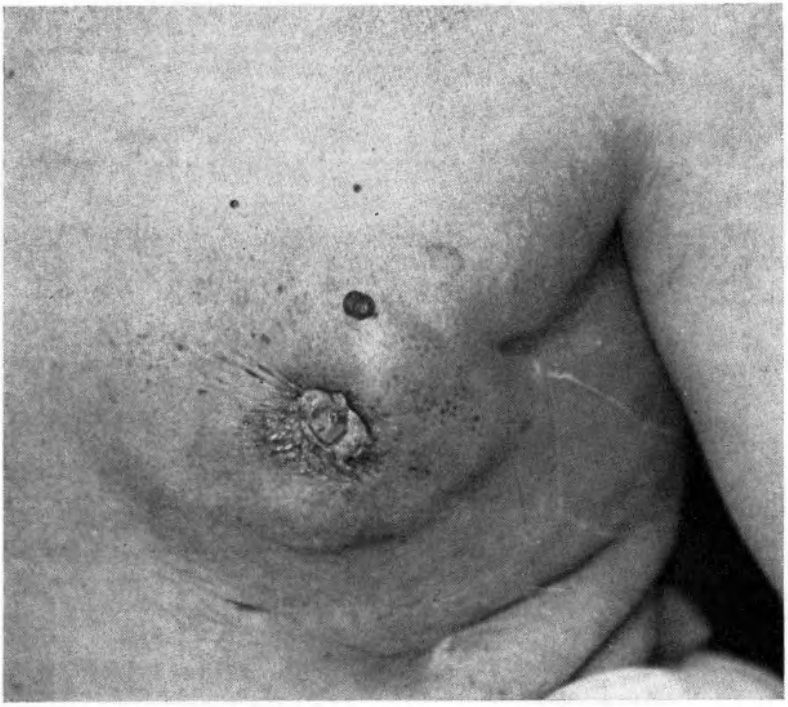


FIG. 546. Mammary cancer treated by external irradiation only. The cancer in this case is inoperable.

ease with the same accuracy as in those cases subjected to radical mastectomy alone or radical mastectomy combined with postoperative irradiation. Many of the reports discussing cases treated by such methods of irradiation do not include:

1. The pathologic criteria used to establish the diagnosis of malignancy.
2. The number and types of cases rejected as unsuitable for treatment and excluded from the series.
3. The exact technic of irradiation.

When the radical mastectomy is the only form of treatment in a surgical clinic, the procedure has usually been standardized for a

number of years and pathologic study of the specimen permits accurate classification. In clinics where irradiation has been relied upon as the major form of treatment, the technic is usually in the process of evolution rather than standardization and the combinations of therapy include irradiation only, irradiation followed by surgery, surgery followed by irradiation, surgery preceded by and followed by irradiation, interstitial radium therapy, and external irradiation, external irradiation combined with interstitial therapy, and a variety of dosages and technics.

In spite of the above considerations, a tentative evaluation may be given of the relative merits of surgery and irradiation.

For cancers confined to the breast (Group I) radical mastectomy only is indicated. These cases without axillary metastasis comprise about 30 per cent of the total of most series recently reported. Surgery alone affords approximately 65 per cent of five-year survivals in this group. Irradiation alone cannot compete with these results and pre- or postoperative irradiation does not add to the per cent cured. This conclusion is based upon our own cases and on the studies of Adair, Portmann, Pack and Livingston, and Hawkins.

In the cases considered operable by modern standards approximately one-half of the patients are found to have axillary metastases when the specimen is pathologically studied. In these cases (Group II), comprising about 30 to 40 per cent of the total in recently reported series, the five-year survivals with surgery alone are between 20 and 25 per cent. In this group, routine postoperative irradiation by modern technic increases the five-year survivals from 25 to 30 per cent in our series, and from 21.7 to 47.9 per cent in the cases reported by Portmann. Postoperative irradiation in this group of cases also decreases markedly the likelihood of local recurrences.

If rigid standards for operability are applied (as defined in the preceding chapter, page 672) the inoperable cases (Group III) will comprise 30 to 40 per cent of the total. In the past, five-year survivals in this group of cases following radical mastectomy have varied from 2.5 to 6.5 per cent. In Portmann's series postoperative irradiation of this group increased the five-year survivals to 8 per cent (those with and without evidence of cancer at the end of 5 years are included). Even better results are obtained with irradiation alone (approximately 10 per cent) and palliative surgical procedures should be reserved for those cases which fail to respond to irradiation.

Finally while irradiation may be applied to structures involved by cancer which are inaccessible to surgery such as the chest wall, the mediastinum and osseous system, it is still true that cures can be hoped for only when the cancer has failed to extend beyond the field

irradiated. For this reason the cases in which cancer extends via the blood stream to form embolic deposits in distant organs are fundamentally beyond cure by irradiation as well as by surgery. New technics in irradiation which employ supervoltage, neutrons, etc. are handicapped in such cases by the same fundamental pathologic considerations that limit the achievements of surgery.

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31

Management of Recurrent and Metastatic Mammary Cancer

The majority of patients with mammary cancer (whether or not they have survived the five-year period) ultimately develop recurrence and extension of the disease which preclude the possibility of a permanent cure. Under such circumstances, measures designed to prolong life and to increase comfort are the major considerations. Not the least important problem is that of maintaining the most helpful and encouraging outlook for the patient and family. Too often the physician assumes that when surgical and radiologic measures are completed, his period of usefulness is over. Such an assumption, however, is unjustifiable. At all times, until the end is imminent, the physician must strive to prolong life, maintain comfort, and provide cheer and encouragement.

While some responsible member of the family must be informed regarding the seriousness of the situation, the patient should not be allowed to infer from the physician or the family that her case is hopeless. She should not be informed of the true diagnosis or prognosis. The attitude should be that some avenue of hope remains and that much can be accomplished by following the proper regime.

It is a mistake, in the author's view, for the physician in charge to predict the length of life. In many cases, after bone or pulmonary

metastasis has supervened, the patient may continue to be up and around and enjoy periods of relative comfort for months or years; after competent authorities have predicted the end within a matter of days or weeks. It is, however, only fair to urge against further consultations or additional therapeutic measures when it is known that the end is imminent. Unless the patient is in this condition, however, it is unwise to risk error in trying to prognosticate the duration of the disease. It is best to tell the family that while there are signs that are universally recognized as unfavorable for cure, the profession does not possess sufficient knowledge to predict which patients may be helped and for how long.

The treatment in late cases of mammary cancer includes:

1. Supportive measures to maintain health.
2. Specific measures to combat complications.
3. Relief of pain.
4. Additional measures to combat the growth of the cancer.

MAINTENANCE OF GENERAL HEALTH

In carrying out specific measures for the relief of mammary cancer it is well to have a definite plan or regime to maintain the general health. If the patient has reacted unfavorably to treatment, or if there is severe anemia, repeated small blood transfusions of approximately 250 cc. are indicated. The patient should be maintained for as long as possible on normal diet and activity and should not be confined to bed unless there is specific indication. None of the variety of diets recommended for cancer has been found helpful in our cases, but an increased vitamin intake has served to increase appetite and maintain strength. Vitamin-B complex by mouth increases appetite and vitamin A in high concentrations is beneficial in advanced cases. Increased amounts of vitamin D (along with calcium and phosphorus) are important if osseous metastasis has occurred.

In the author's experience testosterone and adrenal hormones have been found efficacious. Testosterone propionate is injected two to three times weekly in doses of 10 mg. or pellets (20 to 100 mg. each) are inserted subcutaneously at intervals of six weeks or longer. If the patient has not passed the menopause, menstruation may be inhibited. Hirsutism and voice changes are seldom observed at this dosage level. Adrenalin in oil,[1] once daily, in 1 mg. doses for several weeks, increases the energy of the patient and promotes absorption

[1] A solution containing Vitamin A 50,000 I. U., testosterone propionate 5 mg., and epinephrine 1 mg. per cc. of oil from the Wallace and Tiernan Products Company, is used by the author. If there are multiple bone metastases, injections of testosterone are contra-indicated and pellet therapy must be given with extreme caution because of the elevation of the serum calcium which results from such treatment. (See p. 437.) In such cases it is the author's practice to substitute progesterone pellets, 20 mg. each, and to use injections of this hormone in doses of 5 mg.

of other endocrine medication given parenterally. Occasionally regression of tumor nodules is observed under treatment with testosterone and pleural effusion inhibited after thoracentesis.

SPECIFIC MEASURES TO COMBAT COMPLICATIONS

Among the complications which demand treatment (not previously discussed under irradiation in Chapter 30) may be listed edema of the arm, pleural effusion, cough, painful contractures and recurrent nodules with ulceration.

Edema of Arm

Edema of the arm may appear early following radical mastectomy or irradiation of the axilla, in the absence of recurrent disease. In such cases it is a complication of treatment rather than of the disease. The edema may subside spontaneously during the course of several months. More persistent and severe edema may occur when the lymphatics of the upper arm and axilla are blocked by recurrent disease. Postoperative infection and roentgen-ray dermatitis resulting from irradiation increase the incidence of swelling of the arm after radical mastectomy. Although metastasis to the axillary nodes at the time of operation has no bearing on the incidence of the lymphedema, recurrent disease in the axilla following operation is an important factor, particularly in prognosis. According to Holman et al, primary skin grafting has no influence on the occurrence of swelling of the arm following radical mastectomy.

Since therapy after swelling of the arm has developed is unsatisfactory, preventive measures are important. Every precaution should be taken to secure primary wound healing after radical mastectomy. The improper handling of the skin flaps and collection of serum in the wound post-operatively predispose to sloughing and infection. Roentgen-ray therapy should be given cautiously. If edema of the arm develops, the patient should be informed that this does not signify recurrence of the disease. Try conservative measures first.

The swollen extremity should be supported on pillows (or by a small hammock placed under the arm and elbow suspended by pulleys) while the patient is at rest during the day or night. The patient is usually more comfortable if the arm is elevated to the level of the shoulder intermittently for periods of a half hour to an hour with motion or a more dependent position permitted at intervals. Once a day heat in the form of an electric pad or diathermy should be applied. In addition, heat may be used at other periods of the day, if comforting.

If the swelling of the arm is not extreme (i.e., if the circumference

is less than six cm. greater than that of the normal arm) and if there is no recurrent disease, the deformity is not incapacitating and the patient rarely experiences more than occasional aching. If the swelling and pain are more extreme and recurrent disease is present plastic operations are not indicated, since the pain is produced by pressure of the tumor masses on the nerves and thus will not be relieved. Moreover, the impending fatal outcome in cases with recurrent disease rarely warrants surgical interference. If recurrent disease is not evident and the pain warrants it, a plastic operation may be attempted. Standard reported good results in a case in which an oval segment of skin and fascia were removed from the medial aspect of the arm and the edges sutured to a wound made in the chest wall opposite this segment, the opening of the thorax extending through the deep fascia to the seratus anterior. The arm remains loosely attached to the chest wall so that abduction is limited but the patient is able to comb her hair, feed herself, and utilize the hand. In this operation the lymphatics of the chest wall provide pathways which are adequate for the return lymphatic flow from the arm.

Pleural Effusion

Fluid in the pleural cavity may result from metastasis to the pleura or from lymphatic blockage produced by mediastinal metastasis. Relief may be obtained by irradiation of the affected nodes when the effusion is accompanied by mediastinal metastases which are visible in the roentgenogram. For this purpose, anterior and posterior ports of treatment are used as previously described. (See Chap. 30.)

Thoracentesis is indicated in cases where there is no response to irradiation and where effusion is the result of pleural metastasis, if there are symptoms of intrathoracic pressure. Successful tapping may be followed by periods of one to several months of relief before refilling occurs, although as a rule this is rapid (usually within one to several weeks). This form of palliation should not be denied the patient unless repeated tapping indicates that the return of the fluid is too rapid to give any appreciable relief. Whether or not endocrine therapy aids in inhibiting the return of pleural effusion in these cases is questionable (see p. 701).

Cough

Persistent and intractable cough with paroxysms terminating in vomiting may complicate metastatic mammary cancer. This symptom may result from pleural, mediastinal or pulmonary metastases, or in rare instances from pressure on the recurrent laryngeal nerve produced by tumor or by contractures following irradiation. Careful study should be made to determine the cause of the cough. If medias-

tinal metastasis is found, additional irradiation may be given to that region. If the cancer has invaded the chest wall and involved the pleura, additional irradiation tangential to the body wall may be used.

If tumor tissue is found in the region of the recurrent laryngeal nerve, irradiation through a cone may be given. In other words, any recurrent or metastatic disease which may explain the cough and which is accessible to further treatment should be attacked. If, however, there are miliary metastases in both lungs or widespread pleural involvement, or if there are contractures about the recurrent laryngeal nerve, the cough must be controlled symptomatically. The simplest procedures should be tried first. If talking above a whisper is prohibited for a time and if the amount of motion and activity during the day is restricted, improvement may occur. Fluids taken at frequent intervals and a mixture of chloroform and creosote inhaled from a handkerchief may suffice to inhibit the paroxysms of cough.

Ultimately, narcotics may be needed. Codeine should be given sparingly and combined with aspirin or phenacetin. Larger doses of more potent opiates may be required but these should be avoided if at all possible until the final stages of the disease.

Painful Contractures

The scar of the radical mastectomy or fibrous tissue following irradiation may produce painful contractures. Usually such complications may be avoided by a properly placed incision and by carefully administered irradiation. If they do occur, heat, light massage and passive motion will reduce pain and increase the use of the affected part. Persistent contractures which interfere with the patient's livelihood through restricted use of the arm warrant surgical intervention. Otherwise, operation should be avoided because of the danger of lighting up recurrent disease.

Carcinomatous Dermatitis and Ulcerations

Irradiation treatment of recurrent skin nodules and of carcinomatous dermatitis has been discussed above. When further irradiation cannot be given, recurrent and ulcerated nodules may be treated by electrodesiccation or with the cautery. The proper care of ulcerating lesions and malodorous sloughs is important. The patient should be advised to get into a tub of warm water daily, if her condition permits, to soak the wound for 15 to 30 minutes. Much of the epithelial debris and secretions are thus washed away. In dressing such wounds, we have found that a pad of gauze saturated in azochloramid in 1:500 triacetin solution when applied directly and covered with rubberized

silk inhibits the weeping and odor. If the surrounding skin is protected by a suitable ointment, this deodorizing antiseptic may be used during the period of irradiation. Allantomide ointment is also effective in reducing infection and odor. (Allantoin 2 per cent, sulfanilamide 10 per cent.)

Irradiation Dermatitis

It may be difficult to distinguish between persistent or recurrent disease and the changes produced by irradiation. As pointed out by Castigliano, dermatitis following irradiation may spread beyond the limits of the portals of treatment. The roentgen ray is the traumatizing agent which produces the antecedent discharging lesion, from which the eczematoid dermatitis develops. This type of skin lesion appears from one to several months after sufficient roentgen treatment has been given to produce an exudative radiodermatitis, and in appearance may simulate acute or inflammatory carcinoma. It is usually associated with an ulcerating, discharging lesion and is accompanied by fever of 100 to 103 degrees. The red, angry, elevated skin reaction often extends well up the neck, toward the opposite breast and around the back, beyond the portals of irradiation. The chief diagnostic point is the gradual spread of the reaction from the area irradiated. The dermatitis should gradually recede under treatment with moist boric acid-alcohol dressings and bland ointments if irradiation is discontinued; in inflammatory mammary cancer or carcinomatous dermatitis gradual extension of the lesion is the rule and one or more discrete tumor nodules are usually present.

RELIEF OF PAIN

Pain is the most distressing complication of late mammary cancer. Its control may be specific or symptomatic. Specific measures to relieve pain are those directed toward the foci of the disease which are producing the disturbance. Every attempt should be made to localize the cause of the pain and to investigate the possibility of giving additional treatment. If such specific measures are not available or practical, then symptomatic measures must be employed.

Narcotics and Hypnotics

The important agents available are the narcotics and hypnotics, snake venom and interruption of nerve conduction. Morphine and its derivatives are indispensable in handling the late stages of the disease. The form of the drug used depends upon the tolerance of the patient and upon the experience of the physician in administer-

ing it. In some cases codeine by mouth along with aspirin and nightly administration of some barbiturate will suffice. If the pain is continuous, the narcotic will have to be given every 4 hours to maintain the effect. It is important to guard against giving less than the amount required to relieve the symptoms. On the other hand, it is equally important to avoid rapidly arriving at a dose that is high enough to interfere with the digestion and well-being of the patient. Many of the patients reach a state of cachexia more rapidly by the unwise use of narcotics. Pressure in the chest, anorexia, vomiting and headache are signs of addiction to the drug, complicated by withdrawal symptoms when the amount administered is no longer effective. Since it is very difficult to estimate the length of life in the individual case, the wise physician will never rely upon narcotics alone to control pain and will attempt at all times to use additional measures. The barbiturates, chloral hydrate and scopolamine are valuable drugs which may substitute for opiates during the night or at other times.

Snake Venom

Cobra venom has been advocated in the treatment of all types of cancer both for its effect on the disease itself and for the relief of pain. As evidence has accumulated, it has been found that this toxic substance has no effect on the growth of the tumor, but may lessen the amount of pain. In some patients it apparently has a synergistic effect when used with codeine. In general, however, its results have proved disappointing. The usual dose is 0.1 mg. or 10 mouse units every other day by intramuscular injection. In cases where cobra venom is effective, its action is apparently slower and of longer duration than morphine and its derivatives, and it does not produce addiction or withdrawal symptoms. The initial dose should be given with caution.

Interruption of Nerve Conduction

In cases of severe pain, interruption of nerve conduction may be considered. Injections of novocain should be tried first, to ascertain whether the desired field may be anesthetized. Although such injections are effective for only a few hours, in rare instances pain may fail to return. Following the use of novocain, injections of alcohol or division by surgery may be used. Division of the brachial plexus has been performed in rare instances, but results in paralysis as well as anesthesia. Sectioning of the nerve roots central to their ganglia (rhizotomy) has been practiced, but because of an overlap of the fields of innervation, this may fail to include all of the sensory areas. In most cases of intractable pain resulting from advanced mam-

mary cancer, the spinal segments involved by pain are too high for the performance of cordotomy. In this operation, the portion of the spinal cord containing the lateral spino-thalamic tract (conveying pain and temperature) is cut. The section must be done one or two segments above the affected sensory field, and on the opposite side of the cord. (See Chap. 20, page 473.) However, if this operation inadvertently affects the motor pathways at a high level, there is danger of respiratory paralysis.

Control of Cancer by So-called Specific Therapy

When surgery and irradiation have failed to control mammary cancer, the patient and the family become increasingly receptive to unproved or experimental forms of treatment which are from time to time advocated as specific cures. At the present writing there are no such forms of treatment which have withstood an impartial and thorough test either experimentally or clinically.

When the course of the disease is slow and prolonged, spontaneous periods of relative improvement are frequently observed and cannot be attributed to the form of treatment. In approximately one out of five cases of late mammary cancer, regression of tumor nodules either depicted in the roentgenogram of the chest or palpated in the breast or on the chest wall has been observed in response to endocrine therapy. The regression is at times rather striking and takes place over a period of several weeks or months but has ultimately proved temporary.

The type of treatment used has been testosterone therapy administered in the form of injections or orally as described above. (See p. 700.) Occasionally pellets of 20 to 100 mg. have been implanted. One of the chief reasons for giving endocrine therapy, in addition to its effect on the general health and the occasional regressions observed, is to maintain the morale and optimism of the patient. These individuals always do better if the physician in charge continues to administer some form of therapy which offers hope for improvement. (These attempts at specific therapy are discussed fully in the following chapter.)

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32

Attempts at Specific Cancer Therapy

In attempting to carry out so-called cancer therapy in hopeless cases, there will always be novel modes of treatment which are advocated by enthusiasts, but which are of unproved merit from the standpoint of the profession. Such methods are usually of current interest only, and a detailed consideration of them seldom adds to the permanent store of knowledge in regard to cancer.

It is well to bear in mind three criteria for the evaluation of alleged cancer cures, first proposed by the author more than 10 years ago: (1) the cure shall have been used on a significant number of microscopically proved cancer cases, (2) the cure must be efficacious in the face of recurrences and generalized metastases, and (3) the good results achieved must be permanent and proved by examinations and follow-up studies over a period of from three to five years.

While the long-sought cure of cancer must surpass in effectiveness surgery and radiation when applied to advanced cancer, any agent or device which improves the effectiveness either of surgery or radiation or which relieves pain or prolongs the life of the patient is highly valuable even if it fails to eradicate the disease completely. A review of experimental attempts to inhibit the growth of cancer is worth while from this standpoint, as well as from the possibility that the principle underlying some of these new treatments may eventually be applied with success. Such a review also supplies a convenient index of reference to previous reports on any of the various methods of treatment advocated on an experimental or theoretic basis, and which may from time to time be re-introduced because of newer investigations.

AGENTS INHIBITING THE GROWTH OF CANCER

The agents recently investigated for their possible inhibitory effects on the growth of cancer may be considered under three headings:

1. Physical: including radiant energy and temperature changes.
2. Chemical: including dyes, heavy metals, oxidizing substances and similar compounds.
3. Biologic: including endocrines, organ extracts, diets, vitamins and immunizing substances.

Physical Agents

Irradiation Effects. Rapid advances are being made in the study of the biologic effects of new forms of radiation. A study of supervoltage roentgen-rays and fast neutrons and attempts to augment the action of roentgen-rays by chemical agents are important lines of investigation which are now being pursued. Stone and Robinson have shown that roentgen-rays of 1,000 Kv. produce less skin reaction and more penetration than 200 Kv., but there is little difference in the clinical results between these two extremes of voltage when the roentgen-rays are applied in divided doses. Packard and Exner found very little difference in the biologic effect measures on Drosophila eggs produced by roentgen-rays between 250 and 1,000 Kv.

While supervoltage roentgen-rays enable a slightly greater dose of radiation to be delivered to deeply situated cancers, the clinical advantages are restricted by two factors. First, cancers which are radioresistant retain this property when subjected to supervoltage. Second, cancers which have spread beyond the field of radiation remain incurable whether 200 Kv. or supervoltage is used. The biologic resistance of certain forms of cancer to radiation and the inaccessibility of late cancers which are widely disseminated throughout the body remain fundamental handicaps to successful radiation, despite the fact that more effective and powerful forms of radiant energy are employed.

There have been numerous attempts to augment the biologic effects of deep roentgen-rays by combining this treatment with the injections of various substances prior to radiation. On the theory that dividing cells are more sensitive to radiation, the drug colchicine has been administered prior to treatment with the roentgen-rays. This drug slows the process of cell division (prolongs mitosis). Guyer and Claus injected rats having transplanted carcinoma with colchi-

cine 12 to 18 hours before radiation. They believe that radiation was more effective following such injections. Colchicine, however, is highly toxic and cannot be administered in large amounts. Other workers using the same technic were encouraged by the results obtained in animals but found the material too toxic for human use (Lits).

A group of experiments concerning the action, on cancer, of fast neutrons generated by the cyclotron machine have been reported. This form of radiation is not dependent upon electromagnetic waves but upon the liberation of particles of matter at high velocities (Lawrence and Lawrence; Tuve).

When radiation in the form of roentgen-rays or gamma rays of radium are used, absorption of the radiant energy results in the splitting off of high-speed electrons, and ionization occurs along the path of these electrons. The degree of ionization depends upon the speed of the electrons which is in part dependent upon the voltage. When fast neutrons are used, a particle of the atom, the proton, is liberated. These protons are heavier particles and produce an ionizing effect approximately one hundred times as great as that liberated when the gamma rays of radium are used. When tissues are exposed to such fast-moving particles, they are bombarded, as it were, with atomic bullets and heavy ionization results.

Whether or not the energy liberated in the form of atomic particles by fast neutrons will prove effective in treating cancer cannot yet be stated. The results thus far reported by Gey and his co-workers suggest that the cancer cells are damaged in a manner similar to that resulting from exposure to roentgen-rays or radium. The fast moving neutrons are more penetrating than roentgen-rays or radium and act apparently with greater intensity but it remains to be seen whether or not there is more damage to the cancer cells than to the surrounding normal tissues. The usefulness of roentgen-rays and radium in the treatment of cancer depends upon their selective action on cancer tissue and the greater resistance of the surrounding normal structures.

Radioactive substances have been artificially produced by radiation of certain elements with energetic particles of matter (neutrons) generated by the cyclotron machine. Among the radioactive isotopes produced to date, radioactive phosphorus which has a half life of 14.3 days, has been most widely used in the treatment of malignant disease. Woodard and Kenney in describing their experience with this therapeutic agent state:

> In considering the probable usefulness of radioactive phosphorus in the treatment of various types of tumor, the radiosensitivity of the tumor

must be considered in addition to its capacity to fix phosphorus. Thus, it has been shown by one of us (Kenney) that both carcinoma of the breast and leukemic nodes take up two to four times as much of the isotope as analogous normal organs. This is probably due to the higher metabolic activity of the malignant tissue, and is in no way a specific property of the malignant state. Carcinoma of the breast is moderately radioresistant, so that it is not possible to administer enough radiation by means of radioactive phosphorus to inactivate the tumor without doing serious damage to the organism as a whole.

Temperature Effects. A number of attempts have been made to influence the growth of cancer by raising or lowering the temperature of the affected part or the entire body. In the last century Velpeau discussed a method for treating cancer of the breast by applying ice and brine to the growth which produced beneficial results locally. Mider and Morton have studied the effects of freezing at extremely low temperatures (— 74° C.) on normal and cancerous tissues. They found carcinomas and sarcomas of rats and mice survived the effects of freezing at such extremely low temperature, and could be successfully transplanted. Recently, Smith and Fay have advocated the lowering of the temperature of the entire body for a number of days (so-called hibernation). Patients with advanced cancer are anesthetized and a low body temperature (about 89° F.) is maintained by circulating refrigerated water through coils of tubing applied directly to the body. The effects of refrigeration on late cancer are not curative and alleviation of pain for a period of time appears to be the chief advantage of the treatment. When metastases to the liver or lungs are present life is rarely prolonged. Herrmann has recently reported his experiences with hibernation therapy.

Attempts have been made to control the growth of cancer by raising instead of lowering the temperature—so-called fever therapy. In 10 of 32 patients, Warren noted improvement when the rectal temperature was maintained at 41.5° C. for 24 hours. In experimental animals the response of cancer to heat is variable. Some authors such as Overgaard believe that when the temperature of the cancer is raised by diathermy that response to irradiation is more marked. The authors have been unable to confirm this.

Chemical Agents

Heavy Metals. A large variety of chemical compounds have been used experimentally in the treatment of cancer. While no outstanding success has been achieved, three groups of compounds deserve mention because of the large amount of work and the occasional beneficial results reported. These compounds are (1) the heavy metals

(2) various dyestuffs and (3) agents influencing biologic oxidation processes.

Among the heavy metals, colloidal lead, gold and selenium have been given the most extensive trials. Oschner has advocated the use of colloidal gold and Blair Bell the use of colloidal lead. Todd has been the most recent advocate of the use of selenium. The colloidal metals are supposed to have a direct toxic action on the cancer tissue and to increase the resistance to cancer by stimulating the reticulo-endothelial system.[1] Behan believes that calcium should be used as a supportive treatment in all cancer patients and cites the experiments of other investigators in support of this belief. However, more extended clinical trial of the various heavy metals in cancer cases and animal experimentation have shown that they have little or no therapeutic value.

Dyestuffs. Exhaustive attempts have been made to find dyestuffs which would influence the growth of cancer. Marsh and Simpson found no specific therapeutic value after having administered more than 145 aniline dyes to mice bearing spontaneous mammary cancer. The influence of the vital dyes which affect the phagocytes or wandering cells in the tumor and in the reticulo-endothelial system has been extensively studied. A review of the subject has been presented by Tilghman and Lee. A number of authors have favored the use of the isamine blue and trypan blue. The localization of these dyes, however, is not directly in the cancer cells, but in the phagocytes of the neighboring tissues and in the spleen and lymph nodes. To date no specific action of dyes on cancer cells has been reported. Duran-Reynals has reported on this subject.

Oxidizing Substances. Tumors have the property of producing lactic acid from glucose even in the presence of an adequate oxygen supply. This is known as aerobic glycolysis. Other tissue such as normal cartilage and kidney also have this property which is not therefore specific for cancer. The aerobic glycolysis of malignant tissue, however, has been extensively studied since the experiments of Warburg in 1926. Attempts to modify the growth of tumors by interfering with this capacity to split sugar have been disappointing. The growth of animal cancers is not retarded either by withholding sugars or administering substances such as sodium fluoride which inhibit glycolysis (Krantz, et al.).

In the belief that the respiration of cancer cells is abnormal, unsuccessful attempts have been made to retard the growth of tumors with excessive amounts of oxygen (Ozorio de Almeida, Lund and

[1] The phagocytes of the liver, spleen and lymphoid organs.

Holton) or by administering respiratory poisons such as cyanides (Perry, Mendel).

A study of the effect of organic peroxides on tumor growth has been stimulated by the work of Strong, who reported that heptyl aldehyde would liquefy and inhibit the growth of mammary cancer in inbred strains of mice. Stimulated by these results, Boyland in England has investigated a considerable number of aldehydes and ketones. They found that heptyl aldehyde inhibited spontaneous tumors but not grafted tumors. Because aldehydes are known to form peroxides on exposure to air, these authors attribute the action of the aldehydes to the possible formation of organic peroxides.

Biochemists interested in the growth and respiration of tissues have studied the organic sulfur compounds such as glutathione and cysteine which contain the sulfhydryl radical. Determinations have been made of the relative concentration of these substances in normal and cancerous patients, and of their effect on tumor growth. Osterberg and his co-workers measured glutathione and similar reducing substances in the blood of cancer patients and found that the whole blood in cancer patients contained a normal amount of glutathione but the oxidized glutathione was relatively high in the plasma and low in the red blood cells. The differences between cancerous and other patients, however, was not considered sufficiently great to be of practical significance. Kennaway and Hieger showed that tumor extract contained glutathione and similar reducing substances such as ascorbic acid. However, normal tissue, such as the adrenal and the pituitary, is also rich in these substances and the content of glutathione in normal liver and spleen is particularly high.

It has not been demonstrated conclusively whether glutathione, cysteine, cystine or other of the sulfhydryl containing compounds accelerate or retard the growth of cancer. Reimann and Hammett have reported experiments which show that injections of cystine disulfoxide inhibit the growth of spontaneous mouse cancer, an effect which they attribute to an inhibition of proliferation in the tumor growth by the partially oxidized sulfhydryl group. Carr and his coworkers however found that cysteine hydrochloride and related substances had little or no effect on three different rat tumors and in the Brown-Pearce rabbit cancer.

Biologic Agents

Endocrine Substances. Practically all of the endocrine substances which have been isolated from the glands of internal secretion as well as crude extracts of the glands themselves have been tested for their effect upon the growth of cancer. The isolation or synthesis of chemi-

cally pure hormones has proceeded at a rapid pace in the past decade, but the list of such hormones is still largely incomplete. For this reason, experiments yielding negative results and performed with crude extracts must await subsequent confirmation or be repeated when more active endocrine products are made available. It has already been possible to show, however, that the endocrine glands affect tumor growth. The anterior lobe of the pituitary gland plays a definite role and the presence or absence of the female sex hormone affects the growth of mammary cancer.

PITUITARY CHANGES in mice and rats developing estrogenic mammary cancer have been reported by a number of observers. These endocrine experiments have stimulated interest in the role of the pituitary in the growth of other malignant tumors. Heiman studied the changes in the anterior pituitary gland in tumor-bearing rats including both benign and malignant, spontaneous, transplanted and induced tumors. The tumor-bearing animals showed an increase in the chromophobe cells of the anterior pituitary gland. The percentage of chromophobe cells varied from 73 to 89 per cent in the tumor-bearing animals compared to 50 per cent in the control group. The observations of Wolfe and his co-workers also indicate that pituitary changes are more common in tumor-bearing rats. Ball and Samuels studied the effect of hypophysectomy on transplanted and induced rat cancer and found that the removal of the hypophysis retarded tumor growth when the controls and hypophysectomized animals were maintained at the same level of nutrition.

Korteweg and Thomas studied transplanted and induced cancer in mice which had been hypophysectomized and found that the cancers were retarded but not prevented. Loeb and Kirtz transplanted the anterior lobes of the hypophysis to various strains of mice and found that the incidence of spontaneous mammary cancer was increased, but that the effect was dependent upon the co-operation of functioning ovaries and did not appear in castrated females or in male mice.

There have been numerous clinical attempts to influence the growth of cancer by irradiating the pituitary gland but these have been highly disappointing (Ewing).

SEX HORMONES. Loeb, more than 20 years ago, showed that early castration would prevent the appearance of mammary cancer in female mice of susceptible strains. The author has demonstrated that the mammary cancers in rats induced with estrogen grow more slowly in the absence of continued estrogenic stimulation. These findings have been applied clinically to mammary cancer occurring in women prior to the menopause. The irradiation of the ovaries may bring

about temporary regression of metastatic growth, but the effects are not permanent nor are they observed uniformly in all cases. Because the effects of the male sex hormone are usually antagonistic to the female sex hormone, injections of testosterone have been carried out for the purpose of retarding mammary cancer. Lacassagne reported that injections of progesterone or testosterone into mice also receiving injections of estrone did not prevent mammary carcinoma in a cancerous strain (RIII) nor cause its development in three non cancer strains of mice. Testosterone did not alter the incidence of spontaneous mammary cancers in the females. The dosage of progesterone and testosterone, however, was rather small.

In the mammary cancers induced in the rat by estrogen in the author's laboratory, the appearance of the cancer is not delayed by administering the male sex hormone but cancers already present may be retarded. (Chap. 34, p. 765.) Improvement for a period of 12 to 36 months in patients with incurable mammary carcinoma has been observed. Adair has reported similar findings.

Adrenal Hormones. The relation of the adrenal cortex to cancer has been investigated by many observers in the past decade, much of the work having been stimulated by a report of striking clinical results with an extract of adrenal cortex by Coffey and Humber in 1929. Ball, however, reported no significant changes resulting from administering the extract of Coffey and Humber. Ball's findings were based upon autopsies performed on 116 cases of malignant disease, in 89 of which injections of suprarenal cortex extract had been given. Negative results were also recorded in various malignant tumors of animals by Bischoff and Maxwell, Sugiura and others. The author has tested synthetic adrenal cortical hormone (desoxycorticosterone) on the Brown-Pearce cancer in rabbits, and obtained negative results.

Thymus Gland. Because the thymus gland is active in the early years of life when cancer is rarely present, and atrophic or absent in the latter decades or cancer age, attempts have been made to control the disease with extracts prepared from this organ. Meyer and Simmons reported negative results after administering extract of thymus prepared by the method described by Hanson. Smith and Jones likewise failed to influence the incidence of spontaneous cancer in mice with a similar extract. No potent extract with a demonstrable endocrine effect has ever been prepared from the thymus gland and the data obtained to date are therefore inconclusive. Although Bomskov and Sladovic report a lipoid-soluble thymic hormone which affects the lymphocyte count and the liver glycogen, the author could not confirm these observations.

Thyroid and Parathyroid Hormones. The thyroid and para-

thyroid glands have not been shown to play an important role in the growth of cancer to date. Numerous conflicting observations have been reported. McJunkin and his co-workers reported regression and decreased growth in transplanted rat sarcomas following the removal of the thyroid and parathyroids. Paik found that parathyroid hormone increased the growth of transplanted rat carcinomas. On the other hand, Thompson reported favorable results in the treatment of human cancer with an alcoholic extract of the parathyroid gland. Cramer and Horning report that injections of thyrotropic pituitary hormone inhibit or retard spontaneous mammary cancer in inbred strains of mice but Lacassagne did not confirm these observations. (See Chap. 34, page 770.)

INSULIN. Interest in the blood sugar and carbohydrate metabolism in cancer patients was stimulated by the report of Warburg, indicating that the growth energy of cancer tissue was dependent upon its ability to split glucose to lactic acid in the presence or absence of oxygen (aerobic glycolysis). Attempts to influence the growth of cancer by interfering with this mechanism have been previously referred to. Kawamura and Kamikawa reported that injections of insulin inhibited the production of tar tumors, while injections of adrenalin, saccharose and dextrose enhanced their productions. Attempts to apply such findings to cancer patients however are disappointing, although Freund and Kaminer believe that withdrawal of sugar from the diet has a beneficial effect.

Organ Extracts. Extracts prepared from organs such as spleen, liver, and brain have been tested experimentally and clinically for their inhibitory effects on cancer. A number of European investigators have advocated the use of such extracts in the treatment of hopeless cancer (Fichera, Maisin). The ultimate results however have been disappointing. There is some experimental evidence indicating that extracts of spleen exert a mild inhibitory effect on cancers grown in tissue culture. Sugiura prepared extracts by defatting and grinding the fresh tissues of lung, kidney, heart, liver, muscle, brain, testis, placenta, embryo and spleen and exposed cultures of mouse sarcoma and rat carcinoma to them. The subsequent growth of these tumors on transplantation was inhibited after exposure to the extract of spleen prepared from rats but the other extracts showed no inhibitory effects. On the other hand, Visser and Soetarso could demonstrate no inhibitory influence of the spleen on the growth of cysticercus liver sarcoma in rats.

Diets and Vitamins. The effects of various diets on the growth of cancer have been extensively studied. Bischoff and Long conclude that the restriction of the caloric and protein intake retards to some

degree the growth of rat sarcoma. This is at variance with the clinical observation that cancer continues to grow and spread rapidly in its terminal stages despite the inability of the patient to take proper food. Freund and Kammer have claimed beneficial effects by prohibiting animal fats, sweets and alcoholic beverages and supplying adequate quantities of vegetable oil to the diet of cancer patients. Other observers however have not obtained such results (Christiani).

VITAMINS. The effects of vitamins on the growth of cancer according to experiments performed to date are negligible. Gordonoff and Ludwig studied the effects of the vitamins A, B_1, B_2, C, D and E on cultures of chick fibroblasts and cancer cells. They concluded that vitamin C, D and E were without influence, but thought that vitamins A and B_1 had a stimulating effect on growth. Davidson in a series of articles came to the conclusion that vitamins A, B_1 and E inhibited the growth of tar cancers in mice. Cameran and Meltzer could not check these findings. Various workers have shown that rats deficient in vitamin A tend to develop hyperkeratinization of the mucous membranes but these changes are not precancerous and the administration of vitamin A does not retard tumor development (Sure et al.). Rowntree and his co-workers reported the development of sarcoma in rats following the feeding of vitamin E in the form of wheat germ oil, but these experiments could not be repeated by Carruthers.

Biotin, a member of the vitamin-B complex, has been shown to favor the development of hepatic cancer in rats fed with butter yellow (dimethylaminoazobenzene). Riboflavin gives some protection against butter yellow which displaces the nicotinic acid necessary for the metabolism of the liver cells. In order to counteract the cancer promoting effect of biotin, avidin, a substance from egg white, which combines with biotin has been fed to the experimental animals. A generalized deficiency in biotin is thus produced and impairment of the health of the animals rather than amelioration is observed. Rhoads and Abels administered egg white and Avidin to a patient with mammary carcinoma without observing benefit.

Immunization Against Cancer. It has been well established that various strains of laboratory animals and different individuals in the same strain differ in their resistance to spontaneous and transplanted cancers. Attempts to apply such information to the production of immunity in animals or patients have not proved successful. Lumsden has sought to develop an immunizing serum against cancer. Phelps in testing the serum described in the experiments of Lumsden on cultures of malignant cells came to the following conclusions: (1) that "anticancer sera" have no specific action on malignant cells;

(2) that the antigen in cancer cells which give rise to the antibodies is not peculiar to malignant cells; (3) that the antibodies are probably iso-antibodies formed in response to injections of foreign, though homologous cells; (4) that the antisera, from their nature, probably cannot be therapeutically useful. Goldfeder in a similar study tested various anticancer preparations on cultures of human cancer cells as well as upon mouse sarcoma and showed that the anticancer preparations were without effect. Among the substances tested was the preparation Enzol which is supposed to contain an inhibitory enzyme elaborated by a culture of bacteria grown in the presence of tissue obtained from cancers of the human breast.

Cancers treated by heat (Sugiura and Benedict) or by self-digestion (Casey) have been injected with the hope of raising the resistance to cancer but have shown instead a tendency to decrease the resistance of the host to malignant disease.

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PART VII

THE EXPERIMENTAL PRODUCTION OF BENIGN AND MALIGNANT MAMMARY TUMORS

ORIENTATION

The experimental production of the forms of chronic cystic mastitis, of benign mammary tumors and of mammary cancer has been accomplished with physiologic agents in laboratory animals. This has supplied valuable information to the clinician by demonstrating the relation between physiologic and pathologic states and subsequent tumor formation. In Chapters 33 and 34 experimental data are presented which indicate that hyperfunction and premature aging stimulate the pathologic hyperplasia which precedes the formation of benign and malignant tumors. Both forms of neoplasm result from accelerated regeneration which follows after the normal growth and renewal of mammary tissues has been exhausted by physiologic or pathologic stimuli.

The majority of the conclusions drawn from these experiments are based upon the results observed in the mammary gland of the rat and upon the analogy between these findings and the pathology of corresponding conditions in the human breast. It must be borne in mind in reading these chapters that there is no way to evaluate the factors of species difference. Thus mammary cancer, with various forms of mammary dysplasia and benign tumor formation, may be produced in mice with estrogens within a period of 20 weeks. Corresponding changes are produced in the rat in 40 weeks and in the rabbit in 80 weeks, but in the monkey (*Macaca rhesus*) the author has not observed corresponding changes in six animals during a period of 160 weeks. In Chapter 35 an attempt has been made to describe the mechanism by which the cancer is brought about, based upon the experiments described. The mechanism is given in biologic terms and no attempt is made to specify the hormone agent since estrogen may represent only an initial example of a larger group of endocrine mechanisms which remain to be discovered.

In the experiments described various preparations of estrogen, testosterone and the corpus luteum hormones were used. In some instances the animals were hypophysectomized or adrenalectomy was performed. In other instances lactogenic hormone was added. As pointed out in Chapter 2 on the endocrine physiology of the breast, both the adrenal cortical hormone and thyroxin may affect the mammary gland and other hormones of the pituitary besides lactogenic substance are essential for mammary development. The clinical fac-

tors which may affect the conditions investigated are therefore far greater than those introduced into the experiments outlined.

In regard to the forms of mammary dysplasia produced experimentally, there is a close parallel to the clinical manifestations of the disease. The sequence of changes observed, their variability with differences in dosage and the diffuse involvement of all the mammary glands in the same animal are characteristic of the protean and diffuse nature of the disease as it is observed clinically. Moreover, there is abundant clinical evidence correlating mammary dysplasia with ovarian dysfunction. As shown by laboratory investigations one or more large cysts are usually the result of brief, intense estrogenic stimulation unopposed by corpus luteum function. The cyst may appear before or after the estrogen is withdrawn. Prolongation of the estrogen stimulus results in multiple cysts and even minute doses of luteal hormone will prevent the appearance of the larger cysts. Mastodynia followed by adenosis results from prolonged, moderate estrogen stimulation, with insufficient or absent luteal hormone. If larger amounts of estrogen are used the same results can be achieved by partially counteracting the effects of estrogen with luteal hormone.

Fibroadenomas are produced experimentally if constant and moderately intense estrogenic stimulation is maintained over long periods, but not if excessively large amounts of estrogen are injected daily. This is in line with the clinical observation that fibroadenomas have a tendency to form during adolescence, pregnancy and the menopause when a relatively constant estrogenic stimulation is maintained, rather than in cyclic women where there is a repeated rise and fall in the level of the hormone. Once the fibroadenoma has formed, intense estrogenic stimulation for brief periods accelerates its growth, although an equal amount of the hormone is not so effective during the period of formation. The fact that fibroadenomas are often multiple and frequently associated with mammary cancer in experimental animals is at variance with clinical findings and suggests that the sensitivity of the responding tissue plays a role in the production of the tumor under natural conditions and that the intensity and prolongation of the estrogenic stimulation is not the sole factor.

In the author's experiments benign papillomas or cystadenomas of appreciable size occurred in animals which were hyperstimulated with estrogen to a sufficient degree and time for the production of mammary carcinoma. Even under such conditions the papillomas were far less frequent than the carcinomas. Apparently, papillomas appear in isolated zones of epithelial regeneration after the glandular tissue has been largely exhausted by hypermaturity, aging and

degeneration. The neoplastic epithelial regeneration forms in zones where an unusual amount of undifferentiated epithelium has been left behind during normal development. The estrogen, therefore, is only indirectly concerned in the production of papillomas and other factors may operate under natural conditions to stimulate such growths.

The author has produced mammary carcinoma in rats and rabbits by large variety of estrogenic compounds and many different forms of dosage. The effective dose is 10 or more times the threshold or physiologic dose and must be applied for a period which is 30 or more times the duration of normal estrus. An initial period of estrogenic stimulation below the cancer-producing threshold renders the gland more susceptible to cancer if the same hormone is subsequently applied. It is this preconditioning to cancer by an abnormally intense stimulus during puberty or by a moderately increased dose over a long period during sexual maturity, that may constitute the role of estrogen in the development of human mammary carcinoma. Perhaps girls whose breasts develop too rapidly during puberty and certainly women who suffer from adenosis over many years because of a relative hyperestrinism are rendered more susceptible to mammary carcinoma if high concentrations of estrogen occur during their menopause. Aside from these applications and the warning that indiscriminate therapeutic use of the estrogens during the menopause to control the menopausal syndrome may be harmful, there is insufficient evidence to indicate that estrogen is the determining factor in the production of human mammary cancer. The experiments herein reported are interpreted quite differently by the author who believes that estrogen is only one of a number of agents which may produce premature aging and degeneration of the mammary epithelium, which stimulates by a selecting mechanism neoplastic regeneration.

33

The Experimental Production of Chronic Cystic Mastitis, Fibro-Adenoma and Papilloma

The experimental production of chronic cystic mastitis has been discussed in Chapter 11 and the conclusions based upon these experiments correlated with the clinical features of the disease. These experiments are presented here in more detail.

Growth and secretory activity is stimulated in the mammary ducts by estrogens and the development of the lobule-alveolar structures is influenced by this hormone and the luteal hormones (see Chap. 2). All forms of chronic cystic mastitis can be reproduced in the rat by varying the endocrine control which the ovarian sex hormones exert upon these structures. The presence of the hypophyseal gland is essential for these endocrine effects; during pregnancy the influence of the placental hormones overshadows them. To some extent the adrenal cortical hormones exert an influence similar to that of the ovarian hormones.

Cystic disease is produced by pathologically intense doses of estrogen. A relatively brief period of overstimulation followed by

the withdrawal of the estrogen for a period of several days results in large solitary cysts. Overdosage for more prolonged periods results in multiple cysts of various sizes. In these experiments the pathologic changes of mastodynia precede cyst formation and the changes of adenosis may either precede or follow multiple cysts.

Mastodynia followed by adenosis may be produced experimentally by estrogen stimulation alone using moderate doses over a prolonged period. These changes are more readily produced by combining estrogenic and luteal stimulation in ratios in which the estrogen factor exceeds the luteal factor. If this excess of estrogen is too great, cyst formation also occurs.

EXPERIMENTAL PRODUCTION OF MASTODYNIA AND ADENOSIS

The effect of estrogens in physiologic doses is to produce growth and branching of the mammary ducts—canalicular extension. During this process characterized by differentiation of the duct epithelium, the lobular buds at the end of the ducts increase in size through the multiplication of their undifferentiated basal cells. Daily injections of 2.5 gamma of estrone in oil for periods of 45 to 60 days produce rapid extension of the ducts and enlargement of the lobular buds, in female rats castrated at 21 days. This is similar to the normal adolescent growth observed in the human female breast but there is less fibrous stroma in the rat's breast and apparently this fibrous tissue is less sensitive to estrogenic stimulation than is the human breast.

By Estrogens Alone

Before Adenosis Appears. If the amount of estrogen given is greater or if the time of administration is prolonged the growth of the duct tree is stunted or stopped and the pathologic changes of mastodynia are produced. These changes of mastodynia are characterized by increase in periductal fibrous tissue, by dilatation and secretion in the smaller ducts, by the partial conversion of the lobular buds into irregular acini some of which are dilated and filled with secretion to form minute cysts. A portion of the lobular bud continues to proliferate forming irregular basal-cell sprouts (Fig. 573, Chap. 35).

This dwarfing of the duct tree and the abnormal bushy appearance of the end-buds is the earliest sign of estrogen overdosage. It corresponds to the clinical form of mastodynia described in Chapter 8 as mammary deficiency. It also represents the second stage in all the estrogenic mammary cancer experiments described in the next

chapter. Hence, this form of mastodynia resulting from early estrogen overstimulation has been observed to date in more than 500 animals. In female rats castrated at 21 days mastodynia appeared in 45 to 50 days with 5 gamma of estrone in oil injected daily; in 20 to 40 days if six estrone pellets totaling 15 mg. were implanted, or if 10 gamma of estradiol benzoate or 200 gamma of estrone in oil were injected daily.

TABLE XCII

5 GAMMA ESTRONE

(Injected in Oil Daily)

RAT[1]		DAYS TREATED	DUCTS AND TUBULES	LOBULE-ALVEOLAR STRUCTURES
1645	A	20	Columnar lining cells, secretion	More active cell division in basal-cell buds, occasional acini
1976 a		45	Moderate secretory effect, increased periductal fibrous tissue	Slight secretory effect, some basal-cell regeneration, increased fibrous tissue, MASTODYNIA
3081 a	B	68	Secretory droplets in lumen, atrophy of lining, some lining regeneration, reduced fibrous tissue	Few secretory droplets, persisting foci of basal cells
3092 a		120	Secretory droplets in lumen, atrophy of lining, some lining regeneration, atrophy of fibrous tissue	ATROPHY and collapse of secreting acini, size of basal-cell buds reduced
3124 b		176	Epithelial and fibrous structures atrophic	Shrinkage of lobular buds, occasional mitosis among basal cells
3104 a	C	207	Further atrophy, epithelium and fibrous tissue	ATROPHY* of lobular buds, basal-cell foci condensed
3084 b		239	Further atrophy	Basal-cell foci inactive
3090 b		300	Atrophic state continues	Basal-cell foci beginning to multiply
1976 b	C′	320	Duct lining actively regenerating, renewed periductal fibrosis	Secretion in small cystic acini, proliferation of lobular buds to form small duct adenoma and typical ADENOSIS
1975 b	D	590	Lining atrophic, foci of basal cell regeneration, tubules are collapsed, periductal fibrosis	Acini collapsed, droplets of inspissated secretion, residual foci of basal cell budding, peripheral FIBRO-ADENOMA
1683 c	E	695	Ducts dilated with secretion, degeneration and fibrosis of wall	CYSTS, CYSTIC FIBRO-ADENOMA, lactating lobules, pleomorphic fibro-adenoma

[1] The above table is based upon an experiment in which 100 rats were treated with 5 gamma of estrone daily for periods of six months to two years. All of the animals were females; those tabulated are from a group castrated at the age of 21 days.

After mastodynia has made its appearance the subsequent changes in the mammary tissue depend upon the intensity of the estrogenic

stimulus. If moderate dosage (5 gamma of estrone) is administered, mastodynia is followed by atrophy and collapse of the lobular elements, the epithelial lining of the ducts becomes atrophic and the secretion is absorbed. These atrophic changes in the rat continue from the 70th to the 300th day if the same dosage is maintained. At the end of this time the changes of adenosis make their appearance and after 500 to 600 days fibro-adenomas occur. After 700 days, cystic fibro-adenoma and pleomorphic fibro-adenoma are found (Table XCII).

Thus, mastodynia may be a self-limited condition. This sequence of changes explains the clinical response of mastodynia to short periods of estrogenic therapy, and also the occurrence of small fibro-adenomas and adenosis in patients overtreated with estrogens for long periods (see page 255).

If high doses of estrone (200 gamma in oil daily) are given to rats, mastodynia is followed by cyst formation in a period of three to six weeks and if constant and relatively intense stimulation is maintained by implanting multiple estrone pellets small multiple cysts later complicated by adenosis appear in four to 12 weeks.

As pointed out in Chapter 9, adenosis may be looked upon as a more advanced stage of mastodynia. Frequently it is a late development in the type of breast referred to as "mammary deficiency" (Chap. 8). In all of our experiments resulting in estrogenic mammary cancer, adenosis occurred subsequent to mastodynia but was separated from it by an intervening phase of atrophy or cyst formation according to the dosage used. As described above, if 5 gamma of estrone in oil is injected daily, approximately one year is required for the subsequent appearance of adenosis following the onset of this stage of mammary atrophy and the adenosis is ultimately converted into polycystic disease and cystic fibro-adenoma. In patients, adenosis usually develops after mastodynia or in a small atrophic or quiescent gland and in advanced cases the breasts become riddled with cysts 0.5 to 1 cm. in diameter. If more intense and constant estrogenic stimulation is maintained by implanting pellets in castrate female rats, adenosis may complicate a pre-existing polycystic disease (see Table XCVI).

By Estrogens and Luteal Hormones Combined

Microscopic changes simulating mastodynia and adenosis are produced in rats' breasts by combining injections of estrone with testosterone or progesterone. If instead of the normal ratio of estrone to luteal hormones required for lobule formation, larger doses of estrone are given, or more minute amounts of progesterone

or testosterone, irregular epithelial proliferation appears in the mammary tubules and end-buds and pathologic changes like those of mastodynia and adenosis result.

As pointed out in Chapter 2, the synthetic male sex hormone, testosterone propionate, is closely allied in its formula to the corpus-luteum hormone, progesterone, and may be substituted for progesterone in the experimental production of mammary lobules in the rat and monkey. In the experiments described below the term "luteal hormones" refers to testosterone propionate, progesterone and to progestin which is an extract of the corpus luteum obtained from the ovaries of the pregnant sow or cow, and which probably contains luteal hormones in addition to progesterone. Progestin produces lobules more readily in the rat's breast than progesterone but not as readily as testosterone.

Excessive Estrogenic and Insufficient Luteal Hormone (Brief Imbalance). The experiment presented in Table XCIII indicates that mastodynia is a relatively early response to excessive estrogenic stimulation in the presence of insufficient amounts of luteal hormone. More pronounced lobular irregularity (of the character seen in adenosis) occurs if the luteal hormones are administered in decreasing amounts, particularly in the presence of increasing amounts of estrogen; and finally severe adenosis with multiple small cysts followed by cancer supervenes if high doses of estrogen are administered over prolonged periods alternating with insufficient amounts of luteal hormone. It is significant that the time and the amount of estrogen required for the experimental production of cancer was reduced in the mammary gland where adenosis resulted from an imbalance of the estrogen and luteal hormones. On the other hand, lobule formation was restored and a relatively normal mammary gland was found if increasing large amounts of luteal hormone were administered.

These findings suggest that mastodynia and later adenosis occurs in the presence of decreasing corpus-luteum function in women approaching the menopause. The condition is alleviated by the administration of luteal hormones and if the degree of adenosis is marked the susceptibility of the mammary gland to cancer is increased.

Moderate Estrogen Overdose with Insufficient Luteal Hormone (Prolonged Imbalance). In the next experiment (Table XCIII, XCIV) moderate estrogen overdosage in the presence of insufficient amounts of luteal hormone (in the ratio of 10 gamma estrone to 0.25 mg. testosterone) resulted in early mastodynia followed by relatively normal lobule formation and finally by atrophic lobules after a

TABLE XCIII

MASTODYNIA AND ADENOSIS IN CASTRATE FEMALE RATS [1] RECEIVING COMBINED ESTRONE AND TESTOSTERONE [2] TREATMENTS

	ESTRONE		TESTOSTERONE			
RAT NO.	GAMMA DAILY	DAYS TREATED	MGM. DAILY	DAYS TREATED	HOW GIVEN	FINDINGS
1523, 1524	10	20 to 40	2½	20 to 40	Simultaneously	Mastodynia
1020	10	36	¼	36	Simultaneously	Mastodynia
1022	20	36	¼	36	Simultaneously	Mastodynia
1029	5 to 200 (increasing dose)	30	¼	30	Simultaneously	Mastodynia
1028	20	30	5 to 1 (decreasing dose)	30	Simultaneously	Mastodynia, late
1027	10	40	5 to ¼ (decreasing dose)	40	Simultaneously	Early adenosis
1030	5 to 200 (increasing dose)	30	5 to 1 (decreasing dose)	30	Simultaneously	Adenosis
1125	200	40	½	40	Successively	Mastodynia
896	50	100	1	12	Successively	Adenosis
1233	200	42	½	42	Successively	Polycystic disease
	200	42	½	42	Successively	Adenosis, cancer
1023, 1024	10	40	1 to 5 (increasing dose)	40	Simultaneously	Lobules restored

[1] These rats were castrated and injections were started at the age of 21 days.
[2] The testosterone preparation was testosterone propionate.

period of nine months. Under these circumstances the administration of high doses of estrogen produced adenosis. This abnormality in turn could be converted back into relatively normal lobule formation by the administration of large doses of testosterone propionate (5 mg. for 40 days).[1]

This experiment indicates that in the presence of decreased corpus-luteum function, mastodynia, although followed by adenosis, may be separated from the latter condition by a long period of relatively normal lobule formation. During this period intense estrogenic stimulation precipitates adenosis prematurely, but normal lobule formation may be restored by relatively large doses of testosterone proprionate or luteal hormones.

Estrogen in Strong Physiologic Doses with Insufficient Luteal Hormone. When estrone was given in strong physiologic doses (5 gamma, Table XCV) and insufficient amounts of luteal hormone were administered (testosterone propionate 0.125 mg.) small but

[1] Unfortunately from the standpoint of endocrine therapy, in human beings testosterone is not as effective for lobule formation as it is in the rat and monkey.

TABLE XCIV

MASTODYNIA AND ADENOSIS IN CASTRATE FEMALE RATS [1] RECEIVING COMBINED ESTRONE AND TESTOSTERONE [2] INJECTIONS FOR PROLONGED PERIODS

RAT NO.	TREATMENT DAILY	DAYS GIVEN	BIOPSIED	FINDINGS
3153	Estrone 10 gamma	145	60 days	Collapsed lobules
	Testosterone 0.25 mg.		145 days	Irregular lobules
3150	Estrone 10 gamma	249	33 days	Mastodynia
	Testosterone 0.25 mg.		99 days	Irregular lobules, secretion
			187 days	Irregular lobules
			249 days	Irregular lobules
	Testosterone 1.25 mg.	21	271 days	Lobules, pseudolactation
3151	Estrone 10 gamma	271	60 days	Collapsed lobules
	Testosterone 0.25 mg.		145 days	Lobules, inspissated secretion
			271 days	Atrophic lobules, adenoid foci
	Estradiol benzoate 50 gamma	36	307 days	Adenosis, cystadenoma
3152	Estrone 10 gamma	260	114 days	Lobules, sebaceous adenoma
	Testosterone 0.25 mg.		242 days	Dilated lobules
	Estradiol benzoate 50 gamma	24	284 days	Adenosis
3148	Estrone 10 gamma	249	33 days	Mastodynia
	Testosterone 0.25 mg.		114 days	Secreting lobules
			187 days	Atrophic lobules
			249 days	Irregular lobules, adenosis
	Estradiol benzoate 50 gamma	3		
	Testosterone 1.25 mg.	21	274 days	Irregular lobules, adenosis
	Testosterone 5 mg.	46	320 days	Dilated secreting lobules

[1] These rats were castrated and injections were started at the age of 72 days.
[2] The testosterone preparation was testosterone propionate.

relatively normal lobule formation resulted during the first six months, mastodynia was delayed until the eighth month and adenosis until the ninth month of treatment. When, under these conditions, estrogen stimulation was increased (50 gamma estradiol benzoate for 48 days) cystic disease, intracystic papilloma and early papillary cancer supervened. When five estrone pellets (12.5 mg.) were implanted together with one testosterone pellet (2.5 mg.) the sequence of changes was the same—mastodynia, adenosis and cancer. (Rat No. 1993, Table XCV.)

This experiment indicates that with moderately deficient corpus-luteum function small but relatively normal lobules form, but if the deficiency is of long duration mastodynia followed by adenosis ultimately ensues. Under such conditions, intense estrogenic stimulation results in benign papillomatous growths or in papillary adenocarcinoma. Large cysts may also form.

Estrone in Pellets with Luteal Hormone. In the next experiment (Table XCVI), progesterone instead of testosterone was used as the luteal hormone and the estrone was given in pellet form. The rats

TABLE XCV

MASTODYNIA AND ADENOSIS IN CASTRATE FEMALE RATS [1] RECEIVING COMBINED ESTRONE AND TESTOSTERONE [2] INJECTIONS FOR PROLONGED PERIODS

RAT NO.	TREATMENT DAILY	DAYS GIVEN	BIOPSIED	FINDINGS
3140	Estrone 5 gamma	176	60 days	
	Testosterone 0.125 mg.		145 days	Lobule formation
			176 days	
3141	Estrone 5 gamma	271	33 days	
	Testosterone 0.125 mg.		114 days	Lobule formation
			187 days	
			271 days	Early adenosis with small cysts
	Estradiol Benzoate		320 days	Large cysts—cystic disease
	50 gamma	48		
3143	Estrone 5 gamma	271	60 days	Collapsed lobules
	Testosterone 0.125 mg.		145 days	Secreting lobules
			242 days	Mastodynia
			271 days	Adenosis with cysts
	Estradiol Benzoate			
	50 gamma	48	320 days	Polycystic disease
3138	Estrone 5 gamma	249	33 days	Early lobule formation
	Testosterone 0.125 mg.		99 days	Lobules, sebaceous adenoma
			187 days	Lobule formation
			249 days	Atrophic lobules secretory concretions
	Testosterone 1.25 mg.	21	270 days	Adenosis
	Estradiol Benzoate			
	50 gamma	48	320 days	Papilloma, papillary cancer
3137	Estrone 5 gamma	249	33 days	
	Testosterone 0.125 mg.		114 days	Lobule formation
			187 days	
	Testosterone 1.25 mg.	21	271 days	Irregular lobules
	Estradiol Benzoate			
	50 gamma	3	275 days	Early cysts
	Testosterone 5 mg.	45	320 days	Lobules restored
1993	Estrone pellets 12½ mg.	383	42 days	Mastodynia
	Testosterone pellet 2.5 mg.		123 days	Marked mastodynia
			231 days	Adenosis
			383 days	Adenosis, cancer

[1] These rats were castrated and injections were started at the age of 72 days.
[2] The testosterone preparation was testosterone propionate.

used were between one and two years of age, chosen to correspond roughly to the age group in which chronic cystic mastitis is observed clinically. Some of the rats had been castrated early in life, others at the onset of the experiment, and some were intact. In most of the animals the ratio of estrogen to luteal hormone administered produced mastodynia, followed, after a period of normal lobule formation, by adenosis. The administration of progesterone did not prevent the appearance of fibro-adenoma, fibrosarcoma or mammary cancer in response to the five small estrone pellets, which were implanted in these rats, if the animal survived a sufficient period of time.

TABLE XCVI

MASTODYNIA AND ADENOSIS IN CASTRATE FEMALE RATS RECEIVING COMBINED ESTRONE AND PROGESTERONE

		5 ESTRONE PELLETS		PROGESTERONE INJECTIONS DAILY		
RAT	AGE	MG.	MONTHS GIVEN	MG.	MONTHS GIVEN	BIOPSY FINDINGS
2046	13 mo.[2]	4.5	2	½	1	Early adenosis
		4.5	4	½	3	Adenosis, fibro-adenoma
		4.5	9	½	8	Adenosis
1640	21 mo.[1]	5.1	2	½	1	Mastodynia
		5.1	4	½	3	Lobule formation
		5.1	6	½	5	Adenosis polycystic
1710	14 mo.[2]	5.1	2	½	1	Mastodynia
		5.1	4	½	3	Lobule formation
		5.1	6	½	5	Marked adenosis
1820	16 mo.[1]	3.5	2	½	1	Mastodynia polycystic
		3.5	3	½	2	Mastodynia polycystic
1817	16 mo.[1]	3.5	1	½	0	Mastodynia
		3.5	4	½	3	Mastodynia
		3.5	9	½	8	Fibro-sarcoma
		3.5	11	½	10	Atrophy, dilated ducts, cystadenoma
1675	20 mo. (intact)	3.8	1	½	0	Lobules, some adenosis
		3.8	2	½	1	Adenosis, small cysts, some giant lobules
		3.8	7	½	6	Cancer in pseudopregnant breast

[1]Castrated at one month.
[2]Castrated at onset of experiment.

EXPERIMENTAL PRODUCTION OF CYSTIC DISEASE

Intense Estrogenic Stimulation

Brief Stimulation. One or more large cysts are usually the result of brief, intense estrogenic stimulation unopposed by corpus-luteum function. In the mammary gland of the castrated female rat 200 gamma of estrone in oil injected daily results in the formation of large cysts within a period of from six to 12 weeks (Table XCVII). A more rapid development of large cysts occurs with these high doses of estrone if the treatment is stopped for four or five days after injections have been continued for four weeks. This corresponds with the clinical history of the disease. In patients large solitary cysts make their appearance abruptly, usually near the menopause, when estrogenic output may be high and luteal function absent. If patients with cystic disease who have not yet reached the menopause are carefully questioned, occasionally a history of intermenstrual or functional bleeding may be obtained indicating the decline of luteal function, and the formation of the cyst is noted at the end of a menstrual period, at a time when estrogen stimulation is absent.

Prolonged Stimulation. Multiple cysts are produced by prolonged intense estrogenic stimulation in rats whether the estrogen be implanted as pellets or injected daily in large amounts in oil (see Table XCVII).[1] The appearance of the cyst is preceded by the histologic changes of mastodynia. If the estrogenic stimulation is very constant and intense, however (if multiple pellets are implanted or if 5 or more gamma of estradiol benzoate is given daily), cysts may not occur but instead fibro-adenomas are formed and later these undergo cystic change. Under such constant estrogenic stimulation cancer may appear without the development of cystic disease.

Estrogen with Luteal Hormones

The administration of progesterone or testosterone propionate suppresses or delays the appearance of cyst formation in response to estrogen. If these luteal hormones are given in sufficient amounts and intense estrogenic stimulation is superimposed, adenosis rather than cyst formation may occur. (See Table XCVI.)

TABLE XCVII

EXPERIMENTAL PRODUCTION OF CYSTIC DISEASE IN THE RAT WITH INTENSE ESTROGENIC STIMULATION

FORM OF ESTROGENIC STIMULATION	ESTROGEN	DOSE	HOW GIVEN	SMALL CYSTS PRODUCED weeks	LARGE CYSTS PRODUCED weeks
Interrupted	Estrone	200 gamma no treatment	Daily—21 da. 5 da.	–	4
Interrupted	Estrone	200 gamma	Daily	6	12
Interrupted	Stilbestrol	100 gamma	Daily	8	18
Constant	Estrone	5 mg.	Pellets	8	10

EXPERIMENTAL PRODUCTION OF FIBRO-ADENOMA

Intense Estrogen Stimulation

Fibro-adenomas may be produced in the mammary gland of the rat by prolonged estrogenic stimulation. The constancy with which the hormone level is maintained is more important than the intensity of the stimulus. If a brief but intense degree of stimulation is provided, the effect is chiefly on the epithelium. With a less intense but a constant level, the connective tissue responds selectively.

When large amounts of estrone in oil are injected daily, the rapid absorption and excretion of the hormone results in large cysts. Fibro-adenomas occur if a more constant but less intense stimulus is maintained by absorption from estrogen pellets or if small daily doses at the upper physiologic limits are given over many months. This is in line with the clinical observation that fibro-adenomas have a tendency to form during adolescence, pregnancy and the menopause

[1] Under intense and prolonged doses of testosterone cysts may also occur.

when a relatively constant estrogenic stimulation is maintained, rather than in cyclic women where there is a repeated rise and fall in the level of the hormone. Once the fibro-adenoma has been formed, intense estrogenic stimulation for brief periods accelerates its growth, although an equal amount of the hormone is not so effective during the period of formation.

Physiologic Doses of Estrogen

The daily administration of estrogen in doses at the upper physiologic level will result in fibro-adenomas in the rat's breast if the treatment is continued for a period of 20 to 23 months.

FIG. 547 FIG. 548

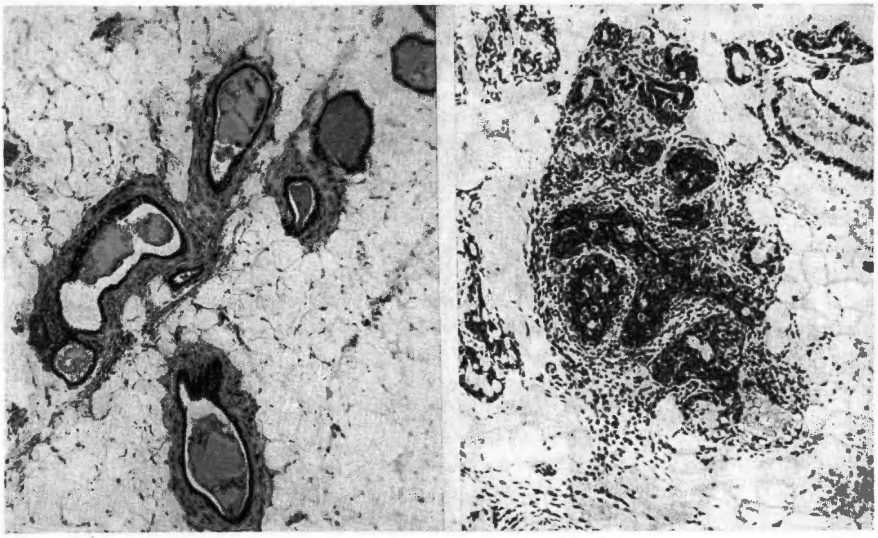


FIG. 547. Early changes preceding the formation of fibro-adenoma. The photomicrograph shows periductal fibrosis following the daily administration of 5 gamma of estrone for a period of 4 months in a castrated female rat.

FIG. 548. Late changes preceding the formation of fibro-adenoma. The photomicrograph shows periductal fibrosis about the terminal tubules. This animal was treated in a similar manner to that in Figure 547, over a period of 12 months.

The initial effects of such stimulation (5 gamma of estrone in oil daily) is a periductal fibrosis (Fig. 547). The increased growth of connective tissue about the ducts is quite marked within a period of three to four months. In the next six months this fibrous tissue undergoes atrophy and sclerosis, but at the end of a year there is renewed proliferation (Fig. 548) about the smaller tubules, and at the end of 20 months small, slowly growing fibro-adenomas are formed

If intense estrogenic stimulation is now applied (200 gamma of estrone in oil daily) the fibro-adenomas grow rapidly and reach palpable size within the next one to three months (Table XCVIII).

TABLE XCVIII

FIBRO-ADENOMA PRODUCED IN CASTRATED FEMALE RATS WITH PROLONGED PHYSIOLOGIC DOSES OF ESTRONE

(Massive doses thereafter)

RAT NO.	AGE WHEN FIRST TREATED	PHYSIOLOGIC DOSE (daily)	MASSIVE DOSE (after 20 months)	MICROSCOPIC FINDINGS SMALL DOSES	MASSIVE DOSES	
					Days	Findings
1683	2 mo.	5 gamma 12 mos.		Fibro-adenoma		
3107	2 mo.	5 gamma 23 mos.		Fibro-adenoma		
1974	1 mo.	5 gamma 20 mos.	200 gamma Pellet in breast	Fibro-adenoma	23	Comedo cancer
					98	Large fibro-adenoma
1975	1 mo.	5 gamma 20 mos.	200 gamma Pellet in breast	Fibro-adenoma	11	Large fibro-adenoma
					41	Comedo cancer

Rats tabulated here are from a series of 12 animals similarly treated.

Use of Pellet

The experimental production of fibro-adenomas in the rat progresses in similar fashion but more rapidly if a more constant estrogenic stimulus is applied by implanting a single pellet containing 2.5 mg. estrone under the skin of the back, and repeating the procedure after one to several months for a total of three pellets. (Table XCIX.) At the end of four to six months, fibro-adenomas of microscopic size are formed, and within eight to 13 months the tumors reach palpable size. (Figs. 549, 550.) Palpable fibro-adenomas also appear in seven to 13 months if multiple pellets are implanted simultaneously. Either estrone, estradiol benzoate, or estradiol dipropionate pellets may be used. Following the implantation of multiple pellets in young rats, small fibro-adenomas may be observed in some animals as early as the second month. The more potent estradiol pellets produce fibro-adenomas in only slightly less time than the estrone pellets. The fibro-adenomas are more readily produced in female than in male rats. A typical fibro-adenoma occurred in a male rat 10 months after the implantation of four pellets of estradiol benzoate, but none at the end of one year in either castrated or noncastrated male rats receiving six pellets of estrone on the 30th and on the 76th day of life.

TABLE XCIX

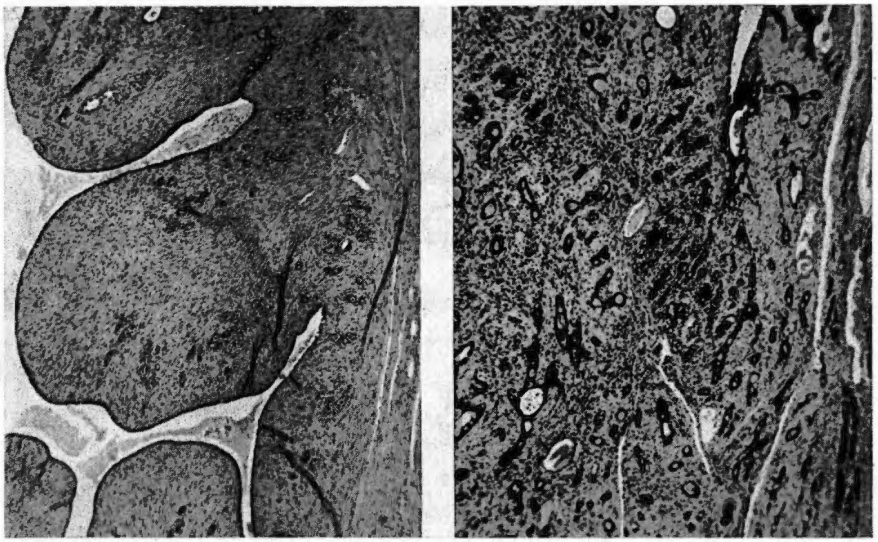
PRODUCTION OF FIBRO-ADENOMAS IN NEWBORN FEMALE RATS WITH ESTRONE PELLETS

NO. OF RATS	CASTRATED	PELLETS IMPLANTED (day of life)	TOTAL DOSE MG.	BIOPSY		AUTOPSY	
				MONTHS	FINDINGS	MONTHS	FINDINGS
6 {1510, 1518}[1]	No	2, 28, 153	7.5	4 to 6	Microscopic fibro-adenoma	8 to 13	Palpable fibro-adenoma, cancer
10 {1646, 2040}	Yes	65, 205, 320 (6 implanted)	15.0	2 to 7	Periductal fibrosis	7 to 13	Palpable fibro-adenoma, cancer
5 {1953, 1957}	No	65, 204, 320 (6 implanted)	15.0	2 to 7	Periductal fibrosis	7 to 13	Palpable fibro-adenoma, cancer
6 {1343, 1349}	Yes	55, 139, 241[2]	7.5			8 to 15	Palpable fibro-adenoma, cancer
4 {1315, 1326}	No	55, 139, 241	7.5			8 to 15	Palpable fibro-adenoma, cancer

[1] Numbers in parenthesis are for laboratory index.
[2] Previously injected with 25 gamma estrone in oil twice daily, 16th to 54th day of life.

Fibro-adenomatous changes are produced rapidly in the rat by the injection of 5 gamma estradiol benzoate or dipropionate in oil daily. These derivatives of estradiol, because of their prolonged action, supply a constant and increasingly intense stimulation to the breast. Under such experimental conditions small microscopic fibro-

FIG. 549 FIG. 550



Palpable Fibro-adenomas Produced in the Rat After 7 Months by the Implantation of Estrone Pellets.
FIG. 549. Intracanalicular myxoma resulting from estrone pellets.
FIG. 550. Typical fibro-adenoma produced with similar treatment. Compare with Figures 551 and 552.

adenomas may be found by microscopic study of the excised breast within three months. These rapidly induced fibro-adenomas do not retain their characteristic features, but develop acinar or cystic structures which resemble isolated mammary lobules in pregnancy or lactation.

Changes in Fibro-Adenoma after Formation

The progressive growth of these benign tumors under continuous estrogenic stimulation is accompanied by a variety of changes in the epithelium of the tubules enclosed by the proliferating fibrous tissue. Cystic dilation, secretory activity which resembles lactation, squamous-cell metaplasia, sebaceous- or sweat-gland adenomas, giant pseudopregnancy lobules, and carcinoma may be found. (See Figs. 264, 265.)

Etiology of Fibro-Adenomas

The experimental production of fibro-adenoma in the rat's breast with estrogen affords a very satisfactory method for the study of the etiology of these neoplasms. While the albino strain of rats used in these experiments develop such tumors spontaneously, such occurred in less than 2 per cent of the control group in our colony and have not been found in rats less than 18 months of age. With estrogenic stimulation, the incidence of the tumors in our strain approaches 100 per cent and the animals are affected at an earlier age.

Mammary fibro-adenomas result from an increased rate of growth or regeneration in the periductal connective tissue. The majority of the tumors form about the terminal tubules. The fibrous tissue about the larger ducts beneath the nipple is much increased but only rarely do tumors of significant size form in this zone. The initial periductal fibrosis stimulated by estrogen is a physiologic response. The supporting stroma of the ducts is diffusely and uniformly affected and the response must be looked upon as a simple hyperplasia since isolated tumor formation does not occur during this stage. Later in the experiments the limits of this physiologic response are reached and most of the periductal fibrosis undergoes sclerosis and atrophy. Apparently, however, if the stimulus is continuously maintained there are isolated foci of embryonic fibroblasts which are capable of a more vigorous and prolonged response and it is these isolated foci which give rise to fibro-adenomas.

It is not possible to state at present whether or not the period of sclerosis and fibrosis which intervenes between the initial phase of connective tissue proliferation and subsequent tumor formation is of etiologic significance. This atrophic phase may indicate that most of the fibrous stroma is incapable of a sufficiently intense or prolonged regenerative response to give rise to tumor formation. On the other hand, it is possible that the hyalinization and degenerative changes that occur as an end-result of the initial proliferation may furnish specific end-products which are an important stimulus for subsequent tumor growth. We have been unable to verify this experimentally for estrogenic mammary tumors. However, this possibility is suggested by the fact that hypertrophic changes in the epidermis of the rat in response to ultraviolet radiation if sufficiently intense will go on to tumor and cancer formation after the withdrawal of the ultraviolet stimulation.

In their potentialities for continuous growth, the experimentally produced fibro-adenomas in the rat's breast differ from those

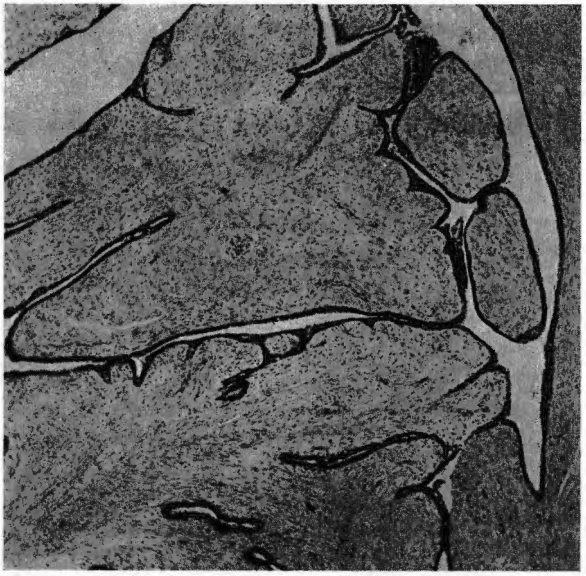


FIG. 551. Typical intracanalicular myxoma excised from the human breast

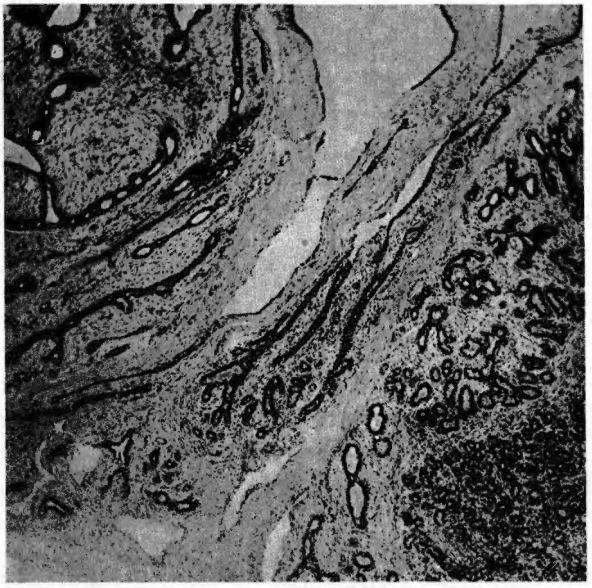
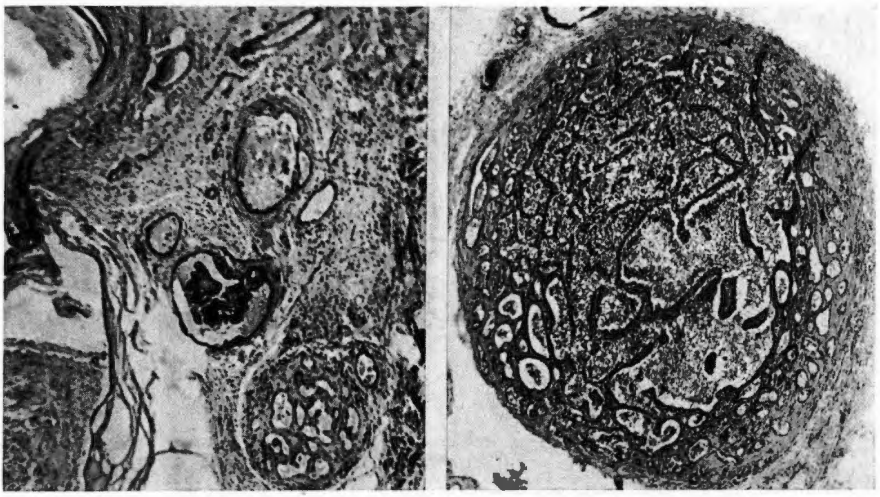


FIG. 552. Typical fibro-adenoma excised from the human breast. (Compare with Figs 549, 550.)

which occur spontaneously. The estrogenic tumors have, to date, become stationary in size, growing from 1 to 5 cm. in diameter and have not been successfully transplanted. Those which occur spontaneously in our colony have been successfully transplanted from host to host for many years in the same manner as reported in the experiments of Heiman and Krehbiel and in those of

FIG. 553 FIG. 554



Fibro-adenomas Produced in the Mammary Gland of the Rabbit.
FIG. 553. Small fibro-adenoma beside a minute intracystic papilloma.
FIG. 554. Larger fibro-adenoma undergoing secretory changes in its center. This animal received 0.5 mg. of stilbestrol di-methyl ether daily for a period of 20 months.

Emge and Murphy (see ref. Chap. 13). With repeated transplantation and continuous growth fibrosarcomas develop in spontaneous fibro-adenomas. Such sarcomatous change was observed but once in our estrogenic fibro-adenomas, and may have been a spontaneous occurrence.

In spite of these observations it is probable that estrogen plays an etiologic role in the development of fibro-adenomas in the human breast as well as in the mammary gland of the rat.

Increase in the size of the human breast in response to estrogen therapy is a fairly accurate index of the response of the fibrous stroma to the hormone. Clinical experience has shown that a fairly constant estrogenic stimulus, or one maintained over many months, is necessary to secure a noticeable enlargement in the adult. Thus, in women with underdeveloped breasts, a satisfactory enlargement

is not obtained by intramuscular injections of estrone in oil given twice weekly over periods of three to six months. However, if a more constant stimulus is maintained by local applications of estrogenic ointment daily, or by daily doses of stilbestrol compounds, given orally, development of the fibrous stroma is indicated by the increased size and firmness of the breasts. A similar effect is obtained if intramuscular injections of estrogen are given once or twice weekly over periods in excess of one year. (Fig. 223, Chap. 11.) In a case of mastodynia treated in this manner for 27 consecutive months the breasts became larger and firmer and at biopsy multiple small fibro-adenomas, apparently the result of treatment, were found. (Fig 238, Chap. 12.)

TABLE C

FIBRO-ADENOMA AND PAPILLOMA IN FEMALE RABBITS

RABBIT NO.	AGE	TREATMENT DAILY	FINDINGS
189	3 months castrated	1 mg. Di-methyl stilbestrol	Biopsy 10 mos. Papillary cystadenoma and periductal fibrosis Autopsy 11 mos. Cysts, enlarged pseudolactating lobules and periductal fibrosis
188	3 months castrated	1 mg. Di-methyl stilbestrol	Biopsy 10 mos. Periductal fibrosis cystadenoma Autopsy 15 mos. Multiple papillomas, small fibro-adenoma, small cancer
186	3 months castrated	1 mg. Di-methyl stilbestrol	Autopsy 7 mos. Multiple cysts of various sizes

EXPERIMENTAL PRODUCTION OF INTRACYSTIC PAPILLOMA

If fibro-adenomas are looked upon as fibrous neoplasms and their epithelial elements as anatomic inclusions only, then benign epithelial tumors of the breast are relatively rare.

Foci of epithelial proliferation are more common. Such foci are frequently seen in the ducts and terminal tubules in cases of adenosis. Here the branches of several ducts may be plugged with epithelium giving rise to so-called duct adenoma and small intracystic papillomas may be found in the dilated ends of the tubules replacing normal acinar structures—so-called cystadenoma. Epithelial proliferations may also form small papillary tags within the lumen of the larger ducts in cases of bleeding nipple. Adenoid proliferations may also

be found in the epithelial structures inclosed within fibro-adenomas and intracanalicular myxomas.

It is difficult to regard these foci of epithelial proliferation as true neoplasms since they rarely give rise to solid tumors of large size and they are prone to regress when the pathologic stimulus is removed. They may, however, become the starting points for benign-tumor formation. This is particularly true of the cystadenomas in the ter-

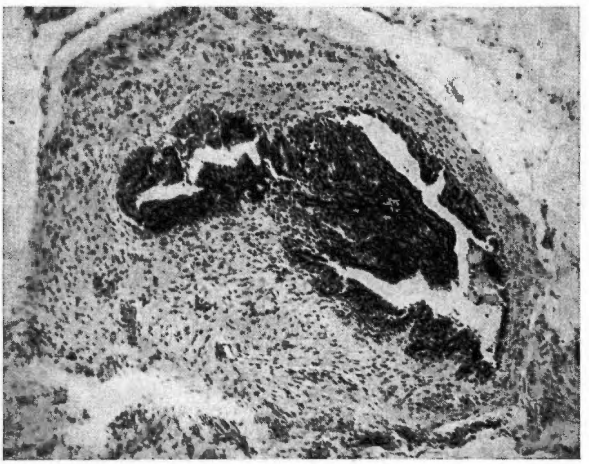


FIG. 555. Intraductal papilloma experimentally produced in the rat. The epithelial tufts of the papilloma are within the lumen of one of the large ducts just beneath the nipple. This animal received 0.5 mg. stilbestrol di-methyl ether daily for 5 months.

minal tubules and also of the papillary infoldings in the larger ducts. Under such conditions, intracystic papillomas of microscopic size are formed and these may show progressive growth. The solid duct adenoma of adenosis may grow progressively, giving rise to the comedo-adenomas but since these tumors eventually metastasize, such growths must be classified as slowly growing comedo carcinomas rather than benign tumors.

It seems proper, to regard as true, benign epithelial neoplasms only those intracystic papillomas arising in dilated terminal tubules or in the mouths of larger ducts and which attain appreciable size.

Intense, Prolonged Estrogenic Stimulation

In the rat, papillomas may be produced in the larger ducts near the nipple or in the regions of the terminal tubules following intense and prolonged estrogenic stimulation (Figs. 555, 556). With one exception the papillomas were not observed in animals treated for less than four and one-half months. The tumors that grew to macroscopic size usually developed in the terminal tubules or at the

bifurcation of the larger ducts near the nipple. The hyperplastic cystadenomas forming within dilated acini rarely gave rise to large

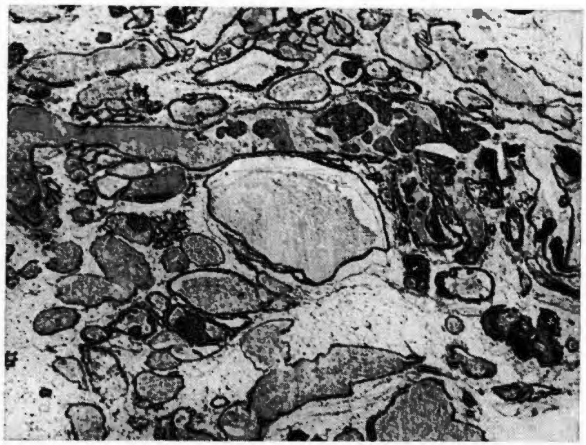


FIG. 556. Intraductal papilloma experimentally produced in the rat. The tumors are forming in the dilated terminal tubules. This animal received 100 gamma of estradiol benzoate daily for 5 months.

papillomas, although in the experiments under discussion they frequently were followed by malignant epithelial proliferation.

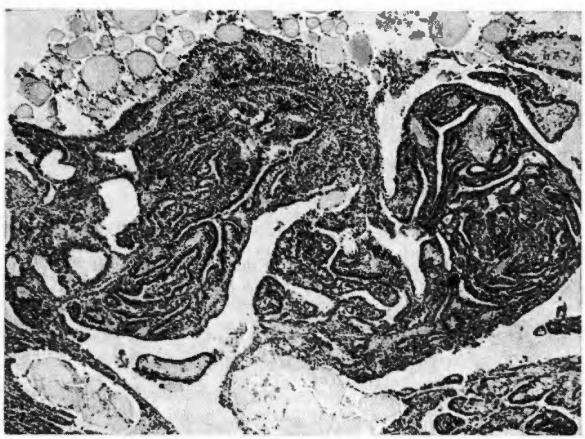


FIG. 557. Benign intracystic papilloma of the rat's breast. The tumor is arising from the wall of a cyst filled with inspissated secretion. This animal was treated with multiple estrone pellets.

The largest papillomas (Fig. 557) were observed following the implantation of estrogen pellets (Table CI). In some of the animals so treated there had been previous estrogenic stimulation since birth

in the form of injections of 25 gamma estrone in oil twice daily for a period of 70 days. The papillary tumors occurred in the same phase of the experiment in which carcinomas were produced. Apparently, the conditions which favor the origin of benign intracystic papillomas are closely allied to those favoring the development of mammary carcinoma and either one or the other or both may occur.

Intracystic papillomas were produced in animals receiving large daily doses of estrogens injected in oil (Table CII). These tumors occurred in four and one-half to 10 months following the administration of 200 gamma estrone daily or 100 gamma estradiol benzoate.

TABLE CI
EXPERIMENTAL PAPILLOMAS

RAT	SEX	AGE DAYS	PELLETS IMPLANTED: TOTAL DOSE	ESTROGEN	MONTHS SINCE ONSET	FINDINGS
1314	F	41	5 mg.[1]	Estrone	8½	Papilloma 2 cm. Calcified lobules and cysts.
1320	F	44	5 mg.[1]	Estrone	8	Papilloma 3 cm. Papillary cancer Lobules.
1652	F castrated	291	17.5 mg.	Estrone	5	Papilloma in lactating fibro-adenoma. Lobular cancer. Papillary cancer. Early fibro-adenoma.
1802	F castrated	186	35 mg.	Estrone	6	Papilloma in giant lobule, cancer.
1673	F	599	12.5 mg.	Estrone	2	Papilloma in cystadenoma. Lobule formation.
1875	F castrated	25	12 mg.	Stilbestrol	11½	Papilloma in cystadenoma

[1] 25 micrograms of estrone injected twice daily for preceding 70 days.

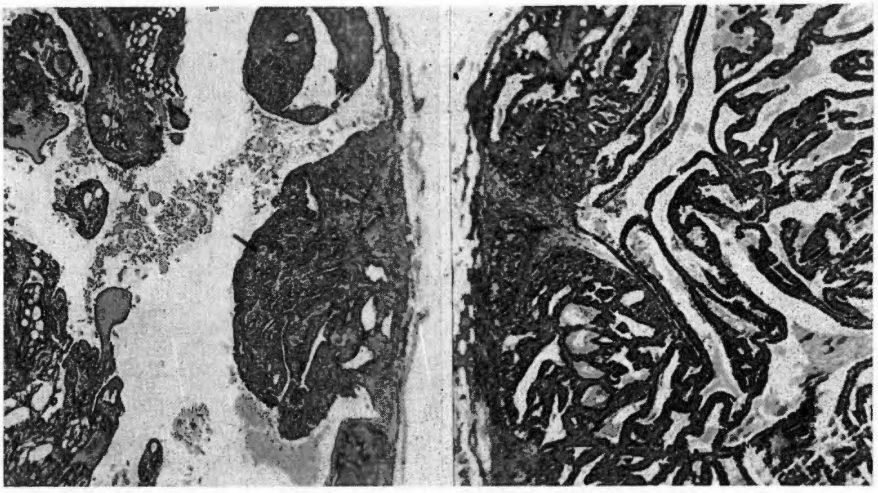
TABLE CII
EXPERIMENTAL PAPILLOMAS

RAT	SEX	AGE DAYS	TREATMENT, INJECTIONS: GAMMA DAILY	ESTROGEN	MONTHS SINCE ONSET	FINDINGS
2638	M	21	200	Estrone	10	Papilloma, papillary cancer
2666	M	45	200	Estrone	7½	Small papillary cystadenoma
2700	M	46	200	Estrone	7	Papillary cystadenoma
2705	M	46	200	Estrone	7	Papillary cystadenoma
2855	F	40	200	Estrone	7	Small papilloma near nipple
2218	F	89	100	Estradiol Benzoate	8½	Intraductal papilloma, papillary cancer
2709	F	44	100	Estradiol Benzoate	7½	Papillary cystadenoma, papillary cancer
3555	M	200	100	Estradiol Benzoate	4½	Papilloma
2680	F	77	100	Estradiol Benzoate	4½	Papilloma, papillary cancer
2590	F castrated	26	500	Stilbestrol Di-methyl Ether	6½	Small papilloma near nipple

One of the animals received 500 gamma of stilbestrol di-methyl ether daily.

The majority of these benign epithelial tumors are formed in the region of the terminal tubules or at the bifurcation of the ducts leading away from the nipple. Their origin here appears to be favored by the persistence of reserve deposits of germinal epithelium which is capable of forming additional tubular or lobular structures.

FIG. 558 FIG. 559



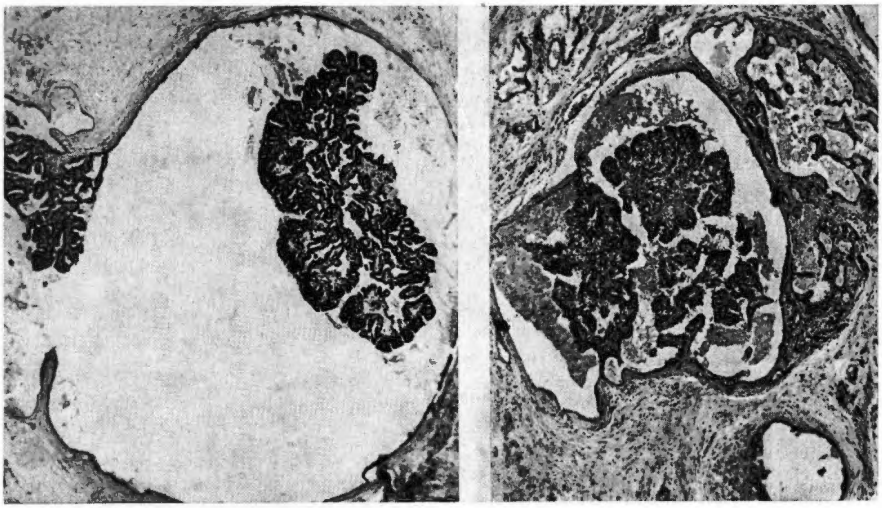
Microscopic Structure of Large Papillomas Produced in the Rat's Breast Following the Implantation of Multiple Estrone Pellets.
FIG. 558. Shows a tumor which is multicentric in origin.
FIG. 559. A similar tumor arising from a single stalk.

Of the hundreds of albino rats in our colony subjected to prolonged and intense endocrine stimulation, there were only 16 animals in which well-formed papillomas were found. Among these, the number of animals in which well-developed lobules preceded the formation of papillary tumors was relatively high. Thus in animals receiving large amounts of estrogen by injections and developing papillomas, 50 per cent were noncastrated males. Lobule formation is a normal occurrence in the intact male rat after the second month of life. In the animals in which estrogen pellets were implanted the formation of large, irregular lobules was a frequent feature in the earlier phases of mammary response. The importance of previous lobule formation for the development of benign papillomas is also suggested in experiments in which rats were given prolonged injections of testosterone propionate or in which pellets of this hormone

were repeatedly implanted. In these animals, lobule formation is stimulated by the male sex hormone. After a period of months these lobules undergo atrophy and are replaced by dilated terminal tubules and acinar structures in which small cystadenomas may be found. (Figs. 558, 559.)

Although preceding lobule formation may have some influence on the subsequent development of intracystic papillomas, these benign tumors do not make their appearances until atrophy and degenera-

FIG. 560 FIG. 561



Experimentally Produced Papillomas in the Rabbit's Breast.
FIG. 560. Papilloma within a duct.
FIG. 561. Intracystic papilloma arising in the remains of a dilated acinus.

tion of the lobules are well advanced. Here again, the onset of the neoplastic growth is preceded by a stage of atrophy and degeneration which separates the neoplasm from the pre-existing state of diffuse hyperplasia. Figs. 560, 561.)

Another feature of the experimental production of benign papillomas which is also true for the production of fibro-adenomas, is the prolonged period of estrogenic stimulation required for their onset. In rabbits given injections of 0.5 mg. of stilbestrol di-methyl ether daily for a period of 20 months multiple fibro-adenomas and papillomas make their appearances simultaneously. (Fig. 553.) In these experiments the estrogen administered was of low potency but of prolonged action giving a constantly maintained stimulus over a period of many months. Even with intense estrogenic stimulation

such as daily doses of 100 to 200 gamma estrone or estradiol benzoate injected in oil, the time required for the appearance of the papillomas may exceed that required for the development of mammary carcinoma.

The author is indebted to the following for their generosity in making hormone preparations available for this study:

Ciba Pharmaceutical Products, Inc. for testosterone propionate (Perandren), progesterone (Lutocylin), and estradiol dipropionate (Di-Ovocylin).

Schering Corporation for estradiol benzoate (Progynon B), progesterone (Proluton), and lactogenic hormone (Prolactin).

Roche-Organon, Inc. for anterior pituitary hormone (Ambinon), and estrone (Menformon).

Wallace and Tiernan Products, Inc. for stilbestrol, stilbestrol di-methyl ether and stilbestrol monomethyl ether, Monomestrol.

34

The Experimental Production of Mammary Cancer with Estrogens[1]

The experimental production of mammary cancer by administration of estrogens (first accomplished in mice by Lacassagne in 1932) indicated that a substance normally produced in the body and possessing physiologic function could lead to cancer. This method has made it possible to reproduce, in laboratory animals (mice and rats), mammary cancers which apparently arise under circumstances similar to the natural conditions that bring about human cancer. It is important, therefore, to inquire into the mechanism by which cancer is thus produced and to compare it with the processes in human cancer.

EFFECT OF ESTROGENIC STIMULATION ON THE AGE OF THE MAMMARY GLAND

The chief effect of estrogen on the mammary gland is to accelerate the development of the duct tree and its supporting fibrous tissue. This is accompanied by ripening or enlargement in the mammary epithelium as well as in the cells of the stroma and by the addition of new elements through cell multiplication. If accelerated develop-

[1] The major portion of this chapter appeared in the Archives of Pathology, 33:334, 1942.

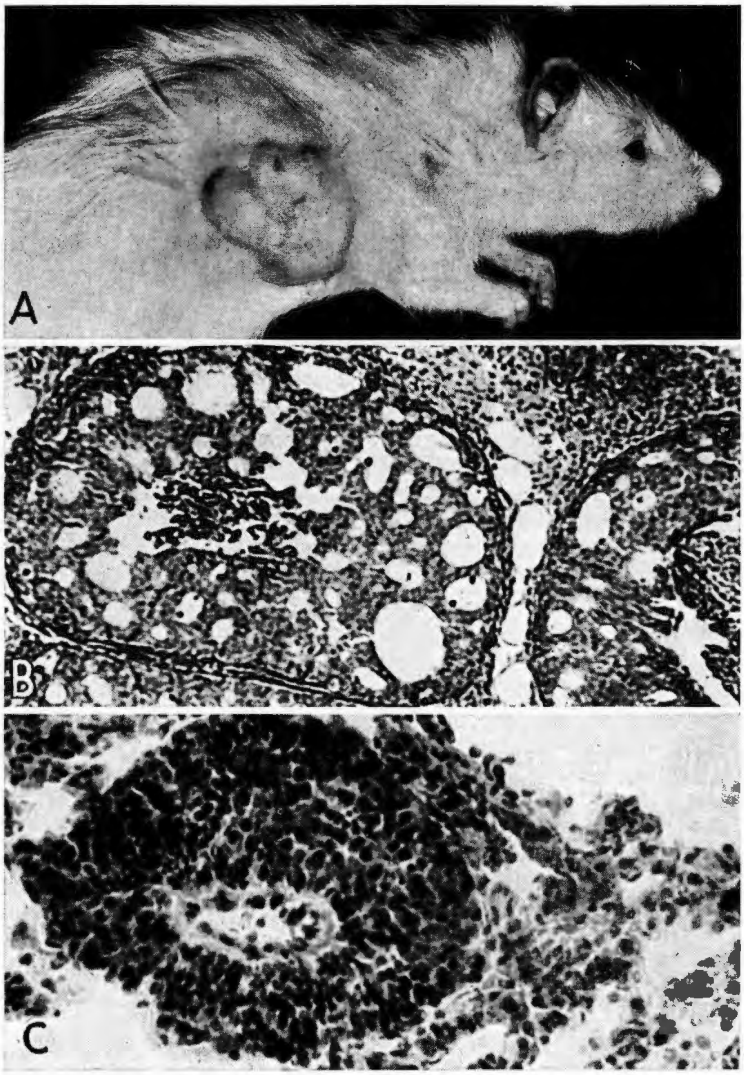


FIG. 562. Estrogenic mammary cancer: *A*, the appearance of the tumor; *B*, its microscopic structure; *C*, a metastasis to the lung.

ment and ripening are maintained by continuous and intense estrogenic stimulation, the regeneration of tissue which supplies adult cells may ultimately be exhausted. Under these conditions aging and degeneration occur. On further stimulation in such a senescent gland, both benign and malignant tumors form.

Apparently, susceptibility to cancer increases with the physiologic age of the breast rather than with the chronologic age of the animal. Repeated experiments have shown that the maximum size of the breast is attained sooner, by estrogenic stimulation, but cannot be made to exceed by any significant degree that of the normal adult. Increasing the amount or the duration of the stimulus beyond physiologic limits therefore can only accentuate maturity and aging in the mammary structures. This brings about pathologic changes which may terminate in cancer. These end stages of estrogenic stimulation occur more quickly if the estrogen is administered in extremely high doses instead of in moderately excessive amounts, or if it acts continuously (by dissolution of implanted pellets)[1] rather than intermittently (by injection of a solution). The essential feature in the estrogenic production of mammary cancer, therefore, is the acceleration or the prolongation of ripening and maturity in the mammary gland beyond physiologic limits. If this condition is satisfied, cancer appears in the breasts of rats which are otherwise immune to the disease, whether these animals are young or old ones, males or females, castrates or noncastrates. (Fig. 562.)

At the present writing, mammary cancers have occurred in 202 of 555 rats of an albino strain which were treated with estrogens. These animals have been maintained on a standard diet and inbred for a period of seven years, and under these conditions no spontaneous mammary cancer has been observed in a colony of more than 5,000 animals. The percentage of rats in which estrogenic mammary cancers develop varies, but when the animals survive the required time, the disease may be present in 100 per cent of the survivors under certain experimental conditions. The majority of the experiments here reported have been carried out to learn the time and the mode of onset of the cancers and only a few animals have been allowed to survive with macroscopic growths. Among these, only two animals showed multiple metastases to the lungs and lymph nodes.

INTENSITY AND DURATION OF ESTROGEN ACTION

A number of estrogenic compounds that vary in potency and in duration of effect may be used for the production of mammary can-

[1] This statement holds for estrogens if one compares in the same group estrogens without a prolonged effect.

cer. The potency of each of these compounds and the length of its action are indicated in Table CIII.

The minimum amount of estrogen necessary to produce a physiologic reaction (cornification of the vaginal smear) in 50 per cent or more of a group of castrated female rats is spoken of as a rat unit and varies from a fraction to several gamma according to the estrogen and the strain of rats used. If the estrogen has no prolonged action, the rat stays in estrus[1] for two to four days. With prolonged action, estrus may last weeks or months. In the normal rat, estrus usually lasts four to five days, and the amount of estrogen present varies from a fraction to several gamma. As little as 3 to 5 gamma of estrone administered daily by injection over prolonged periods will produce pathologic changes.

In woman estrus is roughly the time between two menstrual periods. From observations on castrate women, Shorr and Cohen estimated that from 3,000 to 5,000 gamma of estradiol benzoate a day is necessary to produce human estrus. In woman, therefore, estrus lasts four to five times as long as in the rat and requires 5,000 to 10,000 times as much hormone daily.

TABLE CIII

POTENCY AND PERIOD OF ACTION OF VARIOUS ESTROGENIC COMPOUNDS

COMPOUND	POTENCY IN MILLIONS OF RAT UNITS PER GM.		AUTHORS' ASSAYS	PROLONGED ACTION
	1	2		
Estradiol (alpha)	12	0.5	3.3	No
Estradiol (benzoate)	6	..	1.7	Yes
Estradiol (dipropionate)	5	..	2.5	Yes
Estrone (theelin)	1	0.3	1.0	No
Stilbestrol	3	0.6	3.3	No
Stilbestrol monomethyl ether	..	..	0.4	Yes
Stilbestrol dimethyl ether	..	..	0.04	Yes

[1] The figures in this column were obtained from the following sources: those for estradiol (alpha benzoate) and estrone from B. Whitman, O. Wintersteiner and E. Schwenk (Jour. Biol. Chem., 118:789, 1937); those for estradiol dipropionate from K. Miescher, C. Scholz and E. Tschopp (Biochem. Jour., 32:725, 1938); those for stilbestrol from E. C. Dodds, L. Golberg, W. Lawson and R. Robinson (Nature, London, 142:34, 1938).

[2] These figures are from C. W. Sondern and J. L. Sealey (Endocrinology, 27:670, 1940).

In considering the mechanism of mammary cancer, it is important to bear in mind the ratios between physiologic and patho-

[1] The term "estrus" refers to a group of anatomic and physiologic changes in the sexual organs. The uterus is enlarged and its lining thickened. The breasts also increase in size, and the lining of the mammary ducts is thickened. In the vagina, a similar thickening of the mucous membrane is accompanied by the shedding of ripened epithelial cells, and hence the appearance of cornified desquamated cells in the vaginal smear is taken as an index of estrus.

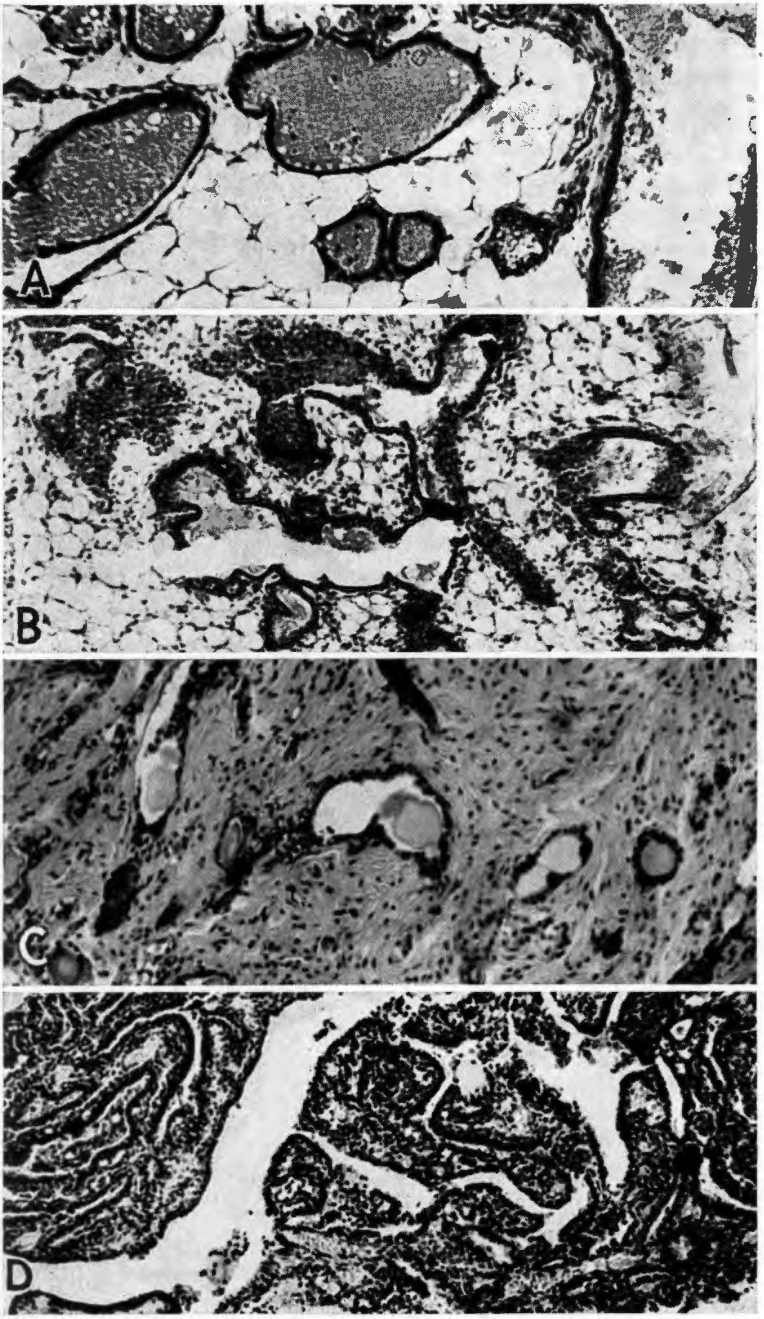


FIG. 563. Pathologic changes in the mammary gland preceding the development of estrogenic mammary cancer: *A*, large cysts occurring after daily injections of estrone in oil; *B*, adenosis and epithelial hyperplasia following moderate daily doses over long periods; *C*, fibro-adenoma following implantation of pellets; *D*, benign papilloma following implantation of pellets.

logic doses of estrogen and the ratio between the dosage for rats and that for man. As will be shown subsequently, mammary cancer results in rats within a period of 120 days (which is approximately 30 times the length of normal estrus) when the amount of estradiol benzoate administered daily is approximately 10 to 15 times the physiologic dose. If the same factors are applied to the human breast, the length of time would approximate 90 weeks and the daily dose of the hormone would approximate 30 to 75 mg. This assumption has only theoretic interest since there is at present no way to evaluate the matter of species differences. Thus, in experiments carried out by us on rabbits and monkeys, cancers have failed to appear when corresponding amounts and periods of estrogenic stimulation were employed.[1] Moreover, the calculated dose for man is based on the assumption that the subject is young or in the period of sexual maturity and that all of the organs are in their normal state. There are conditions (as will be pointed out subsequently) in which the cancer-producing threshold is greatly lowered.

There are two proofs that estrogens exert physiologic rather than direct chemical action in producing mammary cancer. One is that the cancer does not occur at the site of injection but appears, instead, in the organ (the breast) which the hormone influences physiologically. The second is that the periods of time required to produce cancer with estrogens of varying chemical composition are proportional to the physiologic potencies and independent of the chemical formulas (Table CIV B and D). Therefore the estrogens cannot be considered chemically as cancerogenic agents.

Cancer occurs in the rat's breast when the estrogenic stimulation is (1) abnormally intensified, (2) prolonged and continuous or (3) augmented by other influences, such as previous endocrine disturbances. Intense interrupted stimulation is not as efficient as continuous estrogenic action obtained by the implantation of pellets or by the use of estrogens with prolonged action.

Relation of Intensity of Stimulation to Time of Appearance of Mammary Cancer

The total amount of estrogen necessary to produce cancer is the same regardless of the daily dose administered if animals of the same age are treated by injection of estrone in oil. Thus it can be shown that with daily injection of estrone in oil the time required

[1] Mammary cancer recently appeared in one rabbit after 20 months (615 days) of treatment with stilbestrol di-methyl ether (in the dosage of 0.5 mg. daily). Cancers have failed to develop to date in a group of six monkeys stimulated continuously for more than three years with estrone and estradiol compounds implanted as pellets or injected (the total dose of estrogen exceeding 3 Gm. per monkey).

to produce mammary cancer in the rat is inversely proportional to the dose but that the total amount remains fairly constant (30 to 40 mg. estrone). This was found true if daily doses of 50 to 200 gamma were injected. It is possible that with daily doses beyond 200 gamma estrone, increased excretion or destruction would occur and the time required for the appearance of the cancer would not be lessened.

Mammary cancer results when estrone in oil is injected subcutaneously in the backs of rats in daily doses of more than 0.025 mg. (25 gamma). The cancers affect males and females, castrates and noncastrates. The cancers appear in 500 to 600 days when 50 gamma is injected daily, within 350 to 400 days with 100 gamma and within 150 to 200 days with 200 gamma (Table CIV A, B and C).

The relation of the intensity of stimulation to the time of appearance of mammary cancer may be demonstrated in another way by comparing the periods of time required to produce cancers with estrogens of varying potency. The time required varies in accordance with the physiologic strength of the compounds. The most potent estrogen will produce cancer in the briefest time. See footnote, page 749. (Table CIV D.)

Effect of Interrupted Doses (Daily Injections of Estrone in Oil)

Because of the rapid ripening of the lobular buds when large amounts of estrogen are injected daily, immense dilated acinar structures or cysts are formed. These cysts appear within 40 days and are accompanied by secretory changes in the epithelium. The cysts are preceded by increase in the size and the number of the epithelial buds at the ends of the tubules. The cysts have no direct relation to the subsequent formation of cancer and are associated with rapid ripening and secretion in the epithelium of the terminal tubules (Fig. 563 A). When cysts form, the appearance of the cancer may be delayed, and a more prolonged estrogenic effect with continuous epithelial regeneration followed by degeneration and atrophy must occur before cancer appears. This corresponds with observations in the human breast which indicate that cystic disease occurring in women toward the menopause is not associated (except coincidentally) with mammary cancer. It is usually a self-limited disease and associated with a relatively brief period of estrogenic overstimulation at or near the menopause. (See Chap. 33, page 731.)

With intense interrupted estrogenic stimulation (daily injections of estrone in oil) in castrate female rats, lobule formation does not occur in the breast, and as a result the cancers formed are confined

TABLE CIV

INCIDENCE AND TIME OF OCCURRENCE OF MAMMARY CANCERS IN RATS RECEIVING VARYING DOSES OF ESTROGEN IN OIL

RAT	SEX	AGE	CASTRATED	DAYS TREATED	RESULTS
A. 50 Gamma Estrone Daily (3 Cancers at 550–598 Days)					
1	F	1 mo.	No	284	Cystic changes
2	M	1 mo.	Yes	550	Cancer
3	M	1 mo.	Yes	591	Cancer
4	M	1 mo.	Yes	598	Cancer
B. 100 Gamma Estrone Daily (4 Cancers at 359–408 Days)					
1	M	1 mo.	Yes	29	Cystic change
2	F	1 mo.	Yes	37	Cystic change
3	M	1 mo.	Yes	359	Cancer
4	F	1 mo.	Yes	378	Cancer
5	M	1 mo.	Yes	387	Cancer
6	M	1 mo.	Yes	408	Cancer
C. 200 Gamma Estrone Daily (8 Cancers at 137–281 Days and 1 Cancer at 334 Days)					
1	F	1 mo.	Yes	174	Cystic change
2	F	1 mo.	Yes	188	Cancer
3	F	1 mo.	Yes	150	Cancer
4	F	1 mo.	Yes	334	Cancer
5	M	1 mo.	No	300	Cystic change
6	M	1 mo.	No	300	Atrophy
7	M	1 mo.	No	281	Papillary cancer
8	M	1 mo.	No	300	Cystic change
9	M	1 mo.	No	194	Duct cancer
10	M	1 mo.	No	300	Cystic change
11	F	1 mo.	No	234	Atrophy
12	F	1 mo.	No	260	Cystic change
13	F	1 mo.	No	137	Duct cancer
14	F	1 mo.	No	197	Cystic change
15	F	1 mo.	No	224	Lobular and duct cancer
16	F	1 mo.	No	238	Duct cancer
17	F	1 mo.	No	224	Cystic change
D. 100 Gamma Stilbestrol Daily (8 Cancers at 104–222 Days. Compare with B)					
1	M	2 mos.	No	92	Cysts, fibrosis and atrophy
2	F	2 mos.	Yes	104[1]	Cancer
3	F	2 mos.	Yes	163	Sweat-gland adenoma
4	F	2 mos.	Yes	202	Cancer
5	M	2 mos.	No	222	Cancer
6	F	1½ mos.	No	130	Duct cancer; very early comedo cancer
7	F	1½ mos.	No	130	Small comedo duct cancer
8	F	1½ mos.	No	130	Duct cancer
9	F	1½ mos.	No	130	Very early comedo cancer
10	F	1½ mos.	No	130	Very early lobular cancer

[1] This rat received 200 gamma daily.

to the ducts and terminal tubules, and their pathologic variety is thus limited. Under these conditions comedo cancer is the predominant pathologic form (Fig. 564 A).

Effect of Continuous Absorption (Implantation of Pellets)

When an estrogen is injected in oil, absorption is rapid for the first several hours, but soon thereafter the concentration in the tissues diminishes. Under these conditions there are daily variations in the estrogenic level. The agent is more effective if the concentration is maintained by more gradual and constant absorption, as from pellets[1] implanted beneath the skin of the back.

Mammary cancer in the rat occurs with smaller amounts of estrogen when pellets of the agent are implanted (Table CV, CVI). As little as 9 to 10 mg. of estrone in the form of two to three pellets given individually at intervals will produce cancer in 250 to 300 days. Although mammary cancers are produced with less estrogen when pellets are used than when injections are given, not all the animals show the same rate of development of cancer, and cancer does not appear in all of them. In young animals benign tumors (fibro-adenoma or papilloma) may first appear (Fig. 563 C, D). Later, cancer may occur in the benign fibro-adenoma, after the latter has undergone involutional changes. When estrone pellets are used in castrated male rats, most of them die within two to three months from urinary obstruction caused by epidermal thickening in the urethra.

The formation of fibro-adenoma in response to estrone from pellets is due to the selective action of moderate, continuous and prolonged estrogenic stimulation on the connective tissue. The fibrous stroma of the breast is apparently more susceptible to such moderate and prolonged stimulation than to the short intense stimulation of high doses. The fibrosis occurring in the mammary gland, therefore, serves as an index of the duration and the intensity of the estrogenic stimulation. When it is most marked, the stimulation has been moderate, continuous and of long duration.

If the ovaries are present when pellets are implanted, the slow continuous absorption of the estrogen results in more prolonged and increased luteinization of the ovaries and in mammary lobule formation approaching that seen in the breast in pregnancy. Even in the absence of the ovaries estrone from the pellets stimulates moderate, irregular lobule formation. The lobulation is significant, since it influences the pathologic form of the mammary cancer.

[1] These pellets are small plugs of crystalline estrogen, weighing between 2.5 and 3.0 mg. They are made by tightly compacting the crystals in drilled holes in a steel plate. The compactness of the pellet is such that absorption takes place only from the surface, slowly and continuously.

TABLE CV

MAMMARY CANCERS PRODUCED IN RATS BY IMPLANTATION OF ESTRONE PELLETS WEIGHING 2.5 MG. EACH

RATS	SEX	TOTAL DOSE, MG.	DAY OF LIFE ON WHICH PELLETS WERE IMPLANTED	TUMORS PRODUCED	DAYS REQUIRED TO PRODUCE CANCER
7	F	5.5[1]	2d 28th 153d	Cancer[2] in 4; benign fibro-adenoma only in 2 (135 and 190 days)	255 to 350 days[2]
5	M	5.5	2d 28th 153d	Cancers in 2; fibro-adenoma in 0	172 to 300 days

[1] Since the pellets were not completely absorbed, the dose was less than the total weight of the pellets (7.5 mg.) These rats were not castrated

[2] One animal with four small pellets implanted on the twenty-third day of life had microscopic cancer on the forty-fourth day of life; other microscopic cancers appeared from 172 to 350 days after the starting of treatment. In two of the four females in which cancer developed, benign fibro-adenoma of the breast developed preceding cancer. In two additional females, benign fibro-adenoma only developed.

Under these conditions infiltrating lobular cancers may form (Fig. 564 B).

TABLE CVI

EARLY CANCER WITH MULTIPLE PELLETS—TOTAL DOSE 12.5 MG.

RAT	AGE	SEX	CASTRATED	ESTROGEN	DAYS REQUIRED FOR CANCER
1	21 days	F	Yes	Estrone	21
2	26 days	F	Yes	Estrone	25
3	21 days	F	Yes	Estrone	30
4	21 mos.	F	No	Estrone	47
5	21 mos.	F	No	Estrone	60
6	21 mos.	F	No	Estradiol	47
7	60 days	F	Yes	Estrone	60
8	15 mos.	F	No	Stilbestrol	35
9	9 mos.	F	Yes	Stilbestrol	90

The more gradual and continuous absorption of an estrogen from implanted pellets results in a more widespread and extensive epithelial response. Epithelial proliferation may predominate over epithelial ripening and secretion for a period of months. Adenosis with formation of duct adenoma and intraductal papilloma occurs in addition to fibro-adenoma and precedes or replaces the formation of large cysts (Fig. 563 C, D). Again the epithelial changes are not in themselves precancerous. This is proved by their gradual involution and disappearance if the pellets are removed (or by the absence of cancer if the initial low concentration of estrogen is maintained by

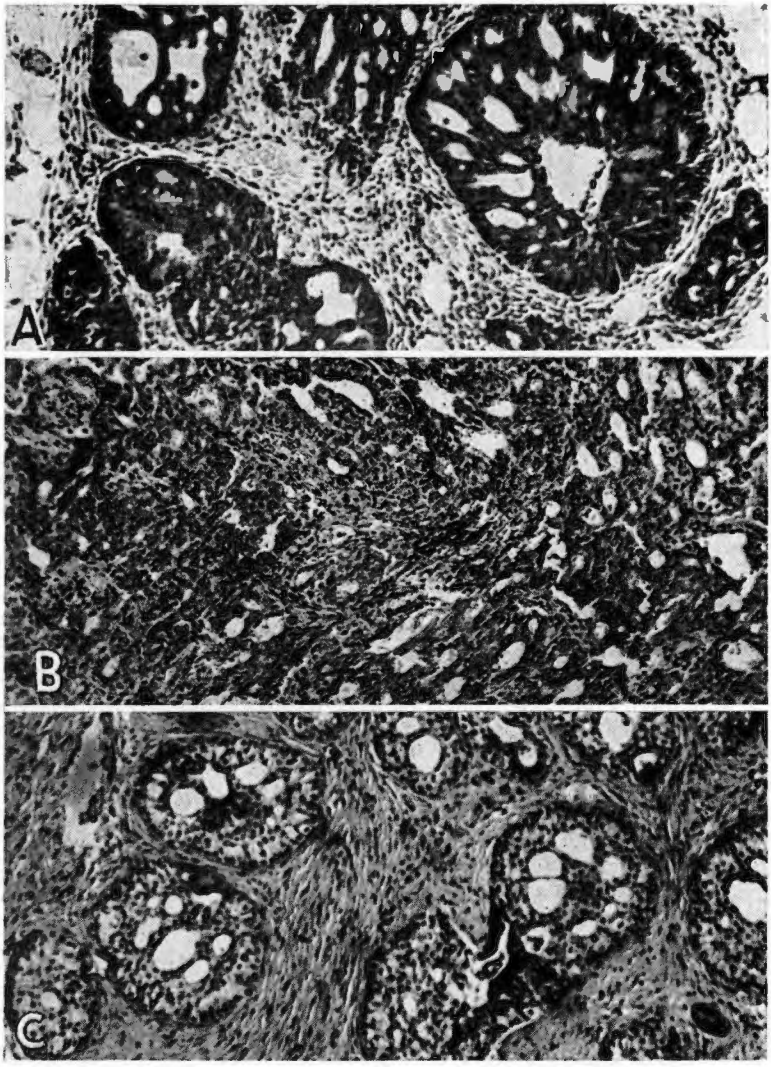


FIG. 564. Varying forms of mammary carcinoma with different methods of dosage: *A*, comedo cancer obtained with interrupted daily doses; *B*, lobular cancer obtained by implantation of pellets; *C*, duct cancer obtained by implantation of pellets.

daily injection of physiologic amounts of the agent throughout the life of the animal in the absence of pellets). Once these epithelial changes have been produced, however, the mammary gland is more susceptible to cancer PROVIDED A STEADILY INCREASING CONCENTRATION OF ESTROGEN IS MAINTAINED by allowing the pellets to remain and by implanting additional ones.

The modified action of estrogen administered by implantation of pellets instead of by injection is also apparent when stilbestrol or estradiol is administered. With daily injections of 100 gamma of stilbestrol, 18 mg. of the substance is necessary for the production of mammary cancer, whereas only 10 mg. is required if pellets are used. With daily injections of 100 gamma estradiol in oil, 25 mg. is required to produce cancer; with implantation of pellets 8 mg. will suffice. The more continuous estrogenic action observed with stilbestrol and estradiol pellets is associated with the formation of fibroadenoma, adenosis and other changes similar to those described in the animals receiving estrone pellets. In general, the total amount of the estrogen necessary to produce cancer may be decreased to one-half or to one-third if the agent is implanted in the form of pellets rather than injected in oil (Table CVII).

TABLE CVII

COMPARISON OF DOSES AND PERIODS OF TREATMENT REQUIRED WITH DIFFERENT ESTROGENIC COMPOUNDS

COMPOUND	DOSE, MICROGRAMS	TOTAL AMOUNT, MG.	DAYS REQUIRED TO PRODUCE CANCER
Estradiol (injected)	100	25	290
Estradiol (implanted)	3 successive pellets	8	310
Estradiol dipropionate	5	0.6	120
Estradiol benzoate	5	0.6	120
Stilbestrol (injected)	100	15.0	150
Stilbestrol (implanted)	5 successive pellets	10.1	105
Stilbestrol monomethyl ether	50	9.5	212
Stilbestrol di-methyl ether[1]	500	116.5	233

[1] The cancer-producing efficiency of estrogen derivatives with a prolonged action is not apparent when the estrogenic potency of the derivative is far below that of the parent compound (Table I).

Instead of estrone, estradiol or stilbestrol pellets, estrogenic compounds with a prolonged action may be used. The tissue changes are similar to those produced by the implantation of pellets.

Estradiol compounds in which a chemical radical is introduced to prolong estrogenic action are more efficient in producing cancer than

the original compound even though the estrogenic potency has been lessened somewhat by the addition of the radical. This is also true of the ethers of stilbestrol which have a prolonged action.

FIG. 565A. FIG. 565B.

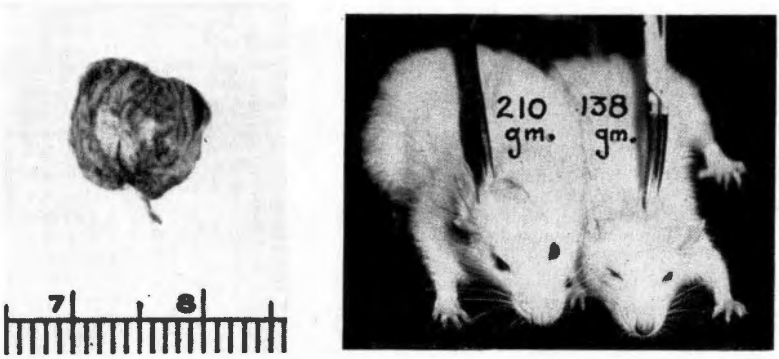


FIG. 565A. Large adenoma of the pituitary gland from a rat developing estrogenic mammary cancer. B. Inhibition of growth by suppression of pituitary function in a rat developing estrogenic mammary cancer. The treated rat weighs 138 grams; its litter mate 210 grams.

Table CVII gives a comparison of the amount of the agent and the time required for production of cancer with derivatives of estradiol injected in oil as compared with the original compound administered by injection or in the form of pellets.

Spontaneous mammary cancer is rare in the rat and is difficult to maintain by transplantation. Estrogenic mammary cancer in the rat, therefore, provides valuable experimental material for

TABLE CVIII

PERCENTAGE OF RATS IN WHICH MAMMARY CANCER DEVELOPED WHEN VARYING AMOUNTS OF ESTRADIOL BENZOATE IN OIL WERE INJECTED DAILY

RATS[1]	AGE AT ONSET OF TREATMENT	DOSE, MICROGRAMS	DURATION OF TREATMENT	CANCERS	PERCENTAGE
5	2 mos.	5	120 days	5	100
5	2 mos.	10	120 days	5	100
12	7 mos.	50	120 days	6	50
12	1½ mos.	100	120 days	9	75
8	6 mos.	100	120 days	5	62
22	7–9 mos.	100	120 days	11[2]	50
6	1½ mos.	200	120 days	4	67
—				—	
70				45	

[1] The numbers include both males and females; none of the rats were castrated.
[2] The majority of these cancers occurred in eighty to one hundred days.

the study of the disease. These cancers can be produced at an early age and relatively quickly if the proper estrogen and mode of administration are used. In our experience, cancers are produced most quickly and in a high percentage of the animals if 5 gamma estradiol benzoate is injected daily except Sundays in rats from 1 to 3 months of age. With this dose, the tumors appear in microscopic form in 120 days, and palpable nodules appear shortly thereafter in 160 to 180 days. When more than 5 gamma estradiol benzoate is given daily, the cancers appear at the same rate, and the percentage of rats in which cancer develops is not increased but tends to decrease.[1]

EFFECT OF PROLONGED REGENERATION

Since the susceptibility to cancer is influenced by the capacity for regeneration in the tissue, the pre-existing physiologic state of the gland is important. If epithelial regeneration below the cancer-producing level has been previously stimulated in the mammary gland, it should be possible at some later date to produce cancer more readily.

In a group of rats 1 month old, intense estrogenic stimulation (200 gamma estrone) was given for 90 days. Biopsy showed that no cancers had developed. These rats were allowed to live one and a half years without further treatment, and at the end of this time biopsy showed advanced mammary atrophy. Then, short intense estrogenic stimulation was given. Cancer appeared quickly in from two to three months. In another group of rats physiologic doses of estrone (2.5 to 5 gamma) were given daily for a period of almost two years, and no cancers appeared. In these animals at the end of this time cancer developed within two months after the injection of large daily doses of estrone.[2] Thus, the effects of a previously intense or prolonged period of estrogenic stimulation may persist as a latent cancerogenic influence in the breast (Tables CIX and CX).

Because of the latent predisposition to cancer in the breasts of these animals, the appearance of these glands under the microscope before the final period of estrogenic stimulation is important. In the group that had intense stimulation for 90 days in early life, the glands were markedly atrophic and nearly replaced by fat. Their structure resembled the so-called "senile, fatty breast" so

1 With the daily injection of 100 gamma of stilbestrol in oil, cancer appeared in approximately 100 per cent of the rats in 140 to 150 days.

2 This experiment was repeated recently in a third group of 12 rats which received 5 gamma of estrone daily for one year. At the end of this time, cancer had not developed. The animals then received 5 gamma of estradiol benzoate daily for 45 days which was sufficient to produce mammary cancer.

often described in pathologic reports on human breasts removed for cancer (see Chap. 19, Fig. 367).

In the group of rats which had been castrated and which received daily injections of estrone in doses within physiologic limits (2.5 to 5 gamma), the mammary glands were markedly fibrosed and the terminal tubules showed irregular epithelial proliferation resembling adenosis or Schimmelbusch's disease in the human breast (Fig. 563 B). It is significant that women with adenosis, when observed at intervals through a period of years (and past the meno-

TABLE CIX

CANCER PRODUCED IN CASTRATED RATS BY ADMINISTRATION OF INITIAL MASSIVE DOSES OF ESTRONE AT THE AGE OF 1 MONTH FOLLOWED BY AN INTERVAL OF NO TREATMENT, THEN BY FURTHER ADMINISTRATION OF MASSIVE DOSES

SEX OF RAT USED	INITIAL DOSE		INTERVAL WITHOUT TREATMENT, DAYS	FINAL DOSE		MICROSCOPIC PICTURE	
	AMOUNT, GAMMA	DURATION, DAYS		AMOUNT, GAMMA	DURATION, DAYS	DAYS AFTER INITIAL DOSE	DAYS AFTER FINAL DOSE
F	200	90	563	2 pellets into breast	89	338, fibrosis 522, infected nipple 620, atrophy 652, atrophy	23, hyperplasia 89, cancer
M	200	90	563	2 pellets into breast	54	144, fibrosis 565, fibrosis, irregular lobules 652, atrophy	23, hyperplasia 54, cancer
M	200	90	563	2 pellets into breast		565, fibrosis 652, atrophy	23, hyperplasia 54, cancer
F	200	90	754	None, control	..	216, fibrosis 620, fibrosis 675, atrophy 741, senile atrophy	90, no change
M	200	90	...	None, control	..	620, atrophy 675, atrophy	90, no change

pause), show a greater tendency toward mammary cancer than those with normal breasts in the same age groups (see Chap. 12, p. 276)

It is in these last two experiments, in which pre-existing changes in the breast (resulting from previous estrogenic stimulation) combine with the effects of a final period of intense estrogenic action to produce cancer, that conditions found in the human breast with cancer are most closely approximated. These experiments suggest that human mammary cancer may result from one or a combination of the following factors:

1. Abnormally intense estrogenic stimulation during the adolescent period of mammary development or during a previous pregnancy. (Some of these patients will recall varying degrees of virginal or gravid hypertrophy.)

2. Ovarian dysfunction in cyclic women resulting in relative hyperestrogenism over a period of years prior to the menopause. (Most of these patients have the characteristic changes of adenosis or Schimmelbusch's disease.)

TABLE CX

CANCER PRODUCED IN CASTRATED RATS BY ADMINISTRATION OF LARGE DOSES OF ESTRONE FOLLOWING PROLONGED ADMINISTRATION OF PHYSIOLOGIC DOSES BEGUN AT THE AGE OF 1 MONTH

SEX OF RAT USED	PHYSIOLOGIC DOSE		MASSIVE DOSE		MICROSCOPIC PICTURE	
	AMOUNT, GAMMA	DURATION, DAYS	AMOUNT, GAMMA	DURATION, DAYS	594 DAYS AFTER PHYSIOLOGIC DOSE	DAYS AFTER MASSIVE DOSE
M	2.5	594	200	98	Irregular lobules and moderate fibrosis	10, negative for cancer
M	2.5	594	200	98	Cystic dilatation, some adenomatous lobules	23, fibro-adenoma 41, precancerous changes 98, comedo cancer
F	5.0	594	200 Pellet, 3 mg. 200	11 13 74 — 98	Cysts and lactating adenoma	11, atrophy 23, comedo cancer 41, duct cancer 68, gross cancer 98, large cancer and fibro-adenoma
F	5.0	594	200 Pellet, 3 mg. 200	11 13 74 — 98	Fibrosis and fibro-adenoma	11, fibro-adenoma 41, comedo cancer 98, gross cancer

3. Intense or continuous estrogenic stimulation occurring at the time of menopause (superimposed on the factors enumerated under 1 and 2).

EFFECT OF AGE

According to vital statistics, the incidence of mammary cancer increases steadily with the age of the population (Table XLVI, p. 396). The atrophy and the degenerative changes found in the senile breast may therefore be etiologic factors in mammary cancer. With respect to estrogenic mammary cancer in the rat, histologic studies

indicate that premature ripening and accelerated regeneration which terminate in degenerative changes may be precursors of cancer. In line with this interpretation a comparison was made of the periods required for the appearance of cancer in young and old rats.

It was found that the time required for the appearance of cancer was inversely proportional to the age of the animal in a series in which estrone pellets were implanted, but there were a certain number of exceptions in which cancers appeared early regardless of the age (Table CXI). With other methods of estrogenic stimula-

TABLE CXI

TIME REQUIRED TO PRODUCE MAMMARY CANCER WITH MULTIPLE ESTRONE PELLETS IN RATS OF VARYING AGES

RATS	AGE	SEX	NUMBER OF PELLETS ADMINISTERED	CANCERS	TIME REQUIRED, DAYS	AVERAGE NUMBER OF DAYS
30	1 wk.	F	One at a time	17	105–532	300
10	1 mo.	Both[1]	Multiple	4 2	175–385 21–25	293
10	2 mo.	F	Multiple	5 2	175–317 26	248
10	4 mo.	Both	Multiple	6 1	101–399 35	248
6	7 mo.	Both	Multiple	3 1	165–255 31	205
4	9 mo.	F	Multiple	2	180–210	195
8	20 mo.	F	Multiple	4 2	64–109 27–48	90

[1] The group was made up of males and females in equal numbers. Cancer developed in both sexes with equal frequency

tion, no significant difference between young and mature rats was found but no old rats 18 months or more of age were included. Thus, as shown in Table CXII, the majority of the mammary cancers were observed within 120 days regardless of whether the injections (100 gamma estradiol benzoate) were begun at the age of 1½, 6 or 11 months. A certain number of early cancers occurred in all of the experimental animals in which continuous absorption of the estrogen took place, particularly if multiple pellets were inserted. These early cancers developed within 21 to 90 days after treatment and were dependent on the method of dosage and were independent of the age of the animals (Table CVI). In a group of 15 old rats (aged 18 to 20 months) injections of 166 gamma of stil-

TABLE CXII

RESULTS WITH ADMINISTRATION OF 100 GAMMA OF ESTRADIOL BENZOATE

RATS USED	AGE OF RATS WHEN TREATMENT STARTED	RESULTS OF BIOPSY		CANCERS AT AUTOPSY AFTER 120 DAYS OF TREATMENT
		AFTER 78 DAYS OF TREATMENT	AFTER 105 DAYS OF TREATMENT	
6 Females	1½ mo.	.....	1 cancer	5
6 Males	1½ mo.	2 cancers	.....	4
4 Females	6 mo.	.....	Fibro-adenoma only	2
4 Males	6 mo.	.....	Adenosis and cysts only	3
2 Females	11 mo.	.....	Adenosis only	1

TABLE CXIII

MAMMARY CANCER IN RATS RECEIVING TESTOSTERONE AND ESTRONE

RAT USED	DOSAGE OF TESTOSTERONE	DOSAGE OF ESTRONE	RESULT
Female castrate	0.5 mg., 1– 18 days	100 gamma, 30– 57 days 200 gamma, 57–162 days	Autopsy after 162 days: cancer and adenosis
Female castrate	0.5 mg., 73–108 days 0.5 mg., 143–180 days	200 gamma, 31– 72 days 200 gamma, 108–143 days	Autopsy after 192 days: comedo cancer
Male castrate	0.5 mg., 285–357 days	25 gamma, 25–285 days 50 gamma, 357–407 days Estrone pellet, 407th day, 493d day	Autopsy after 530 days: cancer, peritheliomatous type
Female castrate	0.115 mg., 80–249 days 1.25 mg., 249–266 days	10 gamma, 80–249 days	Comedo cancer after 266 days of treatment
Female castrate	0.25 mg., 79–249 days	20 gamma, 79–249 days	Duct cancer after 99 days of treatment
Male intact	1 pellet	5 pellets	Cancer after 383 days
Female intact	0.5 mg., 43–73 days[1]	5 pellets	Comedo and lobular cancer after 73 days

[1] Progesterone was substituted.

bestrol daily resulted in cancers in 50 to 60 days. In a group of young rats (aged 2 months) injections of 200 gamma of stilbestrol daily required 100 to 120 days or twice as long to produce the same result.

EFFECT OF OTHER SEX HORMONES

Injections of either progesterone or testosterone over a long period alone will cause increased lobular development in the mammary gland of the rat whether the animal is castrate or noncastrate, male or female. Testosterone is more efficacious than progesterone in producing lobular growth. No cancers were observed in the breasts when injections of progesterone alone were given over a period of several months or when testosterone was given over a period of more than a year; the only significant mammary change was a lobular formation with progesterone and cystic changes with testosterone. However, pathologic changes and cancer formation occurred if injections of testosterone or progesterone were given simultaneously with injections of esterone or when a similar combination of pellets was given (Table CXIII). Under such endocrine stimulation the formation of large mammary cysts was prevented. The degenerative changes preceding cancer appeared in the acinar structures and resembled postlactation involution. The earlier changes resulting from combined hormone stimulation were characterized by irregular epithelial proliferation resembling that seen in the human breast with adenosis. It is significant that the addition of testosterone or of progesterone did not prevent the occurrence of mammary cancer in these experiments. Instead, in some animals, lobular cancers were apparently the result of stimulation by these hormones, since the amount of estrogen used was insufficient by itself to produce the cancers. The gonad-stimulating and the lactogenic hormones of the anterior lobe of the pituitary gland which produce lobule formation and secretion in the mammary gland of intact animals will, however, inhibit but not prevent the growth of estrogenic mammary cancer. This is discussed subsequently.

CHANGES IN THE ENDOCRINE ORGANS IN THE EXPERIMENTAL PRODUCTION OF MAMMARY CANCER

Pathologic changes in the endocrine organs have been reported by most of the workers who have produced mammary cancer with high doses of estrogens in mice (Cramer and Horning). The pituitary gland enlarges because of an increase in the number of chromophobe cells in its anterior lobe. Such changes were found at

autopsy in the animals in the present experiments (Fig. 565 A). In addition these animals showed degenerative changes in the gonads

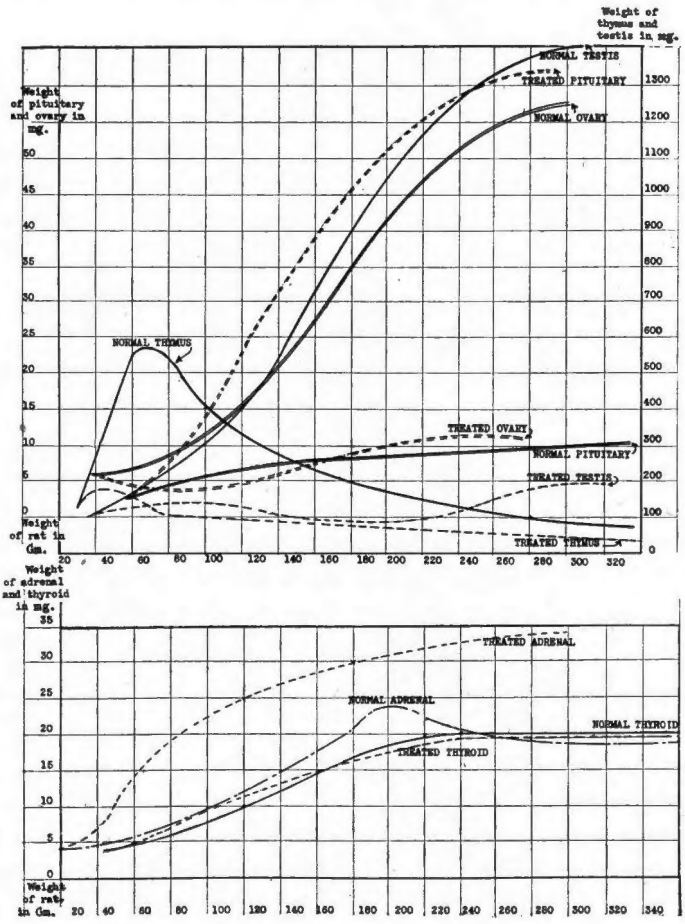


FIG. 566. Effect of developing estrogenic mammary cancer on the endocrine glands of rats: Upper graph, effect of prolonged administration of estrogens on the weights of the pituitary, the thymus and the gonads; lower graph, effect on the weights of the adrenal and the thyroid gland.

with formation of benign cysts or papillomatous cysts of the ovary (2 animals had granulosa-cell cancer, another metastasizing adenocarcinoma and another mesonephroma of the ovary). There was enlargement of the adrenal cortex, and occasionally there were degenerative changes in the medulla. Cystic degeneration occurs in the thymus gland with compensatory hypertrophy of the mediastinal lymph nodes, which may terminate in lymphosarcoma or leukemia (Fig. 567) (Table CXIV).

The most striking and consistent changes are in the pituitary gland and in the thymus. The increase in the number of chromophobe cells in the anterior lobe of the pituitary leads to hypertrophy of adenomatous proportions. Most of the experimental animals have glands five or more times normal size, and hemorrhage may occur in the adenomatous tissue (Fig. 566). The significance of these changes in the development of mammary cancer is not established. Hypophysectomy prevents the physiologic effects of estrogen on the mammary gland, and no cancers develop. The importance of the pituitary gland for the development and normal physiologic response of the breast has been stressed by other work-

TABLE CXIV

LYMPHOSARCOMA AND MYELOID LEUKEMIA IN RATS TREATED WITH ESTROGENS

RAT	AGE	SEX	TREATMENT	DAYS TREATED	RESULTS
1	1 mo.	F	2 hr. radium (30 mg.) over thymus; 100 mg. estradiol benzoate	225	Lymphosarcoma; cancer of breast
2	1½ mos.	F	2 hr. radium (30 mg.) over thymus; 100 mg. estradiol benzoate	229	Lymphosarcoma
3	1½ mos.	F	2 hr. radium (30 mg.) over thymus; 100 mg. estradiol benzoate	210	Lymphosarcoma; cancer of breast
4	3½ mos.	F	5 hr. radium (30 mg.) to mediastinum; 100 mg. estradiol benzoate	145	Lymphosarcoma; cancer of breast
5	3½ mos.	F	6 hr. radium (30 mg.) to mediastinum; 100 mg. estradiol benzoate	165	Lymphosarcoma; cancer of breast
6	4 mos.	F	6 hr. radium (30 mg.) to mediastinum; 100 mg. estradiol benzoate	150	Lymphosarcoma; cancer of breast
7	20 mos.	F	100 mg. estradiol benzoate daily	690	Lymphosarcoma of spleen; cancer in fibroadenoma of breast
8	1 wk.	M	3 successive estrone pellets	150	Myeloid leukemia
9	1 wk.	F	3 successive estrone pellets	420	Cancer of breast; lymphosarcoma of thymus
10	1 wk.	F	3 successive estrone pellets	420	Lymphosarcoma of thymus and spleen; cancer of breast
11	1 wk.	F	3 successive estrone pellets	480	Lymphosarcoma of spleen; cancer of breast
12	1 wk.	F	3 successive estrone pellets	360	Lymphosarcoma of thymus and mesenteric nodes; cancer of breast
13	1 wk.	M	3 successive estrone pellets	420	Lymphosarcoma of thymus; cancer of breast
14	1 mo.	M	5 estrone pellets	300	Lymphosarcoma of breast; beginning of cancer of breast
15	13 mos.	F	6 stilbestrol pellets—repeated in four months	165	Lymphosarcoma; cancer of breast
16	21 mos.	M	5 estrone pellets	60	Lymphosarcoma

ers (Gomez and Turner). It has also been noted in the present group of experiments. Estrogen response was prevented by hypophysectomy (Astwood, Geschickter, and Rausch). Hypophysectomy prevented the appearance of cancer even in those animals which lived the required length of time (six months or more) and in which the removal of the pituitary was apparently incomplete.[1]

Striking involutional changes occur in the thymus glands of rats maintained under continuous overstimulation with estrogen. The glands shrink in size, and the thymic tissue is replaced by cysts lined with transitional epithelium resembling that seen during the embryologic development of the thymus and the thyroid. This thymic involution is marked after prolonged administration of estrogen but also occurs when other sterol hormones, e. g., testosterone and progesterone, are administered. Whether or not it plays a role in the development of mammary cancer is being investigated further.

Changes in the adrenal glands are most frequently found in the reticular zone of the cortical tissue. The size of the cells and their lipid contents are increased. The result is a moderate increase in the size and the weight of these glands in the animals receiving estrogens and in those in which mammary cancer develops. The changes in the adrenal medulla are variable. Degeneration and calcification are occasionally seen, but most often the appearance of this tissue is normal.

No significant changes were found in the thyroid glands of the treated animals (Fig. 566), although marked changes with squamous-cell metaplasia have been reported in response to estrogens by other workers (Mark and Biskind).

The atrophic changes in the gonads are probably significant in the development of mammary cancer. There were no apparent differences in percentage of cancers or in time of their appearance between castrated and noncastrated rats whether these were males or females, but this may be explained by the atrophy of the gonads when estrogen is administered in large amounts.

The size of the ovaries may be reduced from a diameter of 5 to 8 mm. in the normal adult to a millimeter or less in those animals which have had prolonged treatment with estrogen. In the atrophic ovaries, there is a decrease in the number of follicles, and those persisting are decreased in size or undergo cystic degeneration. Luteal changes are absent. The interstitial cells are increased in number but are small and compact. Cysts with intracystic papil-

[1] The hypophysectomized animals used in the experiments were prepared by Dr. R. O. Greep of the Squibb Institute for Medical Research.

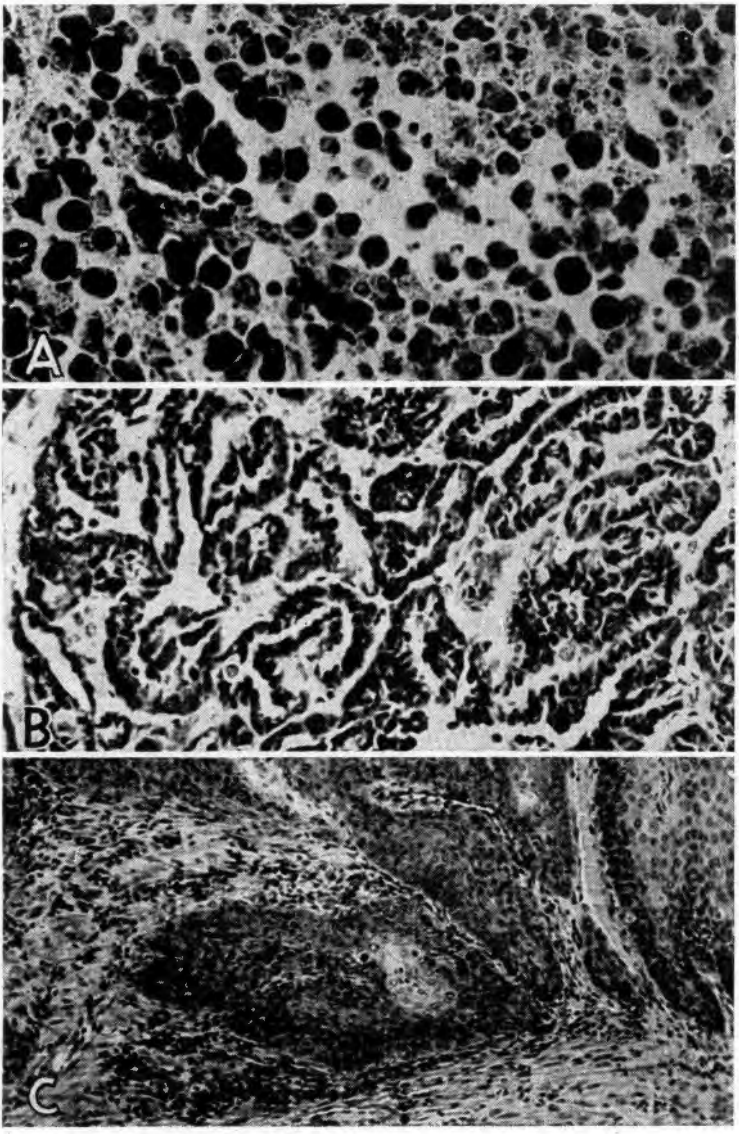


FIG. 567. Cancers associated with the development of estrogenic mammary cancer in the rat: *A*, lymphosarcoma; *B*, cancer of the ovary; *C*, cancer of the cervix.

lomas are occasionally observed. Malignant ovarian tumors occurred in four animals. One of these was a metastasizing adenocarcinoma; another was a small and malignant mesonephroma (Fig. 567). In the animal in which adenocarcinoma of the ovary developed, squamous-cell cancer of the cervix was also present, as well as mammary carcinoma. This was the only animal with a definitely malignant tumor of the cervix, although there was one other with early malignant change in the cervix.

After prolonged treatment with estrogens, the size of the testicle is reduced, the spermatic tubules are small and collapsed, and spermatogenesis is absent. Tumor formation in the testicle has not been observed.

The early effect of estrogenic stimulation of the prostate is an increase in the thickness of the lining epithelium in the prostatic urethra, which becomes increasingly keratinized. The fibromuscular stroma of the prostate is hypertrophied, and the glandular epithelium shows increase in the size of the cells and occasional dilation of acini. Later the fibromuscular stroma practically obliterates the glandular elements and the prostate shrinks in size. Cornification extends into the suburethral glands of the prostatic urethra, and there may be an irregular downgrowth of cells suggesting beginning transitional cell carcinoma in the prostatic urethra. Squamous-cell cancer at this site or adenocarcinoma of the prostate has not been observed.

The thickening of the prostatic urethra leads to urinary obstruction. The ureters become dilated and thickened, and the bladder is also markedly distended and increased in size and thickness.

In the female genital tract keratinization and thickening occur in the mucous membrane of the vagina and cervix. These changes extend into the mucous glands and into the uterus, replacing the normal endometrium. These changes are akin to those observed in the prostatic urethra. Carcinoma of the cervix arising at the base of the thickened cornified epithelium was found in two cases. Adenocarcinoma of the uterus was not observed.

Some workers (Cramer and Horning) have sought to show that estrogenic cancer of the mammary gland is the result of changes in the endocrine system as a whole, particularly in the pituitary body and the adrenal glands, rather than a direct effect on the breast. These authors thought that they could inhibit mammary cancer by injecting a pituitary extract containing the thyrotropic factor. These results could not be confirmed by Asdell and Seidenstein or by Lacassagne. While we have been able to demonstrate that the presence of pituitary gland is necessary for the production of estrogenic

mammary cancer, we have insufficient evidence to prove that the estrogenic effect on the mammary gland is an indirect one.

One of our experiments indicates that the growth of estrogenic mammary cancer may be partially inhibited by injections of anterior pituitary extracts. A group of 12 rats, 1 month old, received 10 gamma estradiol benzoate daily for a period of six months. At the end of 100 days one-third of the animals were autopsied and, on microscopic study of breast tissue, all were found to have mammary cancer. The remainder of the animals continued to receive their daily injections of the estrogen. In all but two, which were reserved for controls, daily injections of anterior pituitary extract were added for the next four months. (These daily injections consisted of 5 rat units of a follicle-stimulating extract and 20 guinea-pig units of a preparation containing the thyrotropic factor [ambinon, Roche-Organon] daily for one month followed by 10 international units of prolactin [Schering Corporation] daily for one month. Thereafter, these two cycles of injections of anterior pituitary extracts were each repeated for one month to complete the four months of treatment.) Palpable cancers developed in the animals which received injections of estradiol benzoate only. In the animals receiving injections of anterior pituitary preparations in addition palpable cancers were not found at autopsy; all except one of the animals had microscopic cancers, however. Cramer, who used injections of ambinon only, believed that the inhibiting effect of this anterior pituitary extract was more marked than indicated in this experiment.

SUMMARY

All of the estrogens of sufficient potency for clinical use will produce mammary cancer in the rat regardless of chemical composition or physiologic potency. To produce mammary cancer, the dose must be well beyond the physiologic limit (10 or more times the threshold dose) and the treatment continuously applied for a period of months (30 or more times the duration of normal estrus).

Variation in the time required to produce mammary cancer is dependent on: dosage, estrogenic potency, duration of estrogenic activity and method of administration. The total dose required to produce mammary cancer is not influenced by the amount of the daily dose but varies with the duration of estrogenic activity and the method of administration. It is difficult to demonstrate that sex, age or castration influences susceptibility to estrogenic mam-

mary cancer; but senile animals (over 15 months) are more susceptible. An initial period of estrogenic stimulation below the cancer-producing threshold renders the gland more susceptible to estrogenic cancer.

Important species differences are evident on the basis of experiments carried out in monkeys, rabbits and rats. Estrogenic mammary cancer in the rabbit is reported.

Administration of testosterone or progesterone simultaneously with, or in sequence to, estrogenic stimulation does not prevent the appearance of mammary cancer. However, the growth of estrogenic cancer is retarded by anterior pituitary extract.

To date, from a toxicologic standpoint, the most important finding with respect to the estrogens is the production of mammary cancer by prolonged administration. In the clinical administration of the estrogens this toxicologic property of these compounds has not yet been verified but must be considered when compounds of high potency with prolonged activity are administered. The species difference remains an unknown factor.

Various changes in the endocrine glands accompany the appearance of mammary cancer, and cancerous change has been observed in other organs.

Preparations for use in this study were supplied by the manufacturers as follows: testosterone propionate, progesterone and estradiol dipropionate by the Ciba Pharmaceutical Products, Inc.; estradiol benzoate and a preparation of the anterior pituitary lactogenic factor (prolactin) by the Schering Corporation; an anterior pituitary extract containing the thyrotropic factor (ambinon) and estrone by Roche-Organon, Inc.; stilbestrol, stilbestrol dimethyl ether and stilbestrol monomethyl ether monomestrol by Wallace and Tiernan Products, Inc.

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35

The Mechanism of Tumor Formation

THE ROLE OF ESTROGENS IN TUMOR FORMATION

While relatively little is known of the chemical or biochemical reactions whereby the sex hormones achieve their effects, the tissue changes which they produce have been repeatedly described. The large number of experiments resulting in estrogenic mammary cancer in mice carried out by other investigators and those of the author performed on rats demonstrate that a distinction must be made between the effects of physiologic and pathologic dosage of the hormone. In physiologic amounts, the estrogens promote the growth of both the epithelial and the fibrous structures in the breast. The size of the individual cells as well as the over-all size of the mammary gland is increased. There is also a corresponding increase in cell division resulting in the addition of new elements. The time required for these developmental changes is less than for the normal when the dosage is maintained at the upper physiologic limit.

With pathologically intense doses of estrogen, the over-all size of the gland is not increased, but may be decreased. The outstanding

effect of continued overdosage is not further mammary development but a state of hyperfunction and secretion. These effects of hyperfunctioning and secretion are accompanied by metaplastic changes in which some of the epithelial structures fall short of their normal end-point of differentiation. Continued overdosage next results in involution, degeneration and atrophy. This is followed by a period in which the gland remains in a relatively quiescent and atrophic

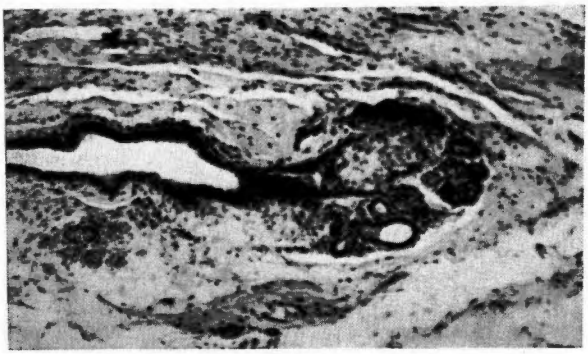


FIG. 568. Duct and lobular bud during normal puberty development. The duct is lined with columnar epithelium, the lobular bud contains a few acini but is made up largely of undifferentiated basal cells.

state. This period of quiescence is characterized by an apparent slowing up or retardation of the developmental changes. Finally, a series of atypical proliferations of both epithelial and fibrous tissues occur which are followed by the formation of benign and malignant tumors (Fig. 577).

The developmental changes which precede the formation of estrogenic mammary carcinoma may be interpreted from three separate points of view. First, they may be regarded as fortuitous or nonessential. If one accepts the hypothesis that the estrogenic compound or its degradation products form a chemical union with the constituents of a normal cell and thereby convert it to a malignant cell, the reaction may be assumed to take place only when a group of exceptional conditions are fulfilled. From this viewpoint, the degenerative changes may represent foci where the concentration of the compound is too great. Other changes may indicate zones where only a moderate physiologic concentration is effected, or where the biochemical state of the cells is not yet ready from the chemical standpoint to react and undergo malignant transformation.

Secondly, the pathologic changes observed may be considered of minor significance, as a contributing factor in the carcinogenic proc-

ess. They may be interpreted as a degenerative change resulting from hyperstimulation which merely serves to provide a focus of lowered resistance, wherein the real cancer agent or so-called "X" factor gains a foothold. From this point of view the changes represent only another form of chronic irritation or injury which pre-

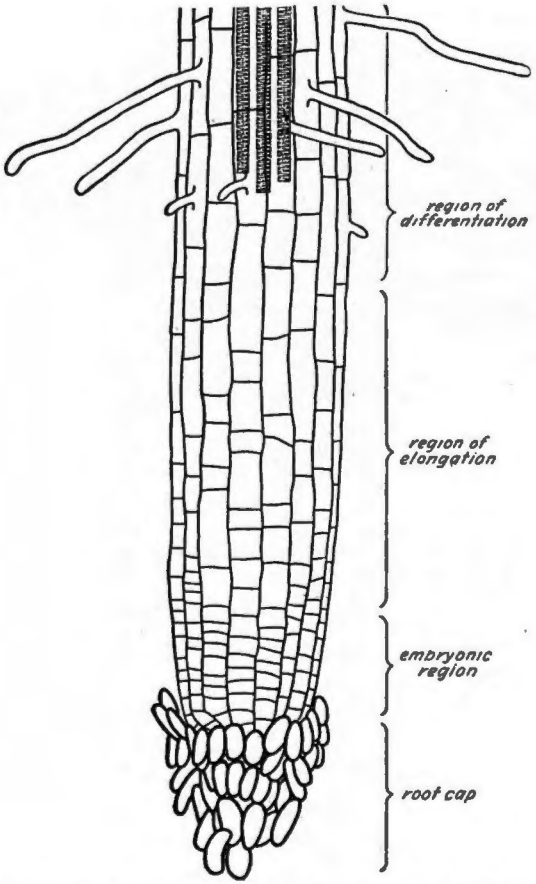


FIG. 569. A diagram of the root tip of red top showing proliferation (embryonic region), enlargement (region of elongation), and differentiation. Compare with Fig. 568. (Reproduced from Botany, Wm. J. Robbins and Harold W. Rickett, 1936, courtesy of D. Van Nostrand Company, Inc., New York.)

disposes in a general way to a mysterious and finite step in carcinogenesis.

Third, the sequence of estrogenic response on the part of the mammary gland may be considered as highly significant. The changes leading up to cancer may be looked upon as essential steps in the cancer process and as forming a definite pattern for the development of malignancy in any tissue, regardless of the means employed to

induce it. In the belief that the latter interpretation is correct, the sequence of estrogenic effects will now be summarized, and their significance for the subsequent formation of cancer will then be analyzed.

FIG. 570 FIG. 571

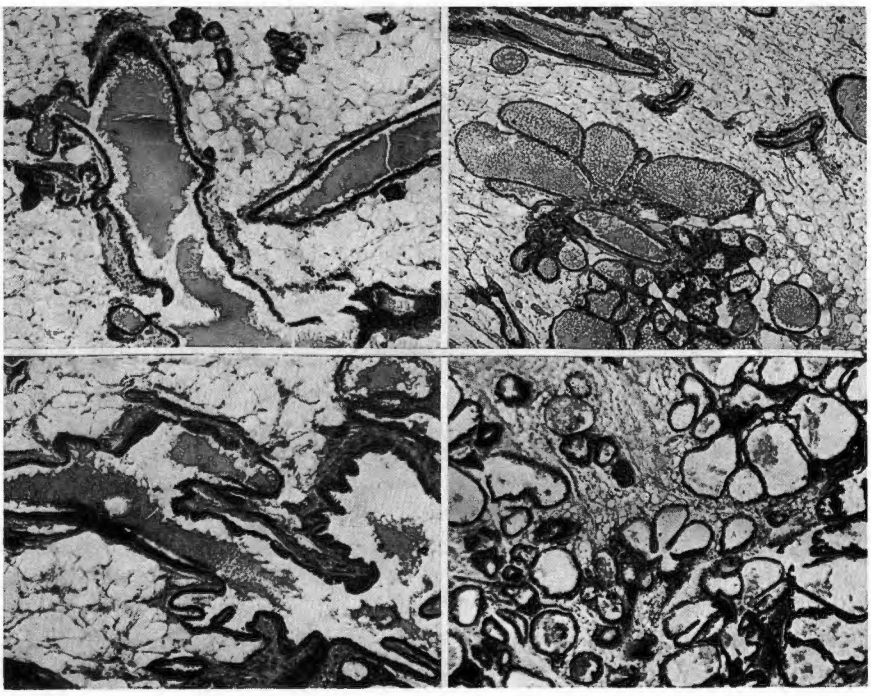


FIG. 572 FIG. 573

Contrasting Changes in Ducts (left) and lobular buds (right) with Estrogenic Overstimulation.

FIG. 570. The photomicrograph shows dilatation of the ducts with secretion, and proliferation of small basal cells in the lobular buds.

FIG. 571. Metaplasia and secretion in the lobular bud. (This is the pathologic picture of late mastodynia.)

FIG. 572. Atrophy and degeneration in the ducts.

FIG. 573. Metaplasia, secretion and hyperplasia in the lobular buds. (This is the pathologic picture of adenosis.)

SEQUENCE OF ESTROGENIC EFFECTS

Differentiation and Budding

When estrogen is administered the earliest response of the mammary gland is an acceleration of normal development. This consists of maturation in the ducts and tubules and proliferation in the

lobular buds. If the dose is physiologic, this process continues slowly and at length, so that as cells are ripened to expand the ducts, new elements are made available by cell division from the lobular bud. Hence, the increase in the over-all size of the gland. With overdosage this period of natural expansion is very brief. Apparently the continuation of normal development depends upon an orderly sequence of epithelial ripening and epithelial division, the former being confined largely to the ducts, the latter largely to the lobular buds. Thus in the normal adolescent rat (or with physiologic doses of estrogen in castrated rats), during maturation, the cuboidal lining cells of the ducts and tubules are changed to secreting columnar epithelium and the widened lumen shows an accumulation of secretion. At first the lobular buds show no change. Soon, however, differentiation extends to a few cells in the proximal part of the lobular bud (Fig. 570). Apparently in response to this partial conversion of its immature cells to secretory epithelium, the germinal cells of the bud divide and the size of the lobular buds is thus increased (Fig. 577 A, 1 and 2).

Hyperdifferentiation of Ducts; Metaplasia in Lobular Buds

With intense estrogenic stimulation expansion of the duct tree is brought to an early halt. The ducts and tubules are progressively distended with secretion. The lining cells show hyperdifferentiation; some are desquamated, and others become atrophic. Immature cells continue to divide in the lobular buds, but parts of, or entire buds, are converted into actively secreting duct epithelium, a form of metaplasia (Fig. 571). In this phase, the growth of the breast is stunted and the terminal tubules and lobular buds show the pathology of mastodynia. This pathologic picture is characterized by distention of the tubules and the conversion of the lobular buds through metaplasia into dilated acinar structures, some of which are lined by duct epithelium, or so-called pale epithelium. These metaplastic acini are distended with secretion to form small cysts. The mammary gland as a whole is stunted and its lobular buds distorted because of the speed of maturation. Further growth is retarded because of the conversion of large numbers if immature cells into adult secreting epithelium which is incapable of further division or cell multiplication.

Later in this stage of hyperdifferentiation, progressively large cysts are formed in the lobular buds as the result of further ripening and secretion in the metaplastic portions lined by duct epithelium. In this way secretory changes become progressively prominent in both the mammary ducts and within the lobular buds. Remnants of

proliferating immature cells indicate the persistence of the lobular buds but this microscopic feature is overshadowed by the secretory effects. Hypertrophy, metaplasia, secretion and cystic dilatation are the outstanding features at this stage (Fig. 577 A-3).

Involution and Atrophy-Hyperplasia

In the next stage, changes in the ducts and tubules are in marked contrast to those found in the lobular buds. Involution, atrophy, resorption of secretion and solidified secretory droplets are found in the ducts. The lining cells are flattened and atrophic (Fig. 572). The picture is one of involution and quiescence with beginning

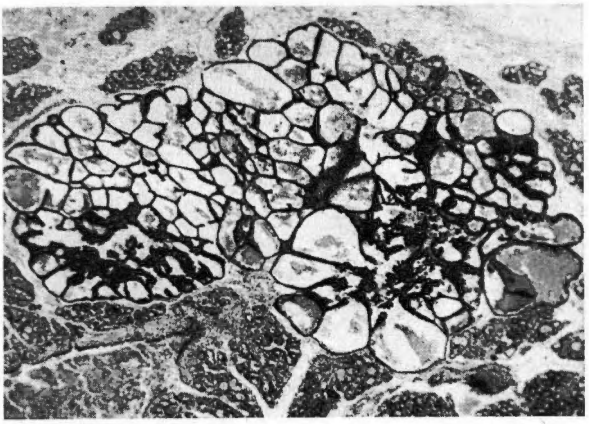


FIG. 574. Late changes in the mammary lobules with estrogenic overstimulation. Formation of cyst-adenomas within the lobular structure, following secretory involutional changes. This animal was not castrated and lobule formation has taken place.

degeneration and disintegration of the epithelial wall and increasing fibrosis and sclerosis about the ducts and tubules. Most of the dilated tubules have collapsed. This aging and involution is brought about because the estrogenic effect is now restricted to previously matured and differentiated cell elements. The number of young developing cells capable of responding to the estrogen has been reduced by the estrogenic ripening effect in the earlier phase of the experiment. In the lobular buds, cystic dilatation is still in evidence; some cyst walls are ruptured and basal-cell proliferation which begins from the remnants of the lobular buds may extend along the ruptured partitions of the cysts to form cystadenoma. In this phase, the pathologic picture in the tubules and alveoli duplicates the pathology of adenosis. A true epithelial hyperplasia becomes progressively more prominent (Figs. 573, 577, A, 4-5).

Atrophy; Fibrosis; Precancerous Proliferation

In this stage, further degeneration and atrophy are present in the ducts and tubules and degeneration and involution also affect the secreting lobular structures. In the latter, inspissated secretion, degeneration of the cyst walls and fibrosis replace many of the structures, but the hyperplastic foci continue to be active and small epithelial neoplasms in the form of papillomas and occasionally cancer may occur in this stage (Figs. 574 and 575).

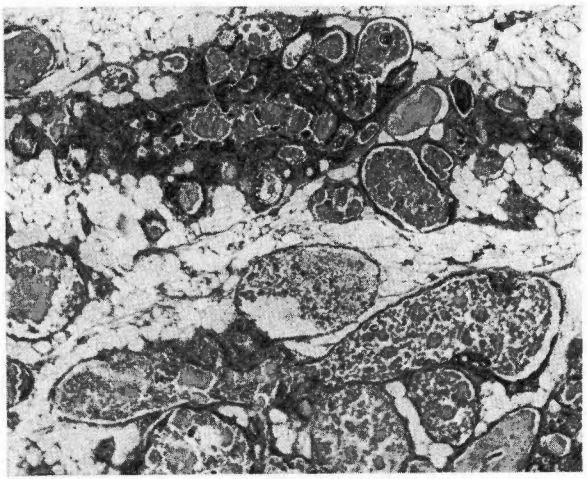


FIG. 575. Secretion and involution in the lobular bud followed by precancerous proliferation. This animal was castrated and lobule formation was inhibited.

Neoplasia; Cancer

In this phase, cancer occurs in the neoplastic and hyperplastic foci in the lobular buds. Hyperplastic foci formerly present in only the terminal tubules and lobular buds are found in the walls of the larger ducts. Cancers may arise in any of the mammary epithelial structures in this stage (Fig. 576).

The sequence of changes described above is essentially the same in all of our experiments whether the synthetic or natural estrogens are used, and regardless of the method or dosage, provided the dose is above the physiologic range. If the animals have not been castrated and the ovaries become luteinized during the early stages of estrogenic stimulation, or if the luteal hormones (progesterone or testosterone) are combined with or alternated with estrogens, the only significant variation observed is in the first stage. In this stage, the lobular buds form true acini, and lobular development equivalent to midpregnancy is observed.

The second stage is somewhat delayed depending upon the intensity of dosage, but again the lobule-alveolar structures show secretory changes and duct-cell metaplasia. Involution and degeneration changes then overtake the duct and lobular structures in turn, to be followed by hyperplasia and neoplasia.

If the estrogen acts continuously in moderate amounts, two modifications are seen during the sequence of changes under discussion. The periductal and peri-acinar fibrous tissues (which have been omitted from the above description for brevity) are more conspic-

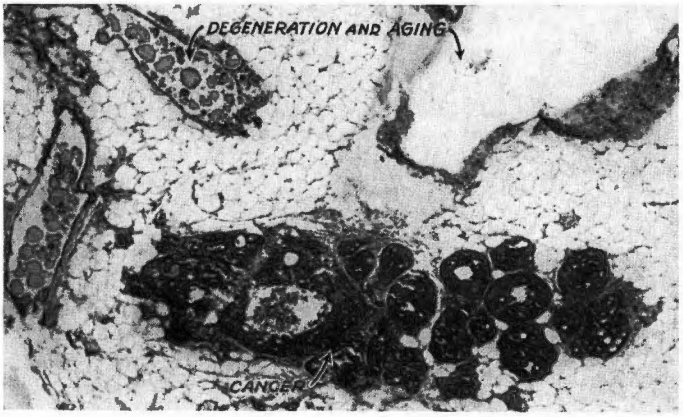


FIG. 576. Early cancer formation occurring as the end-result of over-stimulation with estrogen. The aging and degenerating ducts are shown in the upper portion of the picture. Below are multiplying nests of cancer cells which have arisen from a nest of basal cells such as is shown in Fig. 575.

uous. There is a periductal hyperplasia which is followed by peri-acinar hyperplasia. Then the fibrous tissue about the ducts becomes progressively sclerosed, beginning in the nipple region and extending toward the lobular bud. Finally, renewed periductal proliferation, terminating in fibro-adenomas, occurs near the nipple or about the terminal tubules.

The second variation with moderate dosage is a prolonged period of atrophy and quiescence which separates the second stage of hyperdifferentiation and secretion from the later stages.

In Table CXV the sequence of changes is given in abbreviated form and in the subsequent tables representative specimens have been chosen and described by stages from the actual experiments performed on large groups of rats. These changes also are presented graphically in the drawing shown in Fig. 577.

They may be traced in photographs made from the whole mounts of the gland in Figs. 578 to 583.

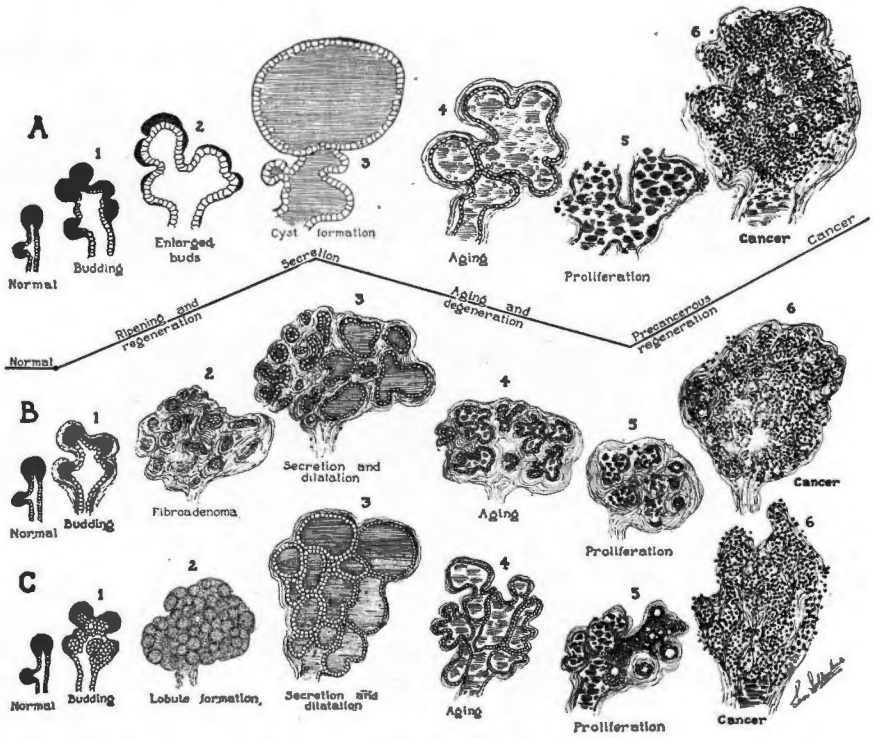


FIG. 577. The sequence of changes leading to estrogenic mammary cancer in the rat. *A* represents the sequence of changes occurring in the breast when cancer is produced by daily injections of estrogen in oil. Under these conditions the formation of large cysts precedes the aging effects and cancer. *B* represents the sequence of changes when cancer is produced by the implantation of estrogen pellets and is preceded by the formation of a benign tumor (fibro-adenoma). *C* represents the sequence of changes when cancer is produced by estrogen pellets in non-castrated rats and is preceded by lobule formation.

TABLE CXV

PATHOLOGIC STAGES IN THE DEVELOPMENT OF ESTROGENIC MAMMARY CANCER[1]

STAGE	DUCTS AND TUBULES	LOBULE-ALVEOLAR STRUCTURES
A. Accelerated development	Differentiation, secretion	Increased budding
B. Hyperdifferentiation, Metaplasia	Hyperdifferentiation, secretion, desquamation, early involution	Metaplastic differentiation, secretion, MASTODYNIA, cyst formation. Residual budding
C. Degeneration and hyperplasia	Involution, degeneration, atrophy	Hyperdifferentiation, involution. Fibrosed buds, hyperplastic budding. ADENOSIS
D. Atrophy, fibrosis, precancerous proliferation	Further degeneration	Lobular degeneration. Neoplastic budding (cancer?)
E. Neoplasia, cancer	Degeneration, neoplastic budding, tumors	Further degeneration. Neoplasia, CANCER

[1] See Figure 577.

TABLE CXVI

10 GAMMA ESTRADIOL BENZOATE

RAT		DAYS TREATED	EFFECTS ON DUCTS AND TUBULES	EFFECTS ON LOBULE-ALVEOLAR STRUCTURE
3972	A	12	Cystic dilation and secretion	Basal-cell sprouts, early lobule formation
3670	B	21	Cystic dilation, beginning atrophy	Dilated, filled acini. Mastodynia.
3674	C	41	Secretion, atrophy, fibrosis	Secretion, atrophy, fibrosis, few basal-cell buds
3569		69	Secretion, atrophy, fibrosis	Secretion, atrophy, fibrosis, condensed buds
3815	D	83	Atrophy, degeneration	Atrophy, degeneration, cancer, neoplastic sprouts
3569 a		104	Atrophy, degeneration	Atrophy, degeneration, cystadenoma
3570 b	E	120	Atrophy, degeneration, basal-cell sprouts	Atrophy, degeneration, cancer, basal cell sprouts
3566 b		120	Atrophy, degeneration, basal-cell sprouts	Atrophy, degeneration, cancer, "lactating" lobules

Rats tabulated here are representative of an experiment which included 50 animals.

FIG. 578

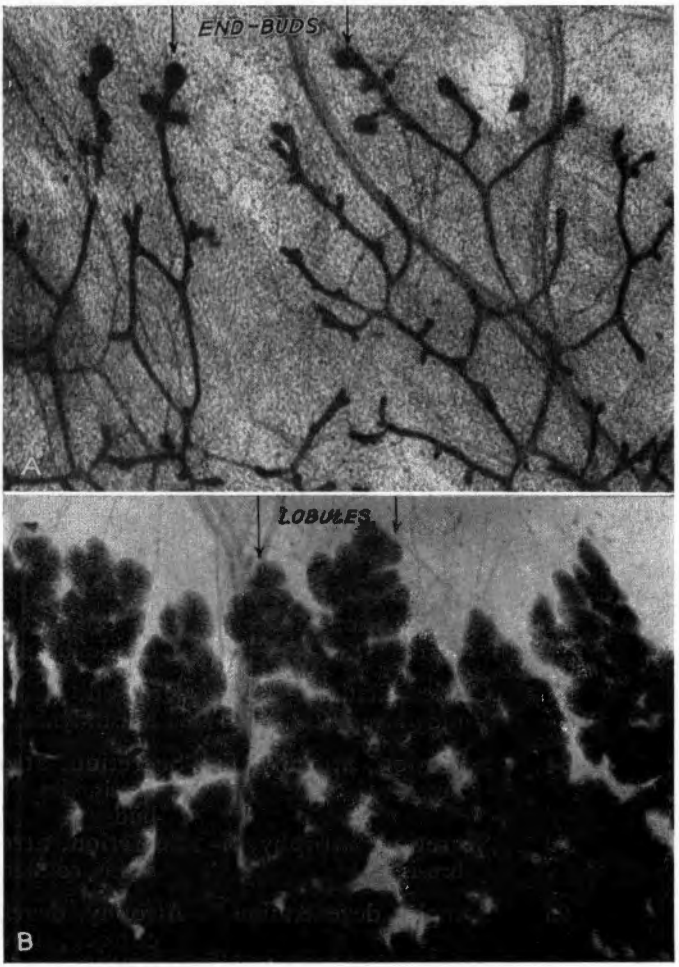


FIG. 579

The Normal Structure of the Breast (whole mount)—Stage A. Table CXV.

FIG. 578. The normal breast of a young pre-puberty rat showing the branching ducts and end-buds.

FIG. 579. The normal breast of a rat in early pregnancy. Lobules have formed from the end-buds.

FIG. 580

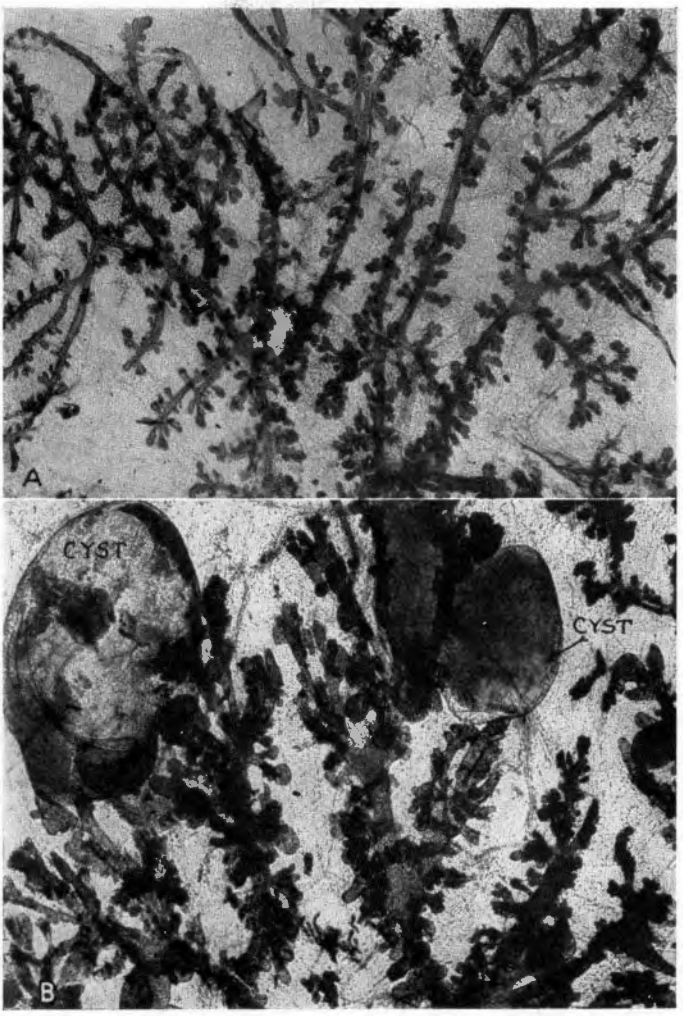


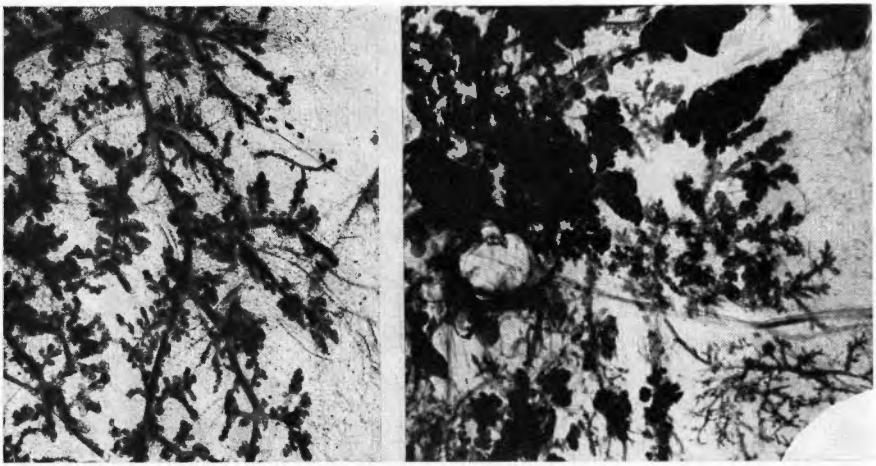
FIG. 581

Early Effects of Estrogenic Overstimulation in the Mammary Gland—Stage B. Table CXV.

FIG. 580. Excessive budding resulting in a dwarfed and bushy mammary tree. These changes represent an early stage of estrogenic overstimulation.

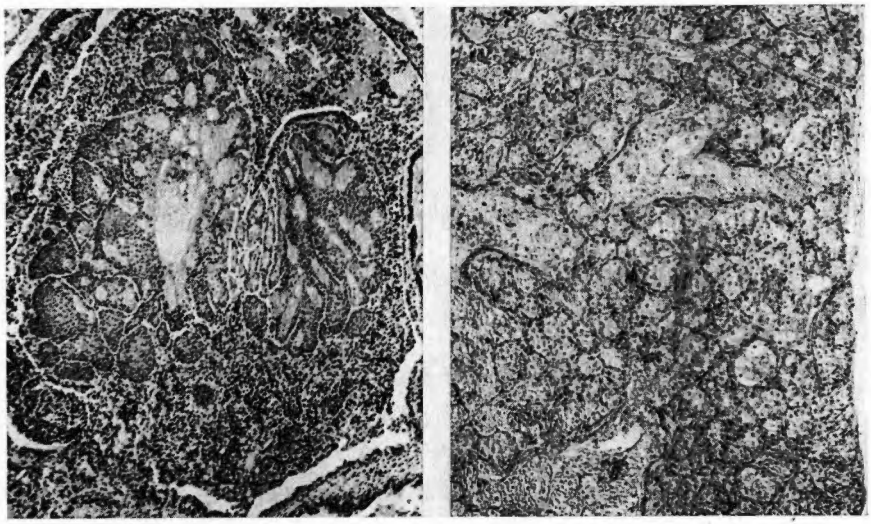
FIG. 581. Abnormal ripening and secretion in the end-buds of the breast with cyst formation. These cysts represent a later stage of overstimulation with estrogen.

FIG. 582 FIG. 583



Late Effects of Estrogenic Overstimulation in the Mammary Gland. Table CXV.
FIG. 582. Secretory dilatation of end-buds and atrophy of terminal tubules indicating an aging effect in the mammary gland—Stage C.
FIG. 583. Epithelial proliferation and early cancer superimposed upon the aging effects seen in 582—Stages D & E.

FIG. 584 FIG. 585



Metaplasia in the Rat's Breast.
FIG. 584. Squamous cell metaplasia in the terminal tubules of the mammary gland. This is the result of prolonged estrogenic stimulation.
FIG. 585. Sebaceous gland metaplasia in the wall of the ducts beneath the nipple. This is the result of overstimulation with testosterone.

SIGNIFICANCE OF THE CHANGES DESCRIBED

In order to understand the role that estrogen plays in the production of benign and malignant tumors of the breast it is necessary to determine how in a single animal such strikingly different effects of development—hyperfunction, metaplasia, involution, hyperplasia and neoplasia—are successively brought about during the course of administering the same dose of the same hormone daily throughout a given period. A brief consideration of the sequence of histologic changes just reviewed reveals that the growth and development of the mammary tissue proceeds through a series of interrelated steps. A number of separate physiologic influences are required to complete the different phases of growth and development. However, when estrogen is employed as the chief growth stimulant the major

TABLE CXVII

200 GAMMA ESTRONE

(Injected in Oil Daily)

RAT		DAYS TREATED	DUCTS AND TUBULES	LOBULE-ALVEOLAR STRUCTURES
42	A	10	Columnar lining cells show active secretion, lumen not yet filled or dilated	Lobular buds enlarged, some acini formed
1123 a		36	Cystic dilation, lumen filled with secretion, early lining atrophy	Multiple small cysts, occasional foci of proliferating basal cells, mastodynia pronounced
2600 a		41		
323		56	Atrophy of lining cells, fibrosis about large ducts, cystic dilation persists	Numerous large cysts
	B			
3578 d		84	Pronounced cystic dilation, atrophy and degeneration of lining cells	Cysts in terminal tubules and acinar structures, some pseudolactating acini, few large cysts
1238		95	Pronounced cystic dilation, atrophy and degeneration of lining cells	Numerous large cysts, basal-cell reduplication in a few alveoli
3578 e		117	Inspissated secretion, atrophy and degeneration of lining cells, periductal fibrosis	Dense inspissated secretion, rupture of acinar walls, periacinar basal-cell proliferation, small foci of basal cells, periacinar fibrosis
	C			
1236		150	Inspissated secretion, atrophy and degeneration of lining cells, periductal fibrosis	Numerous dense foci of basal cells, early ADENOSIS. Cystadenoma forming
1239 a	D	172	Degeneration, rupture of duct walls, secretory concretions	Degeneration, rupture of acinar walls
1233 a	E	186	Disintegration, degeneration and fibrosis of duct walls	Disintegration, degeneration and fibrosis of acinar walls, neoplastic proliferation, CANCER

Each rat is one of a group of 12 animals and is representative of the group.

effect is restricted to phases of differentiation and maturation in the tubular epithelium. Other phases of development, such as multiplication of the epithelial cells destined to form the mammary lobule and differentiation of the lobular epithelium, are not specifically affected.

Because estrogen influences primarily only a single phase of mammary development, the growth and expansion of the gland comes rapidly to a halt in response to this hormone. Instead of continued expansion, in which numerous phases of development must take

TABLE CXVIII

ESTRONE PELLETS

(6 Implanted Twice—6 Weeks Apart
Total Dose 30 mg.)

	RAT	DAYS TREATED	DUCTS AND TUBULES	LOBULE-ALVEOLAR STRUCTURES
A	1919	25	Duct lining columnar, secretory droplets	Solid proliferating buds, early acini
	1918	32	Full secretory effect	Some solid buds, secreting acinar structures
B	1917	39	Large ducts collapsing, others solid with secretion, lining cells flattened	Secretion in acinar structures, remaining basal-cell buds condensed, MASTODYNIA
	1919 a	58	(as above)	Acinar structures replaced by numerous small CYSTS
	1917 a	72	Atrophy of duct lining, collapse of dilated tubules	Cysts smaller, fluid content dense, early and slight basal-cell budding, periacinar fibrosis
C	1918 a	135	Atrophy and degeneration of lining cells, inspissated secretion	Some cysts ruptured, basal-cell budding marked, zones of ADENOSIS
	1917 b	172	(as above)	Degeneration of cysts, foci of adenosis persist, cystadenoma formed
D	1919 c	210	Concretions in lumen, epithelial degeneration, ruptured duct walls, periductal fibrosis	Degeneration of acinar structures, concretions in lumen, early condensed epithelial buds containing cells with dense neoplastic nuclei
	1919 d	300	(as above)	(as above)
	1917 c	317	(as above)	(as above)
E	1919 e	395	Further atrophy and degeneration of duct and tubular walls. periductal fibrosis increased	Disintegration of cystic and acinar structures, numerous foci of proliferating dense basal cells intermingled with degenerating epithelium. Early cancer, early fibroadenoma
	1917 d	402	Degeneration and rupture of duct and tubules progressive, with neoplastic budding in walls Duct cancer	Degenerating walls of alveolar structures rimmed with CANCER cells, multiple cancers in terminal tubules and lobules

Rats tabulated here are representative of an experiment which included 50 animals.

part, the maturation of duct and tubular epithelium is accentuated. This brings about the state of hyperdifferentiation and hyperfunctioning. With prolongation of this effect, the epithelium undergoes aging and degeneration. The end point is a state of atrophy and quiescence following the resorption of these degenerated structures, in spite of the continued estrogen stimulation.

There are three aspects to the pathologic changes resulting from estrogen overdosage. The first is the distortion of development brought about by converting immature elements to a single type of hyperfunctioning duct epithelium. This premature ripening effect which causes the epithelial elements to fall short of achieving the final stages of lobular development by converting them to duct cells is responsible for the metaplasia of the sweat-gland type observed, the cyst formation and other characteristic pathologic features during the early stages of the experiments.

The second estrogenic effect is an actual arrestment of mammary development which results in the quiescent atrophic appearance observed in the later phases of the experiments. This arrest is brought about by an exhaustion of the elements in the transitional phases of development. The cells that are mature enough to be influenced by estrogen and are still capable of further development are rapidly brought into a state of overripening, where further division and growth are impossible and where only death and disintegration await them. Immature embryonic-like epithelium persists during this phase of quiescence and atrophy, apparently because the earliest phases of mammary development are not directly influenced or amenable to estrogenic stimulation.

The third and most important pathologic effect of estrogen in extreme doses over a long period of time is the permanent alteration of the normal sequence of developmental steps in the mammary tissue. This permanent alteration is experimentally demonstrated by discontinuing estrogen after a brief period of high dosage and resuming it months or years later on an apparently quiescent gland (see Chap. 34). Neoplasia and malignant tumor formation rather than resumed development occur under such conditions.

The explanation of this permanent alteration in mammary development concerns the character of the immature and embryonic-like epithelium which persists during the quiescent and atrophic phases of the experiment. These persisting immature cells represent the surviving elements of a prolonged period of hyperdifferentiation. Because of their prolonged exposure to an intense maturing influence *only those cells with a tendency to resist further differentiation remain.* These foci of immature cells, therefore, must pass through

a prolonged refractory period before they respond to differentiating influences. It is these cells that take part in the neoplastic process, and it is significant that one of the chief characteristics of malignant tissue is the tendency for the dividing cells to persist for abnormally long periods in the immature state.

It is apparent, therefore, that excess estrogen stimulation is capable of accentuating a single aspect of mammary growth to the exclusion of other phases of normal development and at the same time of modifying the subsequent response of the immature surviving cells of the mammary tissue. These three phases of pathologic response—(1) distortion or metaplasia, (2) arrestment of further development, and (3) alteration of immature cells—are closely related. The intense ripening effects of estrogen result in metaplasia, that converts *all* of the available mammary epithelium (which is in a susceptible phase of development) into fully mature tubular structures. The immature surviving cells are those which are not amenable to such conversion for the time being and hence the period of developmental arrest supervenes. The continued application of the estrogenic stimulation, however, *does affect these immature surviving cells.* There can be no doubt of this experimentally. If estrogen is not given for a period of 15 to 20 months, biopsy reveals no significant changes in these surviving cells, other than a gradual and moderate decrease in their number. If estrogen dosage is resumed the number of these surviving cells can be more rapidly depleted. (This is because many of them will have arrived at a state of partial maturity, because of the lapse of time, where they are again susceptible to the ripening, metaplastic influence of estrogen.) Following this depletion a sudden burst of cell division or proliferation is observed in these immature cells and within a matter of two to three weeks. Under the further influence of estrogen, this neoplastic proliferation becomes cancerous. It is apparent that the immature surviving cells are affected by further estrogen stimulation in two ways. They are goaded into neoplastic proliferation when their number is sufficiently decreased and the proliferating cells are then acted upon in such a way that their further multiplication and development is cancerous.

The process of cell depletion is important because this is the means whereby a selected group of surviving cells is obtained, which differ in their maturation response from the normal, and which have a sufficient lag in their differentiation to permit a rate of cell division which is neoplastic. The process of further maturation under the continued influence of estrogen is necessary to permit the selective survival of cells with an even longer refractory period of development, a period of delay which is sufficient to change the neoplastic

proliferation to cancer. The degree of specialization in the mammary epithelium is also important because during the initial phases of maturation the cells must lose the power of further division at a relatively early stage of the differentiating process in order to bring about the period of arrestment that provides for the selective survival of immature cells with a refractory period of increased length. The metaplastic influence which converts the mammary epithelium to a more primitive pathway of differentiation, that characterized by the elaboration of tubular structures, is probably important also because the more primitive pathway of differentiation affects tissue which has undergone a previous hypermaturation during an earlier period of normal development. The surviving cells provoked into proliferation following the period of arrestment are therefore those that have previously had their refractory period prolonged during a phase of normal development.

This explanation of the pathologic changes produced by estrogen prior to the appearance of cancer emphasizes the importance of the altered response in the immature surviving cells. There is no way to demonstrate directly that these immature cells have an abnormally prolonged delay in maturation when subjected to the continual ripening influence of estrogen. There are, however, a number of facts which support this interpretation. Throughout the body in all tissues which are capable of regeneration, such as the skin, bone, breast, uterus, intestines and genito-urinary tract, foci of immature cells can be found at all ages, and in organs such as the skin their demonstration histologically is just as easy at the age of 90 as it is at the age of nine months or nine years. There is no question about the immature cells persisting throughout life in most organs. The question is whether they survive because of a continuously maintained rate of division or whether some of these cells persist and survive as immature units because of a prolonged refractory period to further maturation and differentiation.

In plants and in human embryos, the persistence of immature cells which are not surviving by repeated division but by a quiescent state which is refractory to maturation is easily demonstrated. In plants, the immature embryonic cells at the tip of the stem may form axillary buds in which development becomes dormant. Such resting buds may never resume development or may resume growth after a period of years. That such growth is indirectly affected by the interrelations of cell groups is shown in plants by the fact that the removal of the terminal bud of the stem or twig may cause a development of dormant buds and the formation and growth of adventitious buds.

In the human breast the mass of proliferating basal cells which forms the nipple bud shows active multiplication and division in the ninth week (26 mm. embryo; P. 9). Shortly thereafter the process of cell division comes to a halt and the undifferentiated cells of the mammary bud remain quiescent until the end of the third month when, in association with the differentiation of squamous cells which invade the nipple bud, the process of proliferation is again resumed (Figs. 5, 6, 7 and 8).

Finally, such a period of delayed multiplication and differentiation on the part of cells with a prolonged refractory period to further maturation seems the only possible explanation for the prolonged quiescent period observed in the mammary gland following the initial hyperplasia which is seen early in the experiment when estrogenic stimulus is continuously applied.

This analysis of the pathologic effects of estrogen indicates that its carcinogenic action rests primarily on the capacity of the hormone to accelerate the maturation of the mammary epithelium. When this maturation effect is prolonged and continuous it brings about the selective survival of immature epithelial cells which have an increasingly delayed response to the endocrine influence. Eventually these surviving immature cells with a prolonged lag in maturation, bring about a temporary arrestment in the mammary development which provides some of the immature cells with sufficient time to pass out of their refractory state and resume development. It is during this final period of resumed development that these cells show an increased rate of proliferation, and it is during this period that continued estrogenic stimulus further modifies them so that proliferating cells with an increasingly delayed maturation survive as cancer cells.

THE ROLE OF PROLIFERATION AND DELAYED MATURATION IN MALIGNANCY

The renewed proliferative response which precedes the formation of the malignant tumor and which persists after its formation is not a separate and independent characteristic of the neoplastic process. Maturation and proliferation in a regenerating or developing tissue are mutually dependent phases of growth. Apparently the rate of division in the immature cells is controlled by the process of maturation. In turn, the continued multiplication of immature cells provides the maturation process with new candidates for differentiation. Normal variation in the refractory period of recently divided

cells (which are incapable of undergoing immediate maturation) permits the survival of cells with a prolonged refractory period to maturation under a continuous stimulus of overripening, which acts as a selective influence. The interactions of these developmental processes are of cardinal interest in understanding neoplasia.

During the process of cell ripening, particularly when this is accelerated sufficiently to produce premature aging, substances which promote cell division can be isolated from the tissue. Loofbourow, who has termed such substances "intercellular hormones" or "proliferating-promoting factors," has succeeded in isolating such growth stimulants from yeast cultures treated with ultraviolet light. His work was confirmed by Davidson. The experiments of these workers demonstrated that the proliferating factor is liberated only by intact adult cells and they postulated that it was released because of the slowly damaging effect of ultraviolet light which increased the permeability of the cell membrane. Loofbourow's studies indicated that the effects of this potent growth stimulator were duplicated by adenosine triphosphase acting on a substratum of known growth factors consisting of vitamin B complex and amino acids.

Potter and his co-workers measured the concentration of adenosine triphosphase in cancer tissue, in adult normal tissue, in embryonic rat liver and brain, and in embryonic rat liver and brain during and after the process of maturation. Low levels of this proliferating factor were found in undifferentiated normal tissue, but during the process of maturation the levels rose rapidly and were maintained both in normal adult and cancerous tissue. This refutes the idea of Loofbourow that the proliferating substance occurs in damaged or dying cells, and it is necessary to postulate on the basis of this data that the stimulus which acts on the dividing cells is elaborated by the more mature cells during the period of their maturation. It is the continuous and prolonged attempts at maturation on the part of immature cells which have a delayed and protracted maturation cycle which maintains the rate of proliferation in the dividing cells of cancerous tissue.

Potter and his co-workers have also studied the concentration of respiratory enzymes (such as succinic dehydrogenase and cytochrome oxidase), in cancer tissue, undifferentiated normal tissue, differentiating tissue and adult normal tissue. These respiratory enzymes supply the functional energy for fully differentiated cells and their concentration may be taken as an index of the differentiated state. Their concentration is therefore high in adult normal tissue and increases rapidly during normal differentiation of rat liver and brain. However, in cancer tissue these respiratory enzymes are defi-

cient and are associated with a high rate of anaerobic glycolysis. These biochemical data are additional evidence in support of the analysis that the cancer cells are characterized by delayed differentiation.

PHYSIOLOGIC HYPERPLASIA

When a ripening influence is applied to a tissue which is capable of regeneration, immature cells in increased numbers pass into a period of ripening and development and increased numbers of partially mature cells complete their differentiation and pass into the zone of specialized adult cells. Because of the increased number of cells undergoing the ripening process each of which elaborates a proliferating substance, the concentration of this proliferative stimulus is increased. This increased concentration acts on the immature cells and increases their rate of division. Thus, physiologic hyperplasia is characterized by a greater number of adult cells, increased numbers of maturing cells in a transitional stage of development and increased numbers of young dividing cells. The basic process is that of cell maturation which indirectly stimulates the proliferation of the immature cells.

EXHAUSTION OF PHYSIOLOGIC HYPERPLASIA THROUGH HYPERMATURATION

When the ripening effect to which the tissue is subjected is intense and prolonged the continuous passage of immature cells into the adult state gradually depletes the number of immature cells available for ripening, in spite of their increased rate of division. This is because the surviving immature cells are those with an ever more prolonged refractory period to maturation. Ultimately the number of actively maturing cells (those in the transition between the immature and fully developed state) is greatly reduced. These cells are encroached upon from above by the process of increased and accelerated maturation, and are denied replacements from below by the increased refractory periods in the recently divided immature cells.

THE ATROPHIC OR QUIESCENT STATE

As the number of cells in the transitional stage of development decreases an atrophic or quiescent phase in regeneration is reached. This is characterized by a corresponding decrease in the elaboration of the proliferating substance, which is supplied only by the transi-

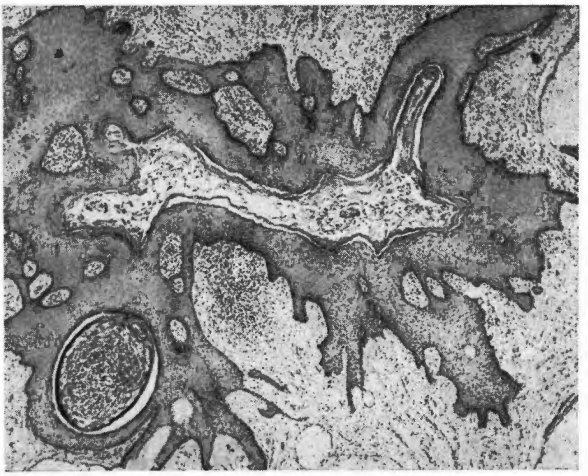


FIG. 586. Metaplasia in the human breast. Squamous cell metaplasia in the openings of the large ducts beneath the nipple.

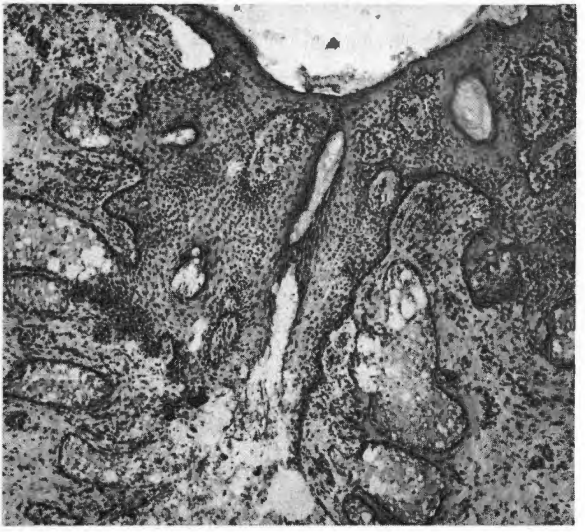


FIG. 587. Sebaceous gland metaplasia in the nipple area in a case of Paget's disease. Compare with Figs. 584, 585.

tional cells. This quiescent state occurs only in a tissue where the fully differentiated cells promptly lose their capacity for elaborating the proliferating substance. Physiologic hyperplasia supported by increased cell division continues for a longer time in a tissue where the maturing cells have a prolonged transitional phase during which they retain the capacity for supplying the stimulus for cell division. During the quiescent stage further maturation merely serves to age and wear out the adult cells. There are no new transitional cells to

FIG. 588 FIG. 589

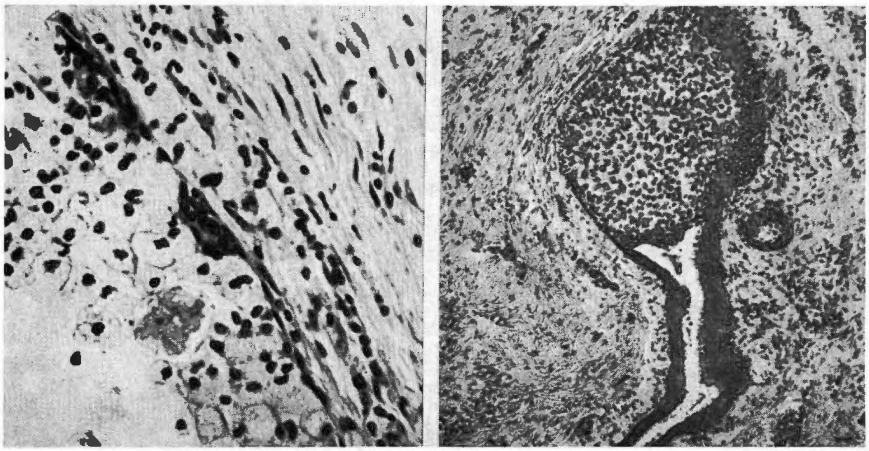


FIG. 588. Hyperplasia of immature cells stimulated by a neighboring focus of hyperdifferentiation. The photomicrograph shows multiplying basal cells in the wall of a tubule where hyperdifferentiation of duct cells is taking place (from a case of human mammary cancer).

FIG. 589. Human mammary cancer arising in a terminal tubule from a focus of proliferating basal cells similar to that shown in Fig. 588.

replace the old cells, nor to elaborate the proliferating stimulus to promote division of the immature cells.

NEOPLASIA AND CANCER

After a sufficient lapse of time the immature cells, in spite of their refractory period, enter the transitional stage and begin the process of maturation which is accompanied by the liberation of the proliferating substance. Now, an entirely different picture is seen and youthful cells rather than aged ones predominate. The tendency to delayed development continues to characterize the refractory immature cells and they now pass through an abnormally long transitional stage of development similar in length to the refractory period which

FIG. 590

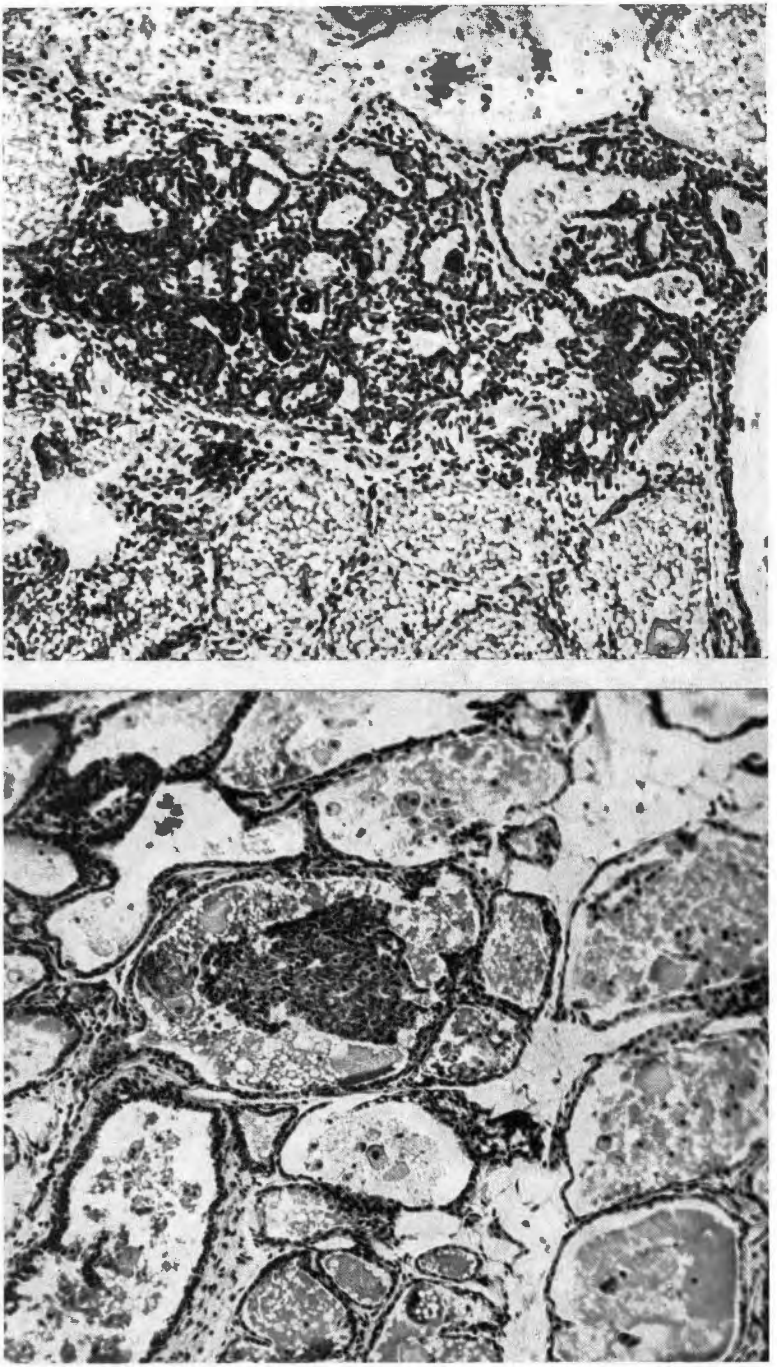


FIG. 591

FIG. 590. Hyperplastic regeneration of immature cells occurring within a degenerating mammary lobule.

FIG. 591. Early neoplasia proliferating from the wall of an acinus of a mammary lobule at its junction with the terminal tubule. This is the next stage following that shown in Fig. 590.

FIG. 592

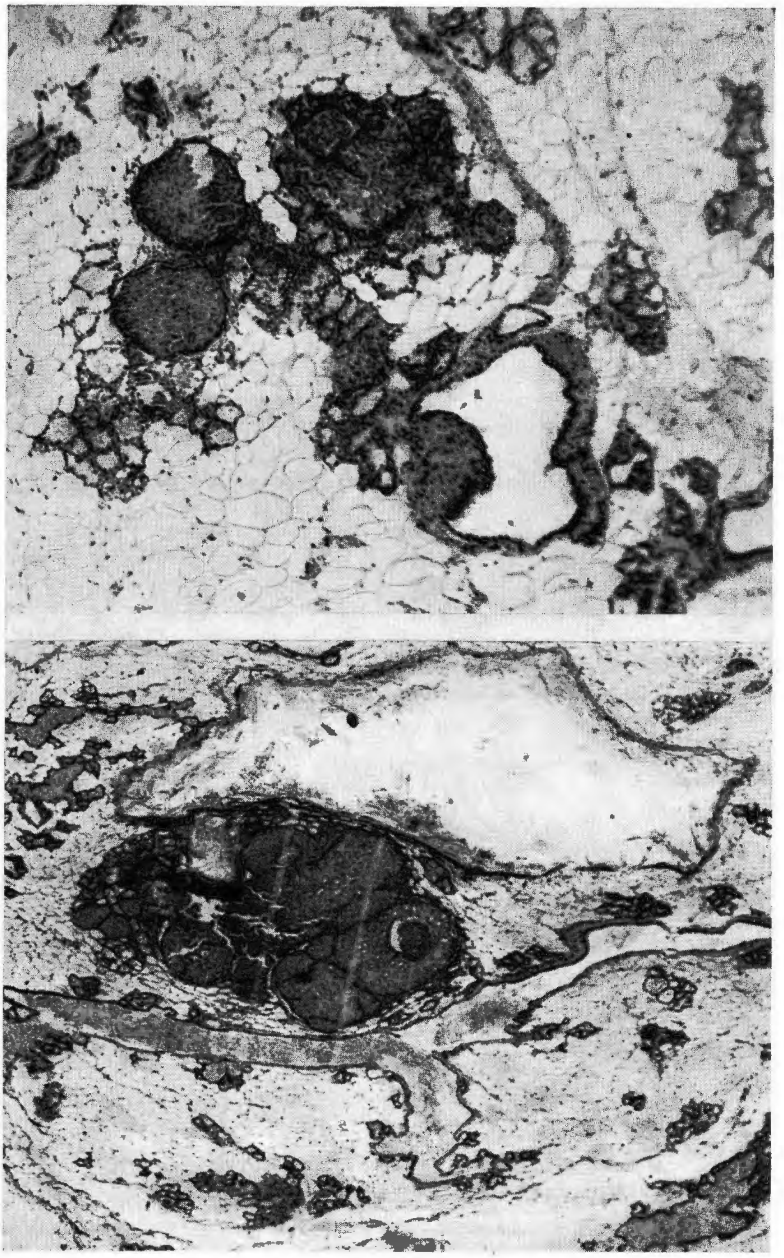


FIG. 593

FIG. 592. Neoplastic but questionably malignant epithelial proliferation in a terminal tubule with invasion of the neighboring lobule.

FIG. 593. Comedo carcinoma occurring in a terminal tubule. This is the next stage following that shown in Fig. 592.

they exhibited in their immature stage. During this prolonged period of development, they continue to elaborate a proliferating substance which serves to increase the rate of division in the immature cells awaiting development. If during the entire time the tissue is under a ripening influence (such as estrogen), the process of selective survival continues to act on the immature dividing cells, leaving those behind with an ever longer refractory period. These continue to be stimulated to division by increasing amounts of the proliferating substance. In this way there is a progressive increase in the cell population which exhibits both a delayed maturation and a prolonged transitional period of development. Cells with an extended transitional phase elaborate increasing amounts of the proliferating stimulus to act on cells exhibiting a prolonged immaturity. In turn, the increased rate of division in such backward cells serves to increase the number and the period of those in the transitional state when they eventually pass beyond immaturity. A vicious circle is thus established whch terminates in cancer. The cancer is characterized by an increased rate of cell division and by abnormally delayed maturation in the dividing cells.

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