AN ATLAS OF THE HUMAN BREAST:

SUBGROSS PATHOLOGY AND HISTOPATHOLOGY

VOLUME I

by

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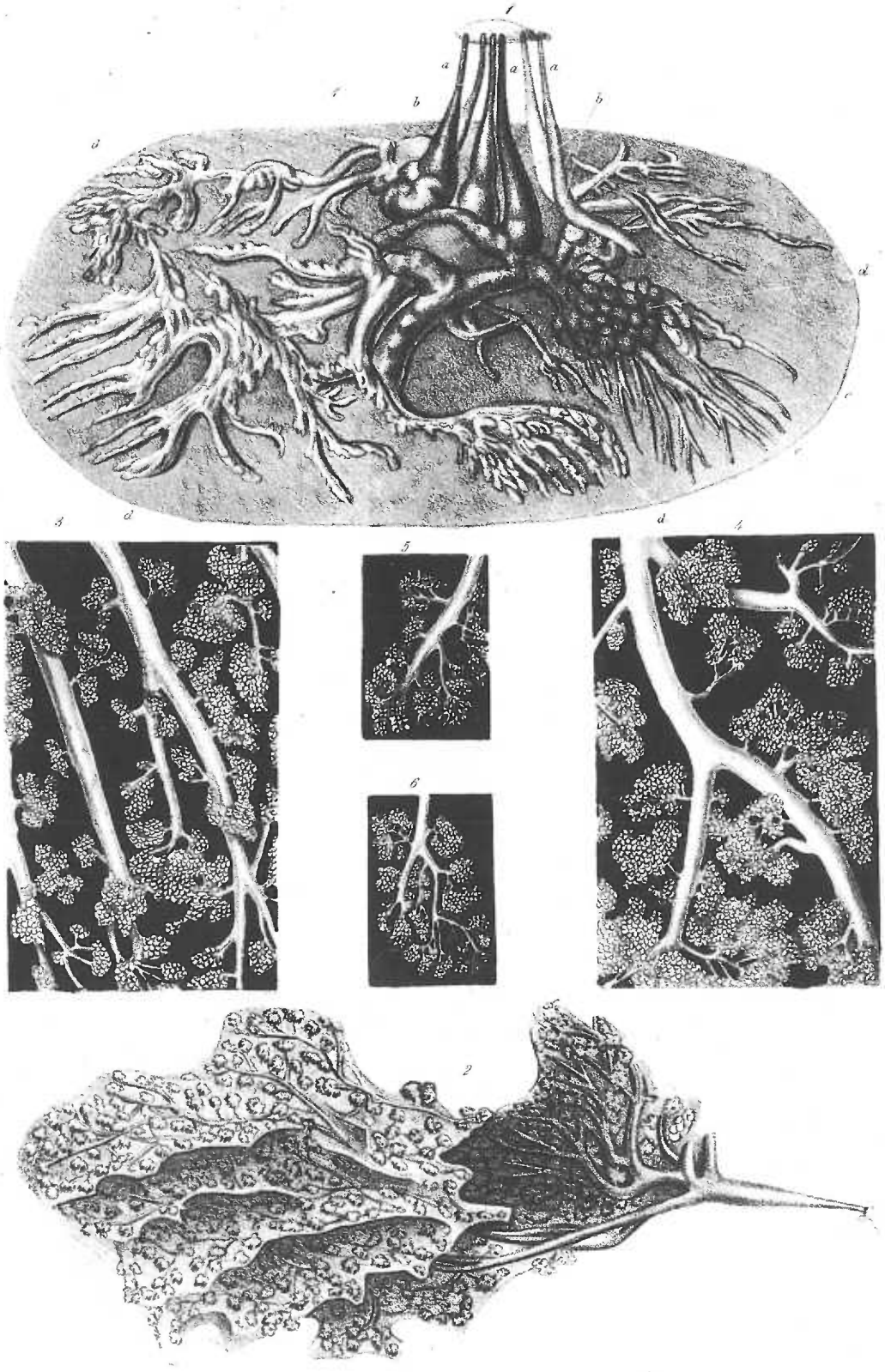
Drawing of the dissected human breast illustrating the main ducts (galactophores) forming lobes (top), ducts with individual grape-like acini forming lobules (center), and a lobe in the fibrous supporting tissue of Cooper's ligaments (bottom). From *The Anatomy and Diseases of the Breast* by Astley Cooper (17), plate VII.



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INTRODUCTION

STATEMENT OF THE PROBLEM

Several workers have devised methods for the study of human mammary gland at the subgross* level. Cheatle and Cutler (13) prepared giant histologic sections which were useful at both the subgross and histologic levels of observation. However, the sections were not transparent, and large numbers of slides were required in order to study entire mammary glands.

A method developed by Ingleby and Holly (56) is similar to our own. The sections were transparent, and about 1 mm thick. The epithelium stained with hematoxylin and was sharply demarcated from surrounding stroma. Ingleby (53) used the method to examine several entire mammary glands and later (55, 57) combined the method with a roentgenologic study of the breast.

Parks (83) studied 150 surgical and 50 entire autopsy specimens of human breasts embedded in low viscosity nitrocellulose, sectioned at 150 to 500 μ, and stained with anthracene blue. The author's manuscript illustrates mammary pathology at the subgross level.

In no instance was there a detailed presentation of the variety of subgross formations present, nor was there discussion concerning the possible use of the methods as tools for further laboratory investigation.

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*The subgross level is defined as a level of observation between the gross and the histologic levels, roughly corresponding to 5 to 20 diameters of magnification.

It is the purpose of this thesis to evaluate a revised method for subgross study of human mammary gland and to construct a detailed atlas of subgross morphology and histopathology.

REVIEW OF THE LITERATURE

Embryology.

The precursor of the human mammary gland is first visible in the 4 mm embryo as a ridge of ectoderm stretching from the upper to the lower limb on either side (86). In the 7 mm embryo, this ridge of columnar cells is referred to as the mammary line or ridge (64, 81) or the milk line or ridge (41, 86). This mammary line begins to shorten in the 9 mm embryo, and by the 6th week (11-12 mm) it has further thickened in the thoracic region to form a hillock of tissue (64, 86). About the 9th intrauterine week (approximately 26 mm), the hillock of epithelium begins to increase in size, penetrating the underlying mesenchyme (64), and forming the nipple bud (41) or primitive mammary bud (86). Between the third and fifth months (20-150 mm) some observers believe that the mammary bud remains relatively quiescent with the rate of growth and differentiation increasing again during the fifth fetal month (86). Other workers think that the nipple pouch along with the early mammary buds (precursors of mammary ducts) develop as early as the third month (54-78 mm) (41). In either case, 16 to 24 solid cords of cells arise from the epithelial nodule (64, 81, 86) and penetrate the underlying mesenchymal tissue. By the end of fetal life, the solid cords have undergone bifurcation and canalization to form lactiferous sinuses with small branching ducts arising from their walls (24, 41, 64, 86).

The origin of the nipple is controversial. Langman (64) feels that the nipple is not formed until shortly after birth when a small epithelial pit, affording exterior communication for the lactiferous sinuses, is "...transformed into the nipple by proliferation of the underlying mesenchyme." In opposition to this, Brauha, cited by Raynaud (86), demonstrated early nipple development in the 4 month fetus. Development continues until the eighth month, when the nipple area becomes depressed. During the ninth intrauterine month, dermal proliferation beneath the nipple area causes flattening which persists until after birth.

The question as to whether the mammary gland is a "modified sweat gland" will be discussed in the section dealing with apocrine epithelium. In any case, the embryological evidence demonstrates beyond doubt that the mammary gland is a specialized accessory gland of the skin (5).

Morphology and Physiology of the Human Female Mammary Gland.

Before the physiology of the human mammary gland is discussed, it is important to become acquainted with the terminology applied to the structural elements of the mammary gland.

The epithelial tissue of the normal breast is confined to the mammary fat pad (31). The major ducts, 15 to 20 in number, extend into the mammary fat pad, and widen immediately below the nipple to form the lactiferous sinuses. As the ducts penetrate the fat pad, they branch several times, terminating in ductules which are grouped into lobules (see Figure 1) (80). Each of the 15 to 20 main ducts forms a complex referred to as a lobe. One or two layers of fusiform myoepithelial cells, located adjacent to the epithelium, surround and confine the

epithelial cells (63). The ducts and lobules are situated in prominent fibrous trabeculae which extend from the subepidermal fascia to the fascial plane over the pectoral muscles (17). These are termed Cooper's ligaments, named after the man who first described them by means of careful gross dissections (see Figure 1). The fibrous portion of the trabeculae associated with the lobules is identified as intra- or interlobular fibrous tissue, depending on its spatial relationship to lobules. The fibrous tissue adjacent to the ducts is the periductal connective tissue and is continuous with lobular connective tissue (80). These various epithelial and stromal elements compose the parenchyma of the breast (55, 80). The remaining portion, and the great bulk of the breast, except in pregnancy and lactation, is made up of connective tissue and fat (55, 80).

In 1933, Dawson (23) defined the various epithelial components of the breast. She combines physiology and histology in defining the lobule, ductule and acinus. The *ductule* is "...a tube-like outgrowth from a terminal duct, forming the 'end-piece' of the glandular tissue in the quiescent (non-secreting) mamma." Therefore, anything larger than the ductule is a duct. There are large and small ducts which any one author may arbitrarily define in units of measure. An *acinus* is defined by Dawson (23) as "...the secreting element, lined by a single layer of epithelium, and normally present only during pregnancy and lactation." As a result she rejects the use of acinus to signify the "end-piece" of the duct found in phases other than pregnancy or lactation. Moreover, this author feels that *alveolus* is not a desirable term, since it is frequently used for labeling any terminal duct

structure without considering its function. By these exacting definitions she has attempted to eliminate the ambiguity associated with the terms acinus, ductule, and alveolus. Dawson further defines a *lobule* as "...a grouping of the terminal glandular structures of the breast..." That is, either ductules or acini can form a lobule. Ingleby and Gershon-Cohen (55) eliminate the physiologic aspects and define a lobule as "...the collection of terminal ductules arising from a duct." In contrast, Taylor and Waltman (99) express doubt that definite histologic or physiologic differences between ducts and acini can be detected. In the text of this thesis, except when otherwise indicated, *ductule* and *acinus* will be used interchangeably to identify the terminal portions of a duct which are grouped into a lobule.

Normal physiologic activity in the breast is an uneven and irregular process; that is, individual breasts exhibit a striking degree of variation from one part to another (2, 24, 25, 53, 55). With this important point in mind, a quick review of the physiology of the breast is in order.

Reynolds and Wines (87) describe a method for evaluating the stages of breast development on the basis of differences in the relative elevations between the nipple, areola, and surrounding breast tissue. His work, although clinically useful, does not have corresponding histologic evaluation. At the subgross and histologic level, there is relatively little change from birth to puberty (24, 53, 55). The growth that does take place is brought about by proliferation of all elements in the breast (1). Prior to puberty the epithelial component consists only of ducts; no lobules have as yet been formed (53). An increase in

estrogenic hormone by the ovary is responsible for this growth (1, 98). Colostral secretion or "witch's milk" is observed in the newborn period, about the third or fourth day, and lasts approximately 20 days (13, 24, 55, 74). In essence, it is secretion by the duct epithelial cells secondary to maternal hormonal stimulation. The secretion is effected in a merocrine manner; apocrine secretion in the sense of "cell decapitation" probably does not occur (74). Mayer (74) gives a comprehensive review of the subject.

At puberty, cyclical hormonal variations cause the menstrual cycle and alter the morphology of the breast. Estrogen stimulation is believed to be primarily responsible for the proliferation and budding of ducts (2, 108), and the formation of the first lobules (24, 55). Estrogen may also stimulate an increase in the periductal stromal tissue (19). Progesterone initiates ductule and acinar formation (108). Hadfield and Stratton-Young (45) suggest that variations in the levels of the "mammogenic triad"--prolactin, estrogen, and progesterone--are responsible for the cyclic changes noted in the breast. Anderson (1) and Copeland (19) agree with Hadfield *et al.* that the pituitary plays an intimate part in the physiologic changes of the breast. Bloom and Facet (5) suggest that the pituitary hormones, prolactin (MH) and somatotropin (STH), have a direct effect on the mammary parenchyma, while adrenocorticotropic hormone (ACTH) and thyrotropic hormone (TSH) have an indirect effect via the action of secretory products of the adrenal gland and thyroid gland, respectively. Although the exact effects of ACTH and TSH are undetermined, full morphologic development is not believed possible in their absence. Womach (108) suggests that

the epithelial cells must be primed by estrogen and progesterone before they react to prolactin. He goes on to say that without the previous action of estrogen, progesterone would not form an effective ductule system. Simultaneously, progesterone inhibits hyperplasia and growth of the duct system to a considerable degree. The exact mechanisms of hormonal interplay in mammogenesis and lactogenesis in the human remain unknown.

Rosenburg (1922) is cited by Anderson (1) and Cheatle *et al.* (13) as the first to give a detailed description of the cyclic changes occurring in the breast. Many authors, including Ingleby (53), have confirmed Rosenburg's findings. Most investigators think that the cyclic changes in the breast involve primarily the epithelium. Ingleby, however, notes myxomatous or hyaline degeneration in the lobular stroma during the premenstrual phase (53). Mulligan (79) supports Ingleby's observations in his descriptions of cyclic changes in both the stroma and the lobular epithelium. Mulligan divides breast response into four phases, as follows: 1) *Day-1*: the lobules are composed of closely approximated large alveoli (ductules), the lumina contain secretion, and the luminal lining consists of two layers of epithelial cells. 2) *Menstruation and pre-ovulatory phase*: the alveoli (ductules) gradually decrease in size beginning at the center of the lobule, secretion decreases, and the epithelial cells are more cuboidal. The stroma exhibits decreased vascularity and increased collagen with some lymphocytes scattered throughout. 3) *Mid-interval phase*: the lobules are one-half the size of the day-1 lobule. The alveoli (ductules) are scattered and few in number, confirming observations by Rosenburg (89)

that many ductules disappear during the intermenstruum. There is also a decrease in the number of lymphocytes. 4) *Post-ovulatory phase*: the size of the alveolar lumina increases and the epithelial cells become progressively more columnar in shape. The stroma is looser with increased vascularity and relatively decreased volume.

Stromal alterations are thought to be of considerable significance by some authors. Dieckman, cited by Ihnen and Perez-Tamayo (50), describes stromal changes as follows: 1) a cellular, loosely woven, lobular stroma in the premenstrual phase; 2) a more compact lobular stroma with thickened and swollen fibers in the early- and mid-postmenstrual phase; 3) an increase in the amount of collagen in the lobular stroma during the late postmenstrual phase; and 4) progressive decrease in stromal cellularity in the interval phase until the onset of the next cycle. Dieckman's work has subsequently been confirmed by numerous studies. Ihnen *et al.* (50) simply state that the normal lobular stroma "...has a loose texture with prominent interstitial spaces."

In pregnancy, the post-ovulatory phase mentioned by Mulligan (79) persists until about the third month of gestation (1). At that time, acini, as described by Dawson (24, 25), are forming, but their development varies considerably throughout the breast (25, 55). The formation of lobules continues, possibly under the influence of luteal hormones of placental origin, plus a mammogenic hormone (19). By term of pregnancy, colostrum (fat-containing) cells have developed from the superficial epithelial cells lining the ducts (1). Shortly after delivery, secretory activity commences under the influence of changes in the hormonal milieu, which may include a decrease in progesterone, allowing

the lactogenic effect of estrogen to act, as well as the release and resultant effect of prolactin in the presence of ACTH (20, 55). Bloom *et al.* (5) suggest that estrogen may be inhibitory as well, with secretion occurring only after estrogen levels decrease. Further information on milk secretion is available in recent reviews (20, 55, 74, 86).

Post-lactational involution is an atrophic change (25), and, like other processes occurring in the breast, is not uniform in its progression (25, 55). Ingleby *et al.* (55) and Dawson (25) describe the replacement of the abundant glandular tissue by fibrosis. Ingleby *et al.* feel two processes are at work: "...(a) degeneration of cells lining the acini, whether epithelial, basal, or myoepithelial; and (b) proliferation and differentiation of myoid cells to form fibrous tissue." The involution process is implicated in many abnormal conditions of the breast and will be referred to in the discussion of those particular lesions.

Finally, the menopause signals more changes in the breast. Dawson (26) indicates that fibrosis and quiescence of lobules is the usual form of involution at menopause. Obliteration of small lobules may occur as a result of periductal fibrosis, or the formation of a thickened hyaline basement membrane.

Benign Breast Lesions (Mammary Dysplasia).

As defined in *Dorland's Illustrated Medical Dictionary*, 23rd edition, *dysplasia* derives its meaning from the Greek combining form *dys-*, signifying bad or disordered, and the Greek word *plassein*, to form, giving an approximate literal translation of "to form in a disordered

manner" or an "abnormality of development". Because most benign breast disease is probably the result of abnormal development rather than some extrinsic insult, mammary dysplasia is a reasonable appellation for the pertinent changes, referred to below.

Anderson (1) defines mammary dysplasia as "...an abnormal interplay of parenchyma and stroma, developed and expressed by failure of reciprocal proliferation and involution", and thus a consequence of abnormal physiology. Layton (65) defines mammary dysplasia as "a general term applied to a group of benign breast lesions that are neither inflammatory not truly neoplastic, and that are referred to commonly as chronic cystic mastitis." He goes on to say the changes reflect hormonal imbalance acting on susceptible breast tissue with cyclical changes of morphology, more specifically hypertrophy, hyperplasia, involution, and atrophy of the parenchyma and stroma. It should be recalled that such manifestations are not peculiar to the breast, but are observed in other organs. "Nodular hyperplasia" of the prostate gland and "involutionary nodular goiter" are examples.

On reviewing the literature, one quickly finds that innumerable names are given to the various forms of mammary dysplasia. They include maladie cystic, matopathia cystica, fibrocystic disease, cystic hyperplasia, Schimmelbusch's disease, mazoplasia, cystiphorous desquamative epithelial hyperplasia, fibroadenomatosis cystica, and, the most well known, chronic cystic mastitis, to name only a few.

The changes included under these labels are variously classified by different authors (38). The lesions include: 1) cysts, 2) duct papillomatosis, 3) blunt duct adenosis, 4) sclerosing adenosis,

5) apocrine epithelium, 6) stasis and distension of ducts, 7) periductal mastitis, 8) fat necrosis, 9) hyperplasia of duct epithelium, 10) fibroadenoma, and 11) tendency to fibroadenoma (fibroadenomatoid tendency). Foote and Stewart (38) believe, however, that only the first five are truly parts of "chronic cystic mastitis". On the other hand, as few as four divisions have been made to classify the changes of mammary dysplasia. Cole and Rossiter (16) subdivide the disease into 1) adenofibrosis, 2) benign parenchymatous hyperplasia, 3) precancerous hyperplasia, and 4) cystic disease. The reviews of Sandison (92) and Davis, Simons, and Davis (21) deal with nomenclature in more detail.

The incidence of mammary dysplasia in clinically normal breasts varies according to the study. Davis *et al.* (21), summarizing the work of others, indicate that the incidence of mammary dysplasia varies from about 10 percent to more than 90 percent, according to the series. All of these studies utilized clinically normal breasts obtained at autopsy. Davis *et al.* (21) summarize eight different studies, totalling 725 breasts. The overall incidence of mammary dysplasia was approximately 60 percent. The largest single series to date is that of Sandison (92) who studied 800 autopsy breasts from consecutive postmortem examinations. The incidence of mammary dysplasia in this series was greater than 70 percent.

The incidence of intraductal epithelial hyperplasia also varies in different series of clinically normal breasts. Sloss, Bennett, and Clagett (93) report 33 of 100 cases with this change, while Sandison (92) gives an incidence of 176 cases in 800, or 22 percent. In addition, the epithelium can exhibit varying patterns, locations, and differing degrees of atypism, all of which are of uncertain significance. A

recent paper by Humphrey and Swerdlow (49) reports severe epithelial hyperplasia in large ducts (6 of 100 cases), in small ducts (17 of 100 cases), and in acini (21 of 100 cases). Such findings have led Sloss *et al.* (93) to state, "Thus, it is concluded that the mere qualitative presence of ... intraductal epithelial hyperplasia in the breasts of women is insufficient to warrant such tissue being considered as disease."

Most authors agree that mammary dysplasia is most frequent in the upper outer quadrant (47).

To help clarify the terminology and statistics associated with the changes of mammary dysplasia, each of the individual lesions will be dealt with in turn. Many of the following statements concerning etiology and pathogenesis are conjectural, and are not based on sound analytical biology. Even so, all of the material is at least of historical interest.

Cysts:

A good deal has been written about cysts and their relationship to epithelial hyperplasia, commonly referred to as hyperplastic cystic disease (2, 29, 92). This subject will be discussed in detail in the section concerning the relationship of mammary dysplasia to carcinoma. It is the purpose of this section to deal with cysts per se, that is, cysts without proliferative epithelial change.

Most authors group cysts as either gross or microscopic. Bloodgood (4), however, did a most exhaustive study resulting in ten different classes of cysts, including the large, fluid-filled, blue-domed cyst which now bears his name. He recognized that there is little, if any,

relationship between single or multiple blue-domed cysts and carcinoma. Ingleby (53) describes two different categories of cysts. The first is "simple cystic disease", with cysts resembling normal developing duct buds, but varying greatly in size and distribution. She suggests that "simple cystic disease" may be caused by a normal physiologic stimulus resulting in altered ductule expression. This presumably occurs when the stimulus is superimposed on the cyclic influences affecting the adult breast. Ingleby's second category is "secretory cystic disease", characterized by ducts which are dilated throughout their length and filled with inspissated material. Here the epithelial cells are larger, cytoplasm clearer, and colostrum corpuscles are present.

"Simple cystic disease" may be histologically identical with "blunt duct adenosis", a term coined by Foote and Stewart (38). They described "blunt duct adenosis" as "...ducts which end abruptly and do not terminate in lobules." The myoepithelial tissue is markedly attenuated or absent and there is variation in the uniformity of the epithelial lining. In addition, both "simple cystic disease" and "blunt duct adenosis" are characterized by: 1) numerous small (1 to 2 mm) and medium (1 cm) cysts; and 2) lack of any relationship to menstrual changes, which is in agreement with Ingleby's idea of the superimposed action of an additional stimulus.

Dawson (26) defines two groups of cysts. One type is referred to as the pale or eosinophil cyst because of the distinctive apocrine epithelium (to be discussed later). The other type results from an apparent fatty degeneration of epithelium, producing colostrum-like cells. These are secondary to degeneration of proliferating epithelium. However, the

epithelium may not uniformly degenerate, but instead may also exhibit focal proliferation, or epitheliosis.

Cysts are usually said to be most frequent in the 40 to 50 year age group (19, 21, 38, 41, 43, 49, 55). Davis *et al.* (21) gives the peak incidence as 35 to 50 years. Haagensen (43) studied 458 patients with cystic disease and found about one-half of the cases were in the 40 to 49 year age group, while only 10 percent occurred between the ages of 50 and 59 years. It is generally recognized, as is indicated in Haagensen's figures, that there is a sharp decline in the incidence of cysts in the postmenopausal age groups. This finding, in conjunction with the marked premenopausal incidence, and the fact that many women with the disease have irregular menses and dysmenorrhea (69, 74), supports the belief that hormone imbalance is important as an etiologic factor in cyst formation (2, 7, 55, 73, 82). Because involutional changes occur in the breast in the menopausal years (26, 55), and because involutional changes are noted in the surrounding tissue of cystic breasts (7, 19), cyst formation may also be related to involutionary changes as well as hormone alterations (9).

Ochsner (82), in attempting to clarify the nature of the hormonal imbalance, cites work by Goormaghtigh and Amerlinck. In 1930, these workers treated oophorectomized mice with prolonged estrogen stimulation and noted "...typical cystic changes in the breast...." Ingleby (52) and Nathanson (80) confirmed the results of these animal experiments. Lewison (69) cites other investigators who used excessive estrogen stimulation in other animals to produce changes similar to cystic disease. Kier, Hickey, Keettel, and Womach (62) studied breast

tissue from fifteen patients with mammary dysplasia, and found a relative increase in estrogen levels, as compared with control values. Zeppa and Womack (109) reported that the histamine content of the breast was much higher in mammary dysplasia (4.33 mg/gm) than in normals (1.02 mg/gm). More importantly, they showed progesterone and estrogen to be potent histamine liberators. Again, Ochsner cites other work which suggests that the effect of increased estrogen levels was time-related. In the presence of persistent high estrogen levels, the patients' breast disease progressed from normal to fibroadenosis, and, if prolonged after the age of 40, to "fibrocystic disease". Thus, authors such as Ingleby *et al.* (55), Anderson (2), Willis (107), and Lewison (69) believe that the underlying etiologic factor is excessive estrogen stimulation. Ingleby indicates that an associated diminution or absence of progesterone may play a part as well. Possibly, as Womach (108) states, a decrease of progesterone may enhance the action of estrogen on the duct system.

The incidence of cystic disease in clinically normal breasts is of interest. Sandison (92) quotes a series of studies which indicate an incidence of approximately 20 percent in non-pregnant women. Davis *et al.* (21), combining the studies of several other workers for a total of 725 patients, found the overall incidence of grossly visible cysts to be 21 percent, while microscopic cysts were found in about 60 percent of the cases. He also states that in 21 (19%) of 104 cases, gross cysts were bilateral, while in 137 (38%) of 360 cases, microcysts were bilateral. One study of prelactating breasts revealed no cysts (25).

The definitive pathogenesis of cyst formation is controversial. Cheatle and Cutler (13) favor the idea that cysts are the result of epithelial hyperplasia in ducts and acini, although they consider duct obstruction secondary to inflammation, connective tissue proliferation, or accumulation of epithelial debris to be of possible significance. They also recognize obstruction by epithelial hyperplasia as a possible pathogenetic mechanism.

Ingleby *et al.* (55) suggest that cysts may be related to intermittent obstruction, inflammation resulting in destruction of inter-duct and ductule partitions, or ductal dilatation. Dilatation could lead to tortuosity, valve-like folds in the duct wall, and isolation of portions of the ducts. The isolated segment of a dilated duct may be classed as a cyst. They conclude, however, that a satisfactory explanation of cyst pathogenesis is not presently available.

Cappell (9) hypothesized that cyst formation results from a combination of some degree of excretory passage narrowing with an increase in the amount of secretion by epithelial cells. Dawson (27) suggests the possibility that the proliferation of cells in ducts leads to duct dilatation with cysts being formed by cell degeneration or lysis. However, it seems improbable that cysts arise from epithelial proliferation; if such were the case, one would see more florid epitheliosis in young breasts with widespread cystic disease than statistical studies suggest. Finally, one would expect to see more of the earlier phases of cyst development with epithelial proliferation, rather than all sizes of cysts lined by low, cuboidal cells. Anderson (2) points out that inasmuch as small cystic dilatation of ducts and acini is common, it is

"...probable that this dilatation is not due to obstruction of the ducts from fibrosis, but is rather an initial increase in size at the time when the acinus was enlarging during hyperplasia. Having failed to return to normal size...it appears as a cyst. Cyst formation...may be looked on as evidence of hyperplasia followed by involution rather than retention due to obstruction."

Adenosis:

Dawson (23) defines the term *adenosis* "...on the analogy of melanosis, acanthosis, etc., and this word is both descriptive and accurate, indicating, as it does, an increase in glandular tissue without suggestion of tumor formation, and thus including in its scope both physiological increase, such as occurs during pregnancy, and pathological increase, evident at other periods and not obviously associated with normal proliferative stimuli." Dawson, in several articles (24, 25, 26, 28), mentions adenosis and its pathologic forms. She recognizes that the process, variously referred to as fibrosing or sclerosing adenosis, fibrosing or sclerosing adenomatosis, adenofibrosis, or simply adenosis, is part of a continuum linking normal glandular growth to an overgrowth of an exaggerated physiologic pattern. The glandular overgrowth is not neoplastic, is followed by regression, and progresses to fibrosis. Dawson draws fine lines of distinction among some of the aforementioned terms. She equates adenosis with Cheatle and Cutler's (13) term "mazoplasia" which he feels is a physiologic process, almost universally present to some degree in the normal breasts of multiparous women until menopause. Dawson specifies fibroadenomatosis as being due to persistent fibrosis during post-lactational involution which is associated

with a persisting adenomatosis. Ewing (35), however, defines fibrosing adenomatosis as marked proliferation of small alveoli secondary to chronic mastitis which leads to progressive fibrosis and to the formation of small groups of acinar cells, suggesting a precancerous process. The lesion is, in fact, rarely associated with malignancy. Geschickter (41) includes minute cysts and epithelial hyperplasia in his definition of adenosis. Dawson (28) emphasizes that one of the characteristic features in fibrosing adenosis "...is the absence of epitheliosis (epithelial hyperplasia) in the ducts but the hyperplastic lobular tissue surrounding the ducts may project into them, if dilated, and thus produce a pseudo-papillary picture." This author does admit that epitheliosis of doubtful pathologic significance may occur in older breasts. Ingleby and Gershon-Cohen (54) divide adenosis into four types: A, B, C, and D. Type A is a lobular hyperplasia secondary to an increase in normal ductules. There is an increase in the number of ductal lining cells. Type B, the most common form, is a slight dilatation of ductules with incomplete lobular development because of failure of formation of peripheral ductule branches. Type B may progress, resulting in cyst formation, and an increase in intraductal connective tissue, which may cause formation of fibroadenomas (to be discussed in a later section). Type C is similar to type B, except that type C is located near areas of carcinoma. In type C, the ductule walls show epithelial and basal cell proliferation without a concomitant proliferation of the myoepithelial cells. This lesion is considered to be precancerous, for it is believed that the development of atypical epithelial cells may progress to malignancy. Type D is more commonly

referred to as sclerosing adenosis, a name coined by Urban and Adair (101). Its main importance lies in the possibility of misdiagnosis as cancer (9). Urban and Adair (101) give a comprehensive description of the lesion (type D), describing an early florid phase, and a later fibrous or sclerotic phase.

Microscopically, Urban and Adair (101) describe the florid phase: "...moderate cellular variability may be seen and mitoses are not infrequent. There is often extensive multiplication of duct-like structures. Newly formed ducts often show papillary and solid epithelial plugging. Sometimes solid epithelial islands in which no lumina are visible result from diffuse proliferation. In purely florid areas, connective tissue does not participate. The tendency to lobulation exists even during the florid phase of sclerosing adenosis." The microscopic appearance of the later fibrous phase, by virtue of connective tissue dominance, is characterized by irregular patterns and haphazard isolation of the epithelial columns. Pleomorphism and invasiveness are simulated because of apparent pressure from surrounding stromal change, but nuclear staining is regular and mitoses are rare. Low power observation, however, reveals the lobular nature of the dysplasia, and staining with silver or PTAH* emphasizes the intact basement membrane around the cell groups (9, 28).

Ovarian hormones may be of etiological importance. Moreover, it is suggested that other hormonal secretions, nervous stimuli, and vascular reactions are involved (19, 23, 27, 28, 55).

Sclerosing adenosis is most frequent in the early part of the fifth decade (19, 38, 54). Type B adenosis, however, occurs more frequently

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*Phosphotungstic acid-hematoxylin.

between 25 and 35 years of age (55, 92).

The overall incidence of adenosis in clinically normal breasts varies from 1.5 percent (38), which represents only sclerosing adenosis, to 16.7 percent (92), which represents all forms of adenosis mentioned above.

Fibrosis:

Fallis (36) characterizes mammary fibrosis as an increase in both inter- and intra-lobular fibrous tissue which is frequently hyalinized. Other authors have reviewed the subject, and suggested a relationship of fibrosis to hormonal imbalance (102), to involutional changes associated with menopause (55), to mazoplasia (13), or to adenosis type B (13). Synonyms include fibromatosis (13), hyperplastic fibrosis (55), adenofibrosis (105), and chronic indurative mastitis (102). Warren (105) believes that adenofibrosis, defined as a diffusely fibrotic or finely nodular change without significant epitheliosis, is most prominent before the menstrual period and is relieved by menstruation. Vassar and Culling (102) describe an uncommon variant of fibrosis confined to the stroma and characterized by a dense amorphous deposit of collagen devoid of any epithelial elements.

Animal experimentation suggests that hyperestrogenism is related to the etiology of pathological fibrosis. Associated menstrual irregularities are also reported (102).

The age range of fibrosis is nonspecific. Warren (105) states that pathological fibrosis rarely persists beyond the menopause. Humphrey *et al.* (49) observed fibrosis in patients 20 years and older. Ingleby's *et al.* (55) "hyperplastic fibrosis" occurs around the menopause and

persists into old age, while Vassar's *et al.* (105) variant has an average age of 33 years with a range of 17 to 49 years.

The incidence of fibrosis in 100 clinically normal breasts is 64 percent in one series (49). This is the only figure available, to this author's knowledge.

As in other forms of mammary dysplasia, the pathogenesis of mammary fibrosis is uncertain. Vassar *et al.* (105) suggests that a focus of mammary tissue develops an irreversible noncyclical phase of growth in which periglandular fibroblasts continually deposit stromal collagen. The process is initiated by "...excessive and prolonged intralobular ground substance deposition, with subsequent transformation into collagenous tissue." Special stains, moreover, show metachromatic material to be intralobular and in much greater concentrations than in normal controls. Earlier, Ihnen and co-workers (50) report work contrary to Vassar's *et al.* findings. They indicate that metachromatic material--hyaluronic acid, chrondroitin sulfate and possibly other substances--neither participates in the synthesis of new fibers, nor acts as an interfibrillary cement, in spite of the observed sequence of simultaneous cellular activity, and deposition of metachromatic material, followed by the appearance and growth of fibers in the metachromatic matrix. Even in this sequence, no new collagenous tissue is found, thus the basis of their statement.

Apocrine Epithelium:

The apocrine epithelium or "pale" epithelium has a typical histologic appearance. Foote and Stewart (38) describe apocrine epithelium as consisting of large, columnar cells with small nuclei and

abundant, brightly eosinophilic cytoplasm.

The incidence of apocrine epithelium in clinically normal breasts ranges from 28 percent (49) to 50.7 percent (40). Most series give an incidence near 40 percent (38, 92). The change can occur in all age groups, with a maximum incidence between 56 and 85 years.

The origin of the apocrine epithelium has engendered much controversy. Dawson (22) critically reviewed the subject and cited the two main views of origin: "1) The structures represent actual or altered sweat gland tissue; and 2) they are derived from ordinary mammary tissue." Ewing (35) agrees with the first hypothesis as indicated by his statement about apocrine epithelium developing "...from the sweat glands incorporated in the breast." Dawson did not find any evidence to support the hypothesis of sweat gland origin. Instead, she feels that an origin from mammary epithelium is strongly supported by the fact that transitional areas between normal and apocrine epithelium are frequently observed. She did indicate there may be some merit in the idea of a metaplastic change "...by the formation of cells which recall an earlier stage of development." Dawson also suggests that the pale change may be a post-proliferative degeneration. Cheatle and Cutler (13) refer to apocrine epithelium as a hyperplastic change, "cystiphorous desquamative epithelial hyperplasia", occurring in acini. This change occurring in ducts gives a different microscopic appearance, supposedly because of dissimilar physiologic functions. No further explanation is offered. Foote and Stewart (38) suggest that hyperplasia followed by metaplasia is responsible for apocrine change.

Lendrum (66) attempted to clarify the issue by applying special stains to both mammary gland epithelium and sweat glands from the axillary region. He found that apocrine epithelial cells from both the breast and from the axillary apocrine sweat glands contained identical granules. On the basis of this morphologic similarity, he concluded that the mammary epithelium and apocrine gland epithelium have a common origin from primitive sweat gland epithelium, and the mammary epithelium shows "...misdirected regeneration to a fully apocrine type." Lendrum refers to the misdirected regeneration as apocrine metaplasia. He, therefore, apparently rejects Dawson's idea that apocrine epithelium results from a type of degeneration. Anderson (2) and Keynes (61) support Lendrum's view that the breast is a modified sweat gland. Sandison (92) apparently agrees with Lendrum's arguments. Bloom and Fawcett (5) indicate that there is a similarity of structure and mode of development between mammary glands and sweat glands.

Cooper (18) states that an alteration in gene expression may lead to apocrine change. Since the genomes of the epithelial cells of breast and sweat glands are identical, the particular gene combinations responsible for apocrine differentiation are expressed in response to environmental factors, as yet unspecified. In other words, Cooper suggests an alteration in cell physiology secondary to a difference in genetic expressivity.

Geschickter (41) states that the appearance of apocrine epithelium in the breast is "...a physiologic change, rather than a true metaplasia." On the basis of animal studies where monkeys were given estrogen, and subsequently developed apocrine epithelium, he thinks estrogen

stimulation is probably the cause of apocrine change in humans. Mulligan (79) supports this view.

Apocrine epithelium is almost exclusively confined to the lining of cysts (22, 84); however, this cell type can arise from duct epithelium (2, 22). Parks (84) theorizes that deficient drainage leads to apocrine metaplasia, simultaneously stimulating the formation of the characteristic multiple small papillomata.

It seems possible that some of the opinions cited above have little more than historical value.

Epitheliosis:

Epitheliosis and epithelial hyperplasia are synonymous terms. Dawson (23) coined the term epitheliosis, defining it as an increase in the number of cells lining glandular structures without necessarily any increase in the absolute number of ductal or lobular elements. Epitheliosis can occur in a variety of forms as an "...increase in the number of lining cell layers, or the formation of cellular buds or papillary outgrowths in the lumen" (23). Ryan and Coady (90) describe three forms of epitheliosis: a solid type, a cribriform variety, and a papillary arrangement. Cribriform epitheliosis is intraluminal epithelium in an acinous arrangement lacking stroma. Papillary epitheliosis does not have a fibrovascular core as is seen in true papillomas.

Others, as well, recognized these patterns (9, 92). Foote and Stewart (38) define epithelial hyperplasia as epithelium more than two cell layers in thickness. Cheatle (12) complicates the picture by dividing epithelial hyperplasias into two groups. Class I is a benign

change referred to as "desquamative epithelial hyperplasia", and is characterized by exfoliation of cells from hyperplastic epithelium lining terminal ducts and acini. Class II, "dysgenetic epithelial hyperplasia", is a collection of living and pathological cells which may develop into one of three conditions: a) retention of normal cellular cytology, but the production of papillomata in ducts and acini; b) epithelial hyperplasia with atypism, but without invading connective tissue; or c) additional hyperplasia with invasion of connective tissue.

It is important to remember that two forms of hyperplasia exist: *adenosis*, which is an increase in glandular tissue manifest by an increase in number and size of lobules, and *epitheliosis*, the increase in the number of cells without an increase in number of lobules. Epitheliosis, then, can be associated with any of the other forms of mammary dysplasia (29, 72).

The etiology of epitheliosis and its possible important relationship to carcinoma will be discussed in the section dealing with preneoplasia. Atypism will also be discussed at that time.

The incidence of epitheliosis in clinically normal breasts varies from 22 percent (92) to 39 percent (38) in different series. Most series give a percentage around 30 (21, 93). Davis *et al.* (21) found an incidence of 30 percent in his own work and this was about the same percentage as found by several other authors. Sandison (92) notes that the most common form of epitheliosis is the papillary type, which, in "pure form", accounts for 47.1 percent of all cases of epitheliosis.

The age range is variable with Sloss *et al.* (93) reporting two peaks in incidence: one peak between 50 and 59 years and the other

between 70 and 79 years. Sandison (92) states that epitheliosis "...does not manifest itself in the younger woman without adenosis or lobular hyperplasia." This author's data also indicate a sharp rise in incidence from 6.1 percent of clinically normal autopsy breasts in the 36 to 40 year group, to 26.7 percent of clinically normal autopsy breasts in the 41 to 45 year group.

Papillomas:

Warren (105) describes the *duct papilloma* as composed of stromal fronds covered by ductal epithelium. Papillomas are commonly attached to the wall of the duct at only one point, and project into the duct lumen. The epithelium is usually cuboidal, rarely columnar. Cappell (9) points out that the stromal bands are composed of both fibrous and vascular elements, and the epithelium is most frequently only two cell layers thick. Duct papillomas most commonly occur in the ampulla of the terminal ducts or in the lactiferous sinuses (2, 29, 104, 105, 107). They are multiple in approximately 17 percent of cases (105). The duct papilloma is occasionally referred to as an adenocystoma.

Duct papillomatosis (38) is a widespread form of the disease which is always multifocal (38, 107), but usually unilateral (107). This lesion is difficult to distinguish from the papillary form of epitheliosis; however, the presence of well-formed stromal cores favors papillomatosis (9, 92, 107).

Duct papillomatosis is more likely to be premalignant than is duct papilloma (9, 18, 38, 105, 107). This possibility will be discussed in greater detail in the section dealing with preneoplasia.

Benign intracystic papillomas arise in cysts and comprise an estimated 30 percent of papillomas (41). However, in another series (92), only 3 of 23 cases of papillomatosis were found in cysts.

The incidence of papillomas in a series of clinically normal autopsy breasts varied from 2 percent (49) to 29 percent (58 of 200 cases) (38). In a series of 800 clinically normal autopsy breasts, 23 cases (2.9%) had papillomatosis (92).

The age range is approximately the same as in epitheliosis, with all of Sandison's (92) examples being over 40 years of age. Sandison's data show no definite peaks in incidence after 40 years.

Papillary cystadenoma is glandular growth exhibiting a somewhat papillary pattern, but which is composed of acini (ductules) without the fibrovascular core characteristic of the papilloma (9, 29).

An incomplete perusal of the literature did not reveal a suggested etiology for duct papillomatosis. However, Geschickter (41) points out that duct papillomas occur in that part of the mammary gland which seems to be <u>least</u> sensitive to hormones: the duct ampulla and lactiferous sinuses.

<u>Fibroadenomas</u>:

In 1923, Cheatle (11) carried out an extensive study of fibroadenomas (43, 92). Three types of proliferation were observed: first, hyperplasia of the fibrous elements interior to an elastic layer surrounding the ducts; second, hyperplasia of the elastic layer itself; or third, hyperplasia of the fibrous tissue exterior to the elastic layer. The first change affects localized ducts or acini, or both, in a more diffuse form. The second type exists only as a diffuse change.

The third is either localized or diffuse involvement of pericanalicular and periacinar areas. Sometimes the proliferation is only intracanalicular in location.

Most authors now classify fibroadenomas as either intracanalicular or pericanalicular (1, 2, 9, 36, 105). Intracanalicular fibroadenomas have an increased amount of connective tissue which projects into or indents the lumina of ducts, producing a distinctive pattern of numerous curved and branching clefts lined by epithelium. Pericanalicular fibroadenomas resemble normal breast, but there is an increase in fibrous and epithelial elements giving the picture of enlarged fibrous lobules.

Fibroadenomas are often associated with adenosis (1, 29, 107) and cysts (1); however, one study did not note any association with dilated ducts in 21 cases of fibroadenoma (40).

The etiology may be related to fibrous tissue proliferation of subepithelial, pericanalicular, or periacinous origin (13), secondary to an increase in estrogen levels (1, 2, 43, 52). Tissue hypersensitivity may be involved as well (1, 50). Fibroadenomas respond to cyclic variations in hormone levels, as does the normal breast. However, the response of the fibroadenoma is out of phase, tending to lag behind the rest of the breast (52). In pregnancy it may rapidly increase in size (46).

The incidence in "normal" breasts according to Franz, Pickren, Melcher, and Auchincloss (40) is 9.3 percent of 225 breasts, while Sandison (92) gives an incidence of 0.5 percent in his series of 800 autopsy breasts. However, Sandison found 110 (approximately 11%) fibroadenomas in an earlier study of 1,010 surgical specimens (91). The majority are found in young women (1) with over 50 percent of

fibroadenomas occurring in the third decade, dropping sharply (to approximately 5%) in the fifth decade (92). The reported average age of incidence varies from 21 years (Giacomelli cited by Haagensen, 43) to 33.5 years (43).

The pathogenesis of fibroadenomas is generally thought to be an overgrowth of connective tissue with resulting pressure causing compromise of duct lumina (2, 84). Willis (107) has noticed small satellite fibroadenomas in areas of adenosis and suggests that they enlarge, coalesce, and form a lobulated mass. Therefore, early growth is by accretion and proliferation. Parks (84) became intrigued with the mechanism of development of duct shapes seen in the two types of fibroadenomas, and points out that the terms pericanalicular, and intracanalicular, imply that the ductule pattern is determined by the connective tissue. "If, however, the epithelium is credited with determining structure, as in other epithelial organs..." then the ducts will develop as they will, and connective tissue will be secondarily evoked around them. Parks (84) suggests the adjectives *tubular* and *laminar* be used to identify the two types of fibroadenomas, thereby stressing the epithelial component, rather than the connective tissue component.

When a fibroadenoma continues to proliferate and acquires a size of 10 cm or greater (1) it is labeled *cystosarcoma phylloides*. Generally a more cellular stroma is present. The stroma is suggestive of fibrosarcoma, even though most are still benign (43). It is estimated that approximately 2 percent of fibroadenomas develop into cystosarcoma phylloides (43). Malignant sarcomas are generally preceded by

fibroadenomas (1), and usually occur in the early years of the fifth decade (1, 29, 43). Haagensen (43) and Dawson (30) report several studies by other authors which indicate that 2 to 23 percent of cystosarcoma phylloides have a malignant component.

Mammary Duct Ectasia and Plasma Cell Mastitis:

Haagensen (42, 43) defines mammary duct ectasia as "...a condition of the breast characterized by dilatation of the ducts, and fibrosis and inflammation around them...." One of the basic features is the absence of epitheliosis. The dilatation involves primarily the terminal collecting ducts or lactiferous sinuses (42, 43, 78). Crystalline bodies (42, 43) or fatty acid crystals (88) are a common microscopic finding. Lepper and Weaver (67) found the composition of the crystalline bodies to be almost entirely neutral fat. Colostrum or fatty macrophages, found frequently in ductal lumina, are part of the histologic picture as well (1, 42). Theoretically, the colostrum cells may result from: 1) fatty degeneration of exfoliated epithelial cells; or 2) macrophages that migrate across the duct wall (25). Sandison (92) finds it difficult to distinguish between ectatic ducts and cysts, and does not differentiate the two at the microscopic level.

The peak age of incidence is between 52 and 62 years (43). Frantz *et al.* (40) found a 25 percent incidence in "normal" breasts. Of those breasts, more than 95 percent are in postmenopausal women.

The pathogenesis (42) may involve an abnormality of the involution process following menopause. Debris becomes stagnant in duct lumina and is irritating, causing reactive fibrosis and inflammation. Keynes (61) feels the prime cause of stagnation is the plugging of duct

outlets. Eventually the intraluminal material breaks through the epithelium and duct wall into the periductal fat, inciting inflammation similar to fat necrosis. Giant cells surround the lipid. When the process is most severe it is termed *plasma cell mastitis* (42, 78, 88).

Rodman and Ingleby (88) suggest that degradation products secondary to the action of lytic enzymes, acting on milk-like substances secreted under certain conditions in non-pregnant breasts, may be the inciting agent.

Anderson (1) discusses the entire subject under the heading of plasma cell mastitis, stating that it is an uncommon disease. A history of difficult nursing can be elicited in 50 percent of cases. The importance of this entity is its clinical mimicry of cancer (1, 43).

Mammary Dysplasia and Carcinoma.

Although most authors believe that there is a positive correlation between the presence of mammary dysplasia and subsequent development of carcinoma, such a relationship has not been definitely proved. Comparison of many clinical series is difficult because of variation in nomenclature, incomplete historical data, uncertainty as to the positive or negative effects of biopsy procedures and treatment, and differences in diagnostic acumen, patients' awareness, geographical location, economic status, etc. Moreover, as Patey (85) points out, histopathology can be present without clinically detectable disease. It is also true that clinical findings can be present with very little associated histopathology.

There is a great deal of disagreement as to the relationship between mammary dysplasia and carcinoma. Historically, Astley Cooper (17) was

the first to record the coexistence of the two diseases. In 1880, Bilroth, cited by Keynes (61), concluded that cancer does not develop in an otherwise "normal" breast. In 1915, McCarty and Mensing, cited by Keynes (61) and Foote *et al.* (38), observed mammary dysplasia in 100 percent of 967 cases of carcinoma of the breast. Early observations such as these generated numerous studies which attempted to conclusively prove or disprove the existence of a positive correlation.

Hodge, Surver, and Aponte (47) quote studies by other workers which indicate that the coexistence of carcinoma and mammary dysplasia averages 1 to 2 percent of cases, giving no significant correlation between the two diseases. In their own series, Hodge *et al.* studied 876 cases, and observed that mammary dysplasia and carcinoma coexisted in 3.1 percent of cases. Geschickter (41) presented a series of 3,700 breasts, of which 2,500 had carcinoma, and 1,200 mammary dysplasia. The two diseases co-existed in only 19 cases.

Most studies favor a positive correlation between mammary dysplasia and carcinoma (2, 3, 10, 14, 21, 41, 43, 48, 68, 69, 72, 73, 104, 105). Clagett, Plimpton, and Root (14) followed 442 patients with mammary dysplasia for 5 to 6 years. Seven (1.8%) developed carcinoma in this period of time. This incidence is approximately five times the incidence in the population at large. In a similar study, Marcuse (72) followed 794 patients with mammary dysplasia. In all, 36 (4.5%) of the patients had coexisting mammary carcinoma. As reported by Copeland (19), the Metropolitan Life Insurance Company gives statistics which indicate an increased risk of mammary carcinoma in women with mammary dysplasia. These data give an overall incidence of mammary carcinoma

for the population at large (United States) of 0.42 percent with a slightly higher risk in the 35 to 45 year age group; the incidence in patients with known dysplasia is 4 percent, or about 10 times greater.

One of the most widely quoted studies is that of Warren (104, 105), who found a 4.5 times increase in the incidence of carcinoma in women with mammary dysplasia, as compared with a partially matched control group (age and geographic location) without the disease. On an age basis, women in the 30 to 39 year group with mammary dysplasia had an incidence of carcinoma which was 11.7 times that of women without the disease. Women over 50 years of age developed cancer at a rate 2.5 times the normal incidence.

Comparisons of the average age of occurrence of mammary dysplasia and mammary adenocarcinoma give indirect evidence of a relationship between the two diseases. Patients developing mammary dysplasia have a peak incidence at approximately 39 years (38, 41, 47, 68), while the peak age of incidence of mammary carcinoma is approximately 50 years (2, 29, 38, 47). Such information suggests that it may take 10 to 20 years for some of the changes of mammary dysplasia to progress to mammary carcinoma (75).

The upper outer quadrant of the breast is most frequently involved by carcinoma (29, 79, 100). Some authors report that mammary dysplasia is uniformly distributed throughout the breast (100). The data of Hodge *et al.*, however, (47) indicate that 60 percent of mammary dysplasia is also found in the upper outer quadrant, supporting the idea that a positive relationship exists between mammary dysplasia and carcinoma.

Bloodgood (4), in 1921, found that of 350 breasts with cysts, 2 developed carcinoma and that these 2 breasts had other associated non-specified benign changes. Thus he concluded, "...there is no relationship between single and multiple blue-domed cysts...and carcinoma." Later, work by Copeland (19) and Ochsner (82) confirmed the low incidence of carcinoma in breasts with only cystic changes. Boyd (7) and, later, Dawson (29) pointed to the importance of cysts with an associated papillomatosis and epitheliosis, both of which have a positive relationship to subsequent development of neoplasia.

Adenosis is a more frequent finding in breasts with carcinoma than in those without (38). Papillomas (38, 97) and epitheliosis (41) are also more frequent.

Fibrosis is mentioned only to exclude it from consideration, as most authors deny any correlation with any epithelial hyperplasia (36, 55, 102, 105).

Apocrine epithelium is generally considered to have little if any preneoplastic significance. However, Cooper (18) and Stewart (95) observed rare instances in which there were transitions from atypical apocrine epithelium to apocrine cell, or "sweat gland", carcinoma.

Anderson (2) considers the solitary papilloma of little importance (see also Haagensen, 43, and Bloodgood, 4). Geschickter (41) studied a series of 54 breasts with intracystic papillomas; 6 percent of the papillomas had focal areas of carcinoma. This is well above the expected rate. Charteris (10) noted an occasional papilloma progressing into carcinoma.

Evidence concerning papillomatosis is more definite. Ewing (35) and Muir (77) have traced a complete series of histopathological

transitions from early papillary projections to frank carcinoma. Ewing cites several other authors who have recorded similar transitions. Warren (105) and Willis (107) noted an increased propensity for carcinoma in breasts with papillomatosis. Willis (107) likens the situation to multiple polyposis of the bowel where a greater incidence of carcinoma is seen. Foote and Stewart (38) indicate that the incidence of atypical papillomas in carcinomatous breasts is 5 times greater than in normal breasts. A definite positive relationship appears to exist.

What is the common denominator in the dysplastic lesions associated with carcinoma? Cheatle (12) and Cheatle and Cutler (13) suggest that epithelial atypism plays a major role in carcinogenesis. Charteris (10), in 1930, felt that epitheliosis progresses almost imperceptibly into carcinoma. Foote and Stewart (38) indicate the existence of a positive relationship between the presence of epitheliosis and carcinoma of lobular origin. Moreover, they found that ductal epitheliosis was present in 57 percent of carcinomatous breasts, as compared with 39 percent of non-carcinomatous breasts. Davis *et al.* (21) state that solid ductal hyperplasia is more likely to be associated with carcinoma than is papillomatosis. Kaier, cited by Dawson (29), followed a series of over 300 cases of mammary dysplasia in which carcinoma developed in 45 percent when ductal epitheliosis was present, compared to 3 percent when another form of dysplasia was dominant. Other workers support a specific relationship of epithelial hyperplasia to carcinoma (29, 40, 82, 90, 100).

In 1933, Dawson (23) concluded that most epitheliosis which eventually gave rise to carcinoma was localized in small, terminal intralobular ducts. She reaffirmed her view in 1958 (29), but broadened it

somewhat, saying that early carcinoma was always an *intraductal* cell proliferation: "malignant epitheliosis". Charteris (10) thought that the precancerous epitheliosis was primarily of ductal origin. In 1962, Humphrey and Swerdlow (48, 49, 97) published several reports further localizing the significant hyperplastic changes to the larger ducts.

Of crucial significance is the frequent presence of atypism in cases of epitheliosis. Foote and Stewart (38) found that atypical cells were five times more common in papillomas than in the epithelium of normal breasts. Tellum *et al.* (100) observed atypism 6 to 7 times more frequently in breasts with coincident carcinoma than in those without. Charteris (10) and Stewart (95) feel that there is a definite progression of epithelial change from normal to simple hyperplasia, to atypism, and finally to malignancy. Muir (78), McLaughlin, Schinker, and Tamisiea (75), and Dawson (27) support this view, as do several authors cited by Sandison (92). In another study, Mulligan (79) observed that atypical hyperplasia was five times more common in cancerous breasts than in breasts without carcinoma.

Jackson and Orr (58) studied a series of 400 breasts, and their data suggest that epithelial hyperplasia is significant only if accompanied by an increase in subepithelial connective tissue. There is a question as to whether the stromal change precedes, or follows, the epithelial change. Cheatle and Cutler (13) suggest that in cases of connective tissue alterations, the remainder of the breast should be searched for a more serious lesion. Cooper (18) observes that the walls of ducts involved by severe epitheliosis usually are thickened by proliferation of fibrous tissue. While Cooper is not certain as to whether

the stromal change precedes, coincides with, or follows the epithelial change, he favors the position that the connective tissue plays a more important role than has previously been admitted.

Because more significance is presently attached to atypism, the recognition of the cytologic and associated histologic changes are important. Ingleby (51) says the earliest sign of "malignant change" is an increase in the size of cells lining ductules. Associated cytological alterations include enlarged, pale nuclei with irregular outlines, variation of cellular size, irregularities of staining, swollen and vacuolated cytoplasm, hyperchromatic nuclei, increased number of mitoses, and loss of cellular polarity (3, 16).

Swerdlow and Humphrey (97) use the following grading system to determine the severity of the changes: (1) *slight*--no atypia and normal organization; (2) *moderate*--cells crowding the duct lumina, no atypia, and normal organization; and (3) *severe*--atypia, loss of polarity, and subtotal to complete filling of the duct lumina with epithelial cells.

Ryan *et al.* (90) uses a more complicated but useful grading system: (1) *grade I (minimal)*--epitheliosis composed of well differentiated cells having a papillary or cribriform pattern; (2) *grade II (moderate)*--more significant epitheliosis in any pattern composed of fairly mature cells; (3) *grade III (marked)*--profuse accumulation of atypical, immature, but histologically benign epithelial cells, often occluding intermediate and larger sized ducts; and (4) *grade IV (malignant)*--intraductal proliferation of any pattern without invasion of stroma.

Preneoplasia (Precancerous).

Stewart (96) feels, "A lesion is to be thought of as precancerous

if cancer is added more often to it than when it is not there." DeOme (33) defines a preneoplastic lesion as one that has an *increased probability* of developing into a neoplasm.

Layton (65) adds that labelling something as precancerous "...does not signify that the lesion leads inevitably to invasive cancer, but only that it may do so." He goes on to summarize the histopathologic definition as a"...proliferation of atypical cells displaying a signal lack of normal maturation and differentiation in absence of stromal invasion." In relation to the breast, Cheatle (12) further defines preneoplasia as histologically malignant epithelium which is not invasive, that is, still confined within the ducts. When myoepithelial elements are present, the epithelium is regarded as non-invasive at that site (63). Evidence presented earlier in this thesis would indicate that epitheliosis is one lesion which is likely to be precancerous in the breast and is the possible common denominator for dysplastic lesions which progress to carcinoma.

Carcinoma-in-situ (Intraductal Carcinoma).

Bonser and Jull (6) describe carcinoma-in-situ as the presence of histologically malignant cells confined to the tissue of origin, and which are potentially infiltrative. Carcinoma-in-situ, then, is thought to arise by progression of epitheliosis. Sternberg (94), Foote and Stewart (37), Stewart (96), and Muir (76) all concur with this concept. These authors also believe that carcinoma-in-situ is surely a precursor to infiltrative cancer, but it may take several years to become infiltrative, with some lesions regressing. This view is supported by the previously mentioned differences in age-related incidences of mammary

dysplasia and carcinoma. The progression of carcinoma-in-situ to invasive carcinoma does not occur by mere extension in space and time, but rather by acquisition of abilities the cells did not possess before (39).

An experiment by Louis (70) demonstrated a presumed difference in biologic behavior between benign and malignant epithelial cells of the human breast. He used a histochemical technique which caused fluorescent staining of cells thought to be benign, but left apparent malignant cells unstained.

Another study by Cohen (15) measured the glucose-6-phosphate dehydrogenase activity in hyperplastic cells and in malignant (neoplastic) cells of the human breast. The results showed the greatest activity in the epithelial elements of intraductal proliferations and intraductal carcinomas. When compared with normals and tumors the invasive elements exhibited activity lower than the same tumor still confined within the ducts. This change suggests that alterations of metabolic pathways correlate with the change from normal to neoplastic behavior.

Dunn (34) summarizes the impressions presented thus far: "the histopathologic picture seems to be a continuum in which dysplasia shades imperceptibly into carcinoma-in-situ and carcinoma-in-situ shades topographically into questionable microinvasion and finally classical invasive cancer...."

Etiology and Mechanisms of Mammary Carcinogenesis.

Willis (107) reports a still prevalent unicentric idea of tumor

origin based on the erroneous hypothesis of Cohnheim*. However, he believes tumors arise, not from a single minute focus, but from a large field of prepared tissue. Others support this view (7, 39, 76, 77, 94).

Foulds (39) believes that tumors emerge focally and not diffusely, "...but it is not obligatory to presume that initiating carcinogenic action is limited to the places where tumors emerge or that the time and site of emergence and the qualitative variety of the tumors are determined, once and for all, at the time of initiation." He goes on to propose an alternative hypothesis that initiation establishes a region of *incipient neoplasia* or literally "the beginnings of neoplasia" which "...is coextensive with the area of exposure to carcinogen and has a permanent new capacity for neoplastic development." Initiation, then, is rapid and irreversible, establishing a region of incipient neoplasia, but is not yet manifest by morphologic changes. It is possible, following initiation, for a lesion to receive repeated stimulus and progress to "...<u>developmental imminence</u>, when lesions emerge without extensive stimulation or in response to minor and nonspecific stimuli which account for the localization."

Womach (108) postulated a similar theory in 1958 based on results obtained by others working with skin carcinoma in rabbits. He says two factors are involved in carcinogenesis: A) *initiating factor*, which is irreversible and may be of genetic or viral origin; and B) *promoting*

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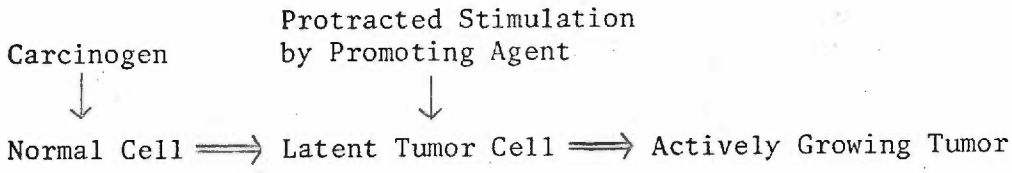
*A theory formulated more than 80 years ago based on the concept that tumors arose from cell-rests or groups of cells which had failed to mature during normal developmental growth. The cell-rests would persist in an embryonic state with an ever present malignant potential. This theory was widely accepted for many years and led to the unicentric theory of tumor origin.

factor, which is nonspecific, slow in action, reversible, and may be hormonal or physical (such as trauma) in origin.

Bonser *et al.* (6) suggest a stage theory of carcinogenesis which is similar to one proposed for mouse mammary carcinoma (31, 32, 33). The following schema summarizes this idea:



General Factors Related to Mammary Carcinoma.

Several variables have been suggested as related to variation in susceptibility to breast cancer. The list includes: (1) inverse relationship to parity (59, 107); (2) positive association with failure to nurse, premature weaning, or other errors of lactation (25, 43, 59, 107); and (3) positive or negative association with ill-defined host factors, such as metabolic, immunologic, and psychologic responses of the patient (8, 44).

Haagensen (43) quotes several studies by other authors supporting the view that there is a genetic basis for susceptibility to breast cancer. Kaplan and Acheson (59) agree that it is almost inconceivable that genotypic susceptibility does not play some role in the pathogenesis of every multifactorial disease. Supporting the genetic role are the strain variations in susceptibility of mice to mammary tumor development (31, 107).

Trauma was mentioned as a possible promoting factor earlier (108); however, Haagensen (43) doubts this after reviewing the histories of afflicted patients.

In a study quoted by Charteris (10), chemical carcinogens were shown to stimulate formation of duct papillomas in rabbits. Such findings support the hypothesis that retention of secretion in ducts may lead to malignancy. The retained secretion could act as a predisposing factor (10). Secretory material, retained for prolonged periods, might undergo changes in chemical composition, with the formation of compounds causing chronic irritation (10, 29). Enzymes acting on retained secretion could be responsible for the appearance of specific carcinogenic compounds which might then act on the epithelial cells to produce neoplasia. The effect of carcinogens in mammary tumorigenesis is supported by work with several different strains of mice (31, 33). Animal experiments, referred to by Willis (107), show an increased incidense of carcinoma in low incidence strain mice following rapid breeding and artificially or naturally produced duct stasis. The suggested mechanism of action was combined estrogen and chemical stimulation by static secretory products.

No direct evidence is available to support a role for oncogenic viruses in the genesis of human breast cancer (59). Kaplan *et al.* (59) quote a review by another author which suggests that viruses could play a role in causation of some cancers at any site. Recent work by DeOme (31, 32, 33) has helped clarify the role of viruses in the mouse mammary tumor system, and will be discussed later.

The carcinogenic effect of radiation on breast tissue was supported in a study cited by Kaplan *et al.* (59). A most recent article presents evidence which, with fair certainty, establishes the carcinogenic effect of radiation on breast tissue (103).

The exact role that hormonal stimulation or hormonal imbalance plays in mammary carcinogenesis is not clear. Evidence has been gathered which implicates a role for estrogens in the genesis of mammary carcinoma (2, 26, 31-33, 43, 59, 77, 80, 107). There is no proof to date, however, of a primary role for estrogens in human breast cancer. Anderson (2) points out an increased risk in females with a delayed onset of menopause, implying a relation to prolonged estrogenic stimulation. Kaplan *et al.* (59) review the castration theory, which postulates that the critical factor which correlates positively with increasing risk of mammary cancer is the total number of menstrual cycles which a woman experiences during her life. This implies that ovarian hormones either initiate or augment carcinogenesis. Willis (107) reviews several animal experiments which indicate strongly that estrogen definitely influences carcinogenesis.

Nathanson (80) suggests several ways in which estrogens could act to produce atypical clones of mammary epithelial cells. First, physiologic amounts of the hormone may act on overly sensitive tissue. This change may be secondary to altered host metabolism, cellular milieu, or action of exogenous agents. Secondly, increased amounts of estrogen may be present due to decreased metabolism of the hormone by normal processes, such as in liver disease. Thirdly, there may be a simple overproduction. Fourthly, atypical hormones may be produced by the host which are in themselves carcinogenic. Lastly, there may be a lack of hormone which normally stimulates the breast, but now allows another agent to act on altered epithelium.

Cooper (18) postulates that *de novo* cancers (7, 96) (those without evident preliminary hyperplasia) may arise from foci of epitheliosis within larger fields of epithelium which overreact to hormonal stimulation. The hormone stimulation may subsequently decrease, possibly because of normal cyclical variation, or because of other reasons, allowing the epithelium surrounding the focus of malignant cells to assume its original "non-stimulated" appearance. If the tissue was removed at that particular time, it would then be possible to reason that the neoplastic foci observed arose in an area without any preceding epitheliosis.

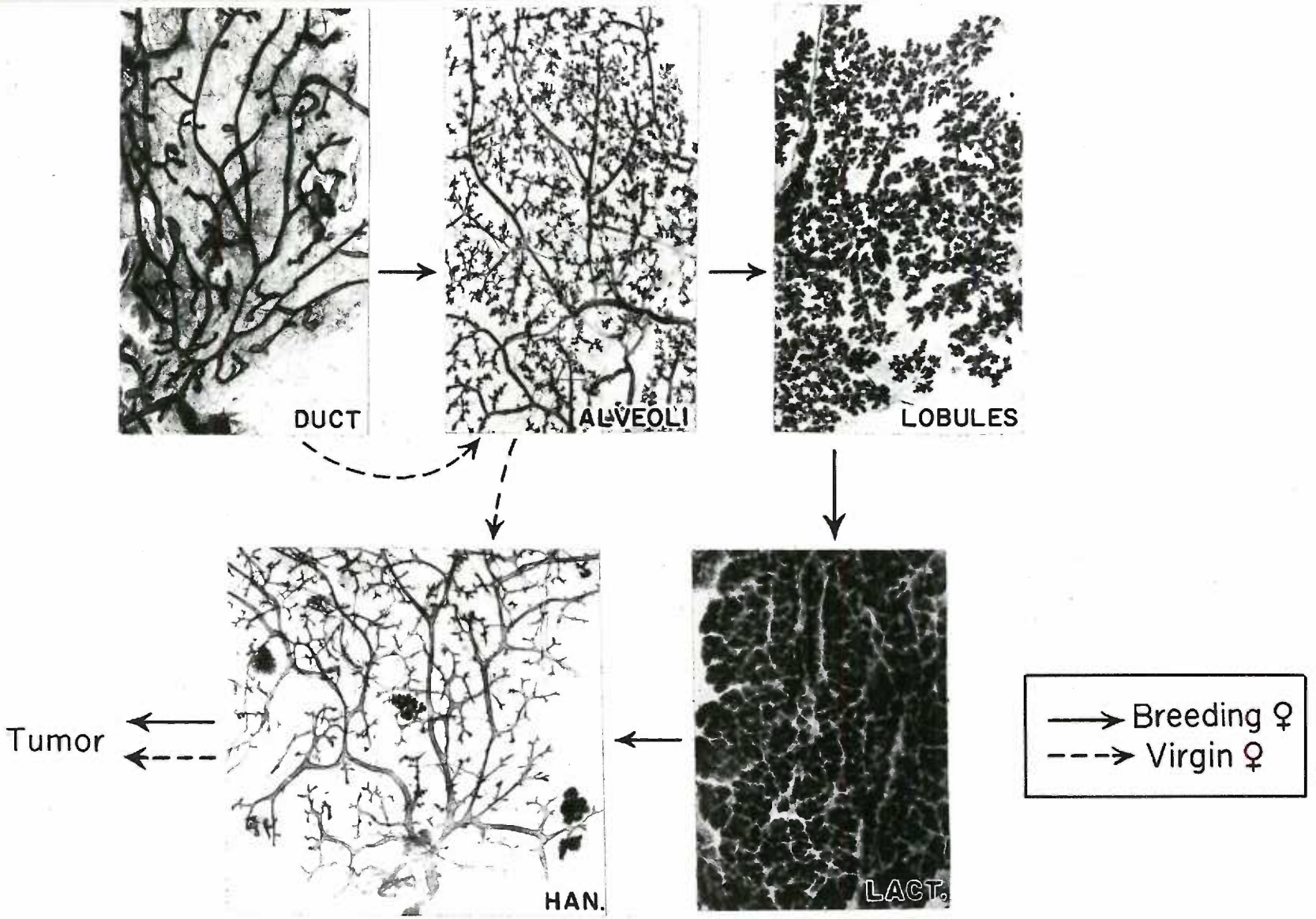
Mouse Mammary System.

The mammary glands of certain strains of inbred mice give rise to mammary adenocarcinomas in high incidence. *At least some of these adenocarcinomas arise from a preneoplastic lesion* (hyperplastic alveolar nodule) *recognizable at the subgross level*. Because of the obvious analogy to the present work, the literature pertinent to mouse mammary tumors will be briefly reviewed (31-33).

Whole mounts of mammary glands of mice reveal the ductal and lobuloalveolar patterns related to different physiologic states (see Figure 2). In early pregnancy the ductal system becomes more complex, progressively developing increased numbers of lobules until the entire fat pad is filled. Following parturition and lactation the hormonal stimulation required to maintain the lobuloalveolar development decreases, and the gland regresses in such a manner that only ducts and a few solitary alveoli remain. In C3H mice (and some other strains)

Figure 2:

The sequential development of the breast of a pregnant C3H mouse shows progression from the ducts to alveoli to non-lactating lobules to lactating lobules. The hyperplastic alveolar nodule (HAN) may develop from the lactating lobules of the pregnant mouse (solid lines) or from the alveoli of the virgin mouse (broken lines). Courtesy of K. B. DeOme, Cancer Research Genetics Laboratory, University of California, Berkeley, California.


DUCT
ALVEOLI
LOBULES
HAN.
LACT.
Tumor
Breeding ♀
Virgin ♀

older than about 6 months some of the lobules fail to regress; these are the precancerous hyperplastic alveolar nodules (HAN). By definition the HAN are partially independent of hormonal control since they exist in the mammary gland of the non-pregnant animal.

By devising a technique allowing transfer of the HAN into cleared mouse mammary fat pads, that is, fat pads free of any epithelial elements (32, 33), it was demonstrated that some epithelial outgrowths from the HAN were preneoplastic (i.e., statistically more likely to give rise to adenocarcinoma than normal tissue). A schema was then proposed showing the cellular alterations occurring in the process.

$$\text{Normal cells} \Longrightarrow \underset{\text{(HAN)}}{\text{Nodule cells}} \Longrightarrow \text{Neoplastic cells}$$

In contrast to normal cell populations, the nodules represent populations of cells possessing increased tumor producing capabilities, though the entire cell population of the nodule may not become neoplastic.

Interest then centered on possible forces, first, driving the "equation" from the normal cells to the nodule cells, and, second, driving the nodule cells to neoplastic cells. Several "nodulogenic" (normal cells to nodule cells) agents have been shown to be involved in the first step of the reaction. They are:

1) *Viruses*--specifically mammary tumor virus (MTV), nodule inducing virus (NIV), and A_3 virus which is a variety of MTV.
2) *Chemicals*--specifically including 3-methylcholanthrene and urethane.

3) *Prolonged hormonal stimulation*--specifically somatotrophic hormone (STH) and mammogenic hormone (MH).

4) *Irradiation*.

Likewise, agents speeding the second portion of the reaction were discovered and include:

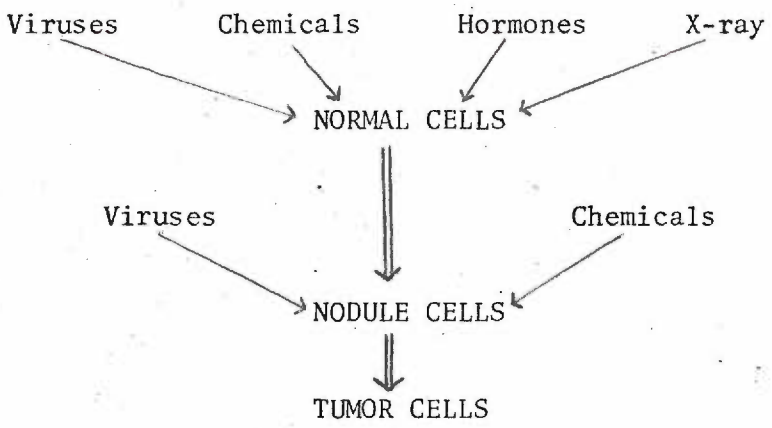
1) *Viruses*--MTV and NIV.

2) *Chemical carcinogens*.

The prolonged hormonal stimulation acts primarily on the normal cells and only slightly affects the progression of nodule cells.

Through several experimental procedures, characteristics could be attached to nodules which differentiated them from normal cells and tumors. Their hormonal requirements are altered; they are less dependent on progesterone or mammotropin for their maintenance. Histologically, HAN's have a normal lobuloalveolar structure. In the absence of virus, three different tissue antigens are identified for the three tissues: normal, nodule, and tumor. In cell culture, the normal cells survive approximately three times the life span of the animal, while tumor cells survive for an indefinite period of time, with nodule cells approaching the latter. Finally, the HAN has the ability to produce a tumor (31-33).

Therefore, the previous schema can be altered to the following:



The question now arises, is this model applicable to the human system? Inasmuch as one suspects that one or more of the lesions of mammary dysplasia may be analogous to the subgross HAN of mice, a first step would seem to be a study of subgross structures in human breast. Therefore, the purpose of this study is to identify the range of subgross morphology in a group of human breasts, in order to provide a tool for future analysis which may lead us to the identification of human analogues of the HAN. Once these precancerous lesions are clearly identified, experimental analysis becomes feasible.

MATERIALS AND METHODS

TISSUE

Whole human mammary glands, free of overlying skin, were obtained either from autopsy or from surgical mastectomy specimens. For purposes of orientation a suture was tied to the medial edge of the breast at the level of the nipple.

A total of 27 breasts were studied, with an age range from newborn to 88 years; 13 patients were 40 years or less, while 14 were older than 40 years. Two breasts were in a prelactating state. Three breasts were from radical mastectomies, and 1 from a simple mastectomy. Approximately 1875 paraffin blocks were taken from the 27 breasts, giving an average of 75 blocks per adult breast.

SECTIONING AND FIXATION

Either fresh or previously fixed tissue was cooled to a temperature of about 4° C in a refrigerator in order to solidify the tissue and facilitate slicing. The entire mammary gland was serially sectioned with a Hobart meat slicer, model 1712, into 1 to 2 mm slices, cut in the parasagittal plane. The sections were kept spacially oriented by means of an India ink marker on the inferior border, stacked in order, and separated by paper towels. The slices were further fixed in 4 to 5% formalin for 24 hours prior to defatting.

DEFATTING

The stacked sections were defatted in plastic or glass vessels in

two or three changes of acetone over a period of 48 hours. The sections were next strung on thread to maintain positional relationships during the remaining steps. Washers, cut from polyethylene tubing, were used as spacers to separate the individual sections.

HYDRATION

The sections were hydrated in a graded series of ethanols (100%, 95%, 70%), one hour each.

STAINING

Staining was accomplished in 2 to 3 hours with Harris' hematoxylin, adjusted to pH 1.0 with 1 N HCl. At this low pH only nuclei were stained; at a much higher pH the specimens stained deep blue and were impossible to interpet.

WASH

Groups of sections were loosely bound in gauze, and washed overnight in running alkaline tap water, utilizing an ordinary pipette washer.

DEHYDRATION

The sections were dehydrated in a graded series of ethanol or isopropanol (50%, 70%, 95%, 95%, 100%, 100%), one hour each.

CLEARING

Clearing was accomplished in two 1-hour changes of toluene.

STORAGE

The sections were stored in methyl salicylate in polyethylene bags (circa 6" x 8" size) which were heat-sealed to prevent leakage. Three to 5 sections were placed in each bag. Care was taken to remove bubbles from the bags and to minimize the amount of methyl salicylate so that the bags remained flat. Each breast, now sealed in a variable number (10 to 50) of plastic bags, was placed in a file folder and stored in a filing cabinet, approximately 10 to 12 breasts per drawer. Excess methyl salicylate was wiped off the outside of the bags with a solution of 50% absolute ethanol and 50% ethyl ether before storage, and absorbent paper spacers (e.g., paper towels) were placed between the bags. The specimens were stored in a dark place to prevent fading of the stain. The procedure to this point required about 6 days.

EXAMINATION

The specimens were next transilluminated by means of a light box and examined with a dissecting microscope (see Figure 3). Focal lesions for photography and future paraffin sections were circled and numbered on the outside of the bag by means of a felt pen containing water-insoluble ink. Lesions were then photographed at 5 to 20 X using a compound microscope or macrophotography equipment. Finally, windows were cut in the bag overlying selected tissue structures, and blocks were cut from the specimens for paraffin embedding. Thus, subgross morphology could be correlated with histopathology.

RESULTS

The sections of human mammary gland, measuring 1 to 2 mm in thickness, numbering approximately 10 to 100 per gland, and stored in plastic bags, appeared as illustrated in Figure 3. The sections were easily transilluminated and photographed, yielding results exemplified in Figures 4, 7, 9, ...330 labelled "Subgross..." in the appropriate captions. Following photography the specific subgross lesions under observation were removed, allowing the preparation of matching histologic sections of good quality for correlation with the subgross morphology, as shown in Figures 5, 6, ...331 labelled "corresponding histology..." in the appropriate captions.

DUCTS

Figures 4 through 39 represent normal duct configurations found in all 27 breasts. Figures 4 and 7 are photographs of the duct pattern in the infant breast. The entire duct system in Figure 4 is sharply delineated from the surrounding fat pad. Figure 7 illustrates large ducts with several duct buds protruding into surrounding stroma. In the corresponding histology (Figures 5, 6, and 8), thickened duct epithelium and amorphous intraluminal material are evident.

The ducts in the adult breast are illustrated in the remaining examples (Figures 9 through 39). In Figure 9, fibrous bands containing ducts (arrow) separate surrounding fat lobules. Mammary ductal and lobular components are usually localized to the fibrous bands between the lobules of fat. Occasionally, epithelial components are found within the fat lobule. The ducts generally appear as simple tubular

structures of varying sizes with thin delicate walls. Others, however, may be thin, arborized formations (Figures 19 and 21) or ribbon-like (Figure 38). The thin walls may occasionally appear thicker as in Figure 27. The thickening is apparently due to closely packed duct buds or evaginations of duct wall epithelium (Figures 28 and 29).

The majority of larger ducts have longitudinal linear folds, here termed "scalloping", easily seen in Figure 11. Cross-sections of ducts (Figures 13, 25, and 27) with scalloping have visible folding of the walls. The correlative histology points out the variation in intraluminal projections, with Figure 14 having less numerous but prominent, thin invaginating stromal ridges, while Figures 26 and 27 illustrate broad but less penetrating bands.

The duct lumen is easily located in all of the examples except where the luminal diameter approaches the thickness of the duct epithelium as in portions of Figure 21.

Figures 34 and 36 represent differing normal duct configuration.

LOBULES

Varying normal lobular configurations with corresponding histology are seen in Figures 40 through 115.

The most frequently encountered formations are in Figures 40 through 69. Generally, smooth lobulated outlines are observed, and entering ducts are usually visible (Figures 40 and 57). The lobules vary in density, shape, and location. Figures 52 and 60 represent less dense lobules, while Figure 46 illustrates the most dense. The majority of lobules are intermediate between these two extremes. Lobules are most

commonly spherical or discoid in shape, and less commonly cylindrical or fan-shaped. The shape generally conforms to the fibrous bands, e.g., lobules are flat when found in flat fibrous bands, and spherical in cylindrical bands. Although the lobules are generally localized to the fibrous bands, an occasional lobule may be found in a lobule of fat cells.

The location of lobules in relation to ducts and surrounding breast tissue is not constant. Many lobules are connected to large ducts by obvious smaller duct branches as in Figures 40, 46, 50, 57, 62, and 68. In other instances lobules are located very close to large ducts, but a connecting duct is not definitely observed (Figures 42, 48, and 66). In still other instances lobules are observed lying free in the stroma without any visible associated ducts.

The vast majority of the lobules (greater than 90%) are contained within the fibrous supporting network of the breast. The remainder (approximately 10%) are in the fat lobules as seen in Figure 64. In such cases the outline of the lobule may show multiple concave indentations which are approximated to the corresponding convex surface of the surrounding fat cells. Fat cells may also occur in lobules located in fibrous tissue. In those instances, they appear as translucent circular areas as in Figure 60.

Some lobules are poorly defined because of haziness or low density as in Figure 60. Haziness of lobular outlines may sometimes be due to a cellular infiltrate as seen in Figure 193 at arrow 1.

The corresponding histology in Figures 40 through 69 is within normal limits. An intralobular infiltrate of chronic inflammatory cells

in Figure 47 may account for the extreme density of the corresponding subgross structure of Figure 46.

Typical atrophic lobules are seen in Figures 70 and 72. The borders of the lobules are less well defined and the individual components are more delicate. The histology of Figures 71 and 73 indicates decreased epithelial components and a relative increase of intralobular collagenous stroma.

Lobular configurations are further illustrated in Figures 74 through 95. Note the lobular stromal component in the subgross of Figures 74 through 87, and indicated by an arrow in Figure 74. The corresponding preparations illustrate the stroma seen in the subgross photographs. Figures 74 through 87 show ductules which arborize (Figures 74, 83, and 85), or are composed of fine tubular elements (Figures 76 and 78) or of more coarse tubules (Figure 87).

Histologically, the stroma of the "normal" discoid lobules in Figures 89 and 92 varies from loose connective tissue (Figure 90) with prominent myoepithelial cells (Figure 91) to dense cellular stroma (Figure 93). Figure 94 shows another poorly defined discoid lobule with prominent fat cells.

Subgross Figures 96 through 114 illustrate lobular formations, which are infrequently encountered in the present material. Figures 96 and 97 exhibit a whorled pattern. Histopathologically (Figure 98) there is an atrophic fibrotic lobule. Figures 99, 101, and 105 are subgross representations of atrophic fibrotic lobules, confirmed by histopathology.

Figure 103 has a large duct (arrow) with thickened walls and an

adjacent spherical density. The histopathology illustrates epithelial components which are most likely responsible for the increased thickness of the wall and for the adjacent spherical density.

The lobule of Figure 107 has an unusual shape which is somewhat similar to those of Figures 109, 111, and 114. In Figure 107, however, intraluminal spheroids of secretory material (arrow) are visible. Histopathology correlates nicely in all four instances. Note in Figure 115 the ductule lumina appear to be communicating with one another in the plane of the histological preparation.

PRELACTATING BREAST OF PREGNANCY

Figures 116 and 119 are lobules from the breast of a mother on the eleventh postpartum day. Note the prominent rounded lobulations, the clearly visible acini, and the normal histology. Differences in the physiologic response of the epithelium are exemplified by the presence of secretory vacuoles in epithelial cells in Figure 118 and absence of such vacuoles in Figure 120.

Figures 121 through 126 are from the breast of a second postpartum woman. At the subgross level the lobules are dense and cellular with outlines which may be sharply defined or somewhat indistinct. Individual ductules and acini, while not always evident in the subgross preparation, are clearly visible histologically. These differences in appearance of lobules from the same breast suggest that lobular response to the hormonal milieu is variable.

In both of the above breasts, the lobular hyperplasia is accomplished at the expense of the adipose tissue which visibly decreases in

amount. Even so, the ducts and lobules remain primarily localized to the fibrous tissue with only an occasional "invasion" into the fat lobules as in Figure 123 and Figure 124. In one instance a single hyperplastic lobule similar to those described above was observed in a resting mammary gland from a postmenopausal woman (Figure 127).

CYSTS

Figures 130 through 142 are cystically dilated acini or ductules with smooth, thin walls and visible lumina. All lack apparent inspissated secretion at the subgross level, though thin secretory material is occasionally seen in the histologic preparations. Micro- and/or macrocysts were found in every adult breast examined.

Figures 143 through 152 are typical examples of cystically dilated ducts. Figure 143 represents cystic dilatation of a terminal duct. The remaining figures (144 through 152) are larger segments of dilated ducts, many containing inspissated secretion. In Figure 149, sharply defined secretory material with a smooth, ridged surface is noted. Indistinct, intraluminal material composed of "fatty macrophages" or "colostrum" cells (15, 49) is present in a terminally dilated duct (Figures 153 through 155).

APOCRINE EPITHELIUM

Apocrine epithelium (Figures 156 through 170) is found only in acini or terminal ductules. Most, but not all (Figure 169), of the acini and terminal ductules are dilated. In the majority of subgross preparations (an estimated 75%), apocrine epithelium appeared as a

thickened cyst wall with discrete, regular, knobby densities projecting into the lumen (Figures 156 and 159). In other instances, the cyst wall of the subgross structures is thickened, but has a smooth luminal surface (Figures 161 and 163). The histopathologic preparation in all examples shows typical apocrine epithelium.

SCLEROSING ADENOSIS (ADENOSIS)

Figures 171 through 178 illustrate the usual subgross appearance of sclerosing adenosis. There is usually a lucent fibrous core with radiating epithelial bands, ducts, and cystic ductules. This explains the "cockleburr" or stellate pattern observed in the subgross preparations. The histopathology of this typical subgross pattern is consistently identified as sclerosing adenosis. Less severe forms of sclerosing adenosis do not always exhibit such an easily recognized subgross pattern (Figures 96, 97, and 98).

FIBROADENOMA

The subgross formations typical of fibroadenoma are exemplified in Figures 179 through 189. The fibroadenoma is a well localized fibroepithelial mass which characteristically is translucent, allowing the confined, flattened, and distorted ducts to be visible.

Figure 181 is unusual in that the ducts are cylindroid and faintly outlined. Figure 186 is unusual because the epithelial component is more prominent than would be predicted from viewing the subgross photograph (Figure 185). No attempt was made to separate the pericanalicular and intracanalicular fibroadenomas at the subgross level of observation.

DUCT ECTASIA

Figures 191 and 193 have dilated ducts, inspissated intraluminal material, and periductal haziness, most probably due to the chronic inflammatory cells in the surrounding ductal stroma. Mammary duct ectasia exhibited these changes in all instances.

PAPILLOMA AND PAPILLOMATOSIS

Figure 196 illustrates the only solitary papilloma found in the 27 breasts examined. It is photographically similar in appearance to inspissated secretion; however, in stained tissue under the dissecting microscope, the papilloma is blue while secretion has a golden hue. The histopathology in Figure 197 shows a fibrous core covered by cytologically normal epithelium.

Figures 198 through 208 illustrate one pattern of papillomatosis. Papillomatosis consists of fine to coarse stippling seen as granular densities in dilated ducts or lobular structures. The important distinguishing feature is the *irregularity* with regard to size, shape, and density. Figure 200 is a lobular formation with a folded and stippled appearance. Figures 204 and 208 are examples of stippling in segmentally dilated ducts. The histopathology in all of the above cases exhibits multiple stromal invaginations covered by normal to minimally hyperplastic epithelium without evidence of cytologic atypism.

Figure 210 is the photograph of a lobule-like structure which has a finely stippled wall indistinguishable from the examples in Figures 198 through 208. However, upon histologic examination (Figure 211), a normal lobule is seen with loose intralobular stroma. This is the only

example of the stippled appearance being associated with a normal lobule.

Figures 212, 214, and 216 are cross-sections of large ducts with easily identifiable intraluminal projections. The epithelium of the papillomata in Figures 212 and 214 is normal to slightly hyperplastic and apocrine epithelium covers the stromal cores of the papillomata shown in Figure 216. There is no detectable difference between the two types of epithelial coverings at the subgross level.

Figure 219 illustrates a duct with intraluminal circular lucencies, apparently secondary to formations of epithelium and stroma arising from the duct wall.

Figures 221, 223, and 225 illustrate ducts with large, smooth, lobulated intraluminal projections. Similar, but smaller projections are noted in Figure 227. The stromal stalks are covered by cytologically normal epithelium in each instance.

EPITHELIOSIS

Figures 229 to 239 are subgross and histologic photographs of lobular structures with minimal to severe epitheliosis. The subgross formations have visible, regularly thickened ductule walls, some of which have ragged intraluminal surfaces (Figure 234). The histopathology illustrates the corresponding severity of the epitheliosis.

Lobular configurations without obvious areas of thickening of ductule walls are shown in Figures 240 and 243. Corresponding histopathology in both cases reveals severe epitheliosis with cytologic atypism.

Most commonly, epitheliosis is found in ducts with the subgross appearances of Figures 246 through 262. The characteristic subgross features include duct dilatation (Figure 246), total luminal obliteration (Figures 252, 256, and 259), and/or partial luminal obliteration. Partial luminal obliteration may be due to simple epithelial thickening (Figure 250), or to a more complex cribriform pattern appearing as an irregular "bubble-filled" lumen. Varying degrees of epitheliosis with and without cytologic atypism are seen in the corresponding histologic preparations.

Figure 263 is a lobule with prominent acinar (ductule) components. The histopathology (Figures 264 and 265) illustrates another type of epitheliosis termed "cystophorous desquamative epithelial hyperplasia" by Cheatle and Cutler (97).

INFILTRATING CARCINOMA

Cloud-like densities with hazy, indistinct borders are typical of an infiltrating carcinoma (Figures 266, 269, 273, and 275). The advancing border of the neoplasm, represented by the irregular scalloping in the subgross preparations, is seen invading the fat (Figures 266 and 273). In Figure 273, a projection of tumor encircles a duct. In Figure 269, several ducts are visible within the borders of an infiltrating carcinoma. In all four examples, histopathology confirms the diagnosis of infiltrating ductal carcinoma. Subgross and corresponding histopathologic morphology is easily correlated in each instance.

A large, poorly defined duct, partially surrounded by dense tissue similar to that seen in the previous four examples, is subtotally filled

with intraluminal material (Figure 277). The surrounding tissue density is secondary to extravasation of blood into the stroma as the result of the surgical procedure (radical mastectomy). The duct lumen is filled with exfoliated cells and necrotic debris (Figure 278).

NON-NEOPLASTIC LESIONS RESEMBLING CARCINOMA

Figures 279-282 show non-neoplastic lesions which resemble infiltrating carcinoma at the subgross level. The borders of the formation of Figure 279, however, are better defined than in Figures 266, 269, 273, and 275. Histopathologically (Figure 280), there is a duct with periductal fibrosis, a moderately severe periductal inflammatory infiltrate, and a lumen containing macrophages. The epithelium is not atypical.

Figure 281 closely resembles an infiltrating neoplasm, having irregular scalloped borders and dense elongate base resembling a solid duct. It is, however, an atrophic lobule located near a thick fibrous band (Figure 282).

OTHER NORMAL BREAST STRUCTURES

Sebaceous and sweat glands appear as illustrated in Figure 283.

A normal artery (Figure 286) has smooth, uniform walls and a visible lumen. The exterior (Figure 288) and sagittal section (Figure 290) of an arteriosclerotic artery reveal localized rounded densities, possibly calcified material, in the vessel wall.

The lymphatics of the breast are not easily identified. The only subgross photograph of lymphatics is in Figure 292, where delicate

lymphatic walls are barely visible (arrow).

Three typical Paccinian corpuscles or pressure receptors are illustrated in Figures 295 through 300.

UNUSUAL BREAST LESIONS

Figures 301 through 315 are examples of a structure found within the borders of the mammary fat pad in 5 of the 27 breasts. In the subgross preparation, the lesion has a smooth undulating surface and is either solid (Figures 301, 312, and 314), stippled (Figures 303 and 305), or has cleft-like spaces within its borders (Figures 305 and 307). Commonly there is a surrounding, well-defined halo of less dense tissue (Figures 301 and 314) with a visible entering duct (Figures 301, 312, and 314). Less frequently, the border of the lesion is indistinct (Figures 305 and 312). Corresponding histopathology shows a loosely packed mass of lymphocytes, occasionally arranged in intersecting cords (Figures 302 and 308). In Figure 313, scattered, isolated spaces lined by macrophages are noted, while in Figure 315 the lymphocytes appear to be adherent to a background network of intersecting connective tissue bands. In all instances a fibrous capsule totally or partially encapsulates the structure (Figure 304). A subcapsular space is usually prominent. Lymphoid follicles and germinal centers were never identified in these structures. In Figure 306 the lymphocytes are outside the capsule and between surrounding fat cells.

A lesion (Figure 309), morphologically similar to those just described, has visible ducts within the dense tissue. Though the

arrangement of surrounding lymphocytes (Figures 310 and 311) is similar to that seen in Figure 315, the histologic pattern is typical of plasma cell mastitis. A capsule is not present.

Another lesion found in 3 of the 27 breasts studied is illustrated in Figures 316 through 323. Subgrossly, the lesion is an isolated cystic structure with thin delicate walls. It is *always* found in the fat lobules. The lumen is visible and free of identifiable material. In the histologic preparation, the cyst is lined by one to several layers of large pale cells with small, pyknotic nuclei. In Figure 323, the cells lining the cyst closely resemble surrounding fat cells.

Figures 324 and 326 are photographs of sharply defined calcified masses. The first (Figure 324) is located in fibrous tissue. The second (Figure 326) is located in fat. These structures are easily identified under the dissecting microscopy because of their translucency and yellow-blue color.

Figure 328 shows a lesion composed of intertwining broad bands of fibrous connective tissue. This is the only such structure found in the 27 breasts, and its significance is unknown.

A small lobular formation (Figure 330) is relatively unremarkable except for its slightly increased density. Histologically, a few small, central ducts are surrounded by an encapsulating mass of small vacuolated cells. The exact character of the cells and spaces is unknown, though they may be lymphatic in origin.

DISCUSSION

For the present purpose, subgross morphology is defined as a level of observation between the gross and the histologic levels, roughly corresponding to 5 to 50 diameters of magnification and most readily analyzed by means of a dissecting microscope.

Present understanding of the pathology of the human female breast is largely based on studies at the histologic level. The shortcomings of such studies are apparent: 1) selective sampling permits the examination of only a small portion of the organ; 2) quantitative studies of lesions occurring in the entire breast are almost impossible because of the large number of microscopic sections required; 3) it is difficult to follow the course of various structures through the tissue mass; and 4) three dimensional appreciation of the normal or diseased organ is difficult to achieve.

While the present method resembles that of Ingleby and Holly (56), several modifications are introduced: 1) controlled staining at low pH, resulting in exclusive staining of nuclei, and 2) storage in methyl salicylate in sealed plastic bags, which avoids exposure of the worker to volatile toxins, and which permits photography through the intact bags. Tissue blocks, moreover, may be cut from the 1 to 2 mm thick sections for ordinary paraffin-embedded histologic preparations. The method is practical for detecting and quantifying all focal pathologic lesions in entire mammary glands, provided the lesions are visible at the subgross level and recognizable with the dissecting microscope. By analogy to the mouse mammary carcinoma system, we would expect the more significant anaplastic and preneoplastic lesions of human breast to be

visible by this means, to increase in frequency with age, and to be more common in cancerous breasts than in non-cancerous breasts.

The present work is essentially an atlas of subgross pathology of the human breast. The object is to provide a tool to be used for age-related statistical studies of various focal lesions in cancerous and non-cancerous human mammary glands.

DUCTS

Ducts normally appear as thin-walled tubular structures of various sizes with a clearly visible lumen. The lumen is usually empty, but may be filled with secretory product or exfoliated cellular debris. "Normal" duct wall thickening secondary to epithelial hyperplasia is seen in the developing ducts of the infant breast. In any other situation, epithelial hyperplasia is considered abnormal.

Scalloping or folding of duct walls is seen frequently. The pattern is the result of ridges of epithelium-covered fibrous tissue invaginating into the duct lumen. Ingleby (53) referred to the ridges and felt they were primarily involved with the development of duct buds. In the present study their function is not apparent. The ridges do not always lead to sites of duct branching as Ingleby (53) reported. The ridges do vary in size, and a gradual transition from small ridges through intermediate stages to the formation of large intraluminal projections, composed primarily of fibrous tissue, can be visualized. Figures 25, 13, 227, and 225 illustrate this possible sequence.

The duct system is generally localized to the sheets of supportive fibrous tissue in the breast. Occasionally a duct is located in a

lobule of fat cells. The significance of this finding is unknown. Occasionally small ducts may be confused with blood vessels. However, blood vessels of small size are usually located in fat lobules, so that location is helpful in differentiating ducts from blood vessels. Larger blood vessels frequently have smooth, even walls and blood in their lumina. Once a structure is properly identified, it can be traced without difficulty through consecutive sections until it terminates within or leaves the mammary fat pad.

The significance of fusiform and segmental duct dilatation as well as duct wall thickening will be discussed in later sections.

LOBULES

There is considerable variation in lobular shape and size in normal breasts. Lobular shapes may be spherical, cylindrical, disc-like, ovoid, or fan-shaped.

Whether lobules are composed of small ducts called *ductules* or of *acini* has been discussed by many authors and is referred to in the Introduction. Dawson (23) makes reference to a physiologic difference between duct and acinar epithelium, indicating that only acinar epithelium has secretory capabilities. Taylor and Waltman (99) do not think it is possible to make this distinction. Secretory material is seen in infant ducts in the present study, suggesting that the mere presence or absence of secretion is unimportant in determining whether a structure is a ductule or acinus. This does not say, however, that biochemical differences do not exist between the secretory products of the two structures. Acini, as described by Dawson (23), were present in

the prelactating breasts and in one postmenopausal breast (Figure 127). The epithelium is one cell layer thick. Ducts and other lobular epithelium examined had epithelium two cell layers thick. This study, then, identifies a histologic difference between the lobular structures of the prelactating breast and resting breast on the basis of thickness of epithelium, which is in agreement with Dawson's description.

The subgross appearance of lobules may be altered by the presence of fat cells which cause characteristic circular translucencies within lobules. Increased lobular density and/or perilobular haziness is the result of larger numbers of nuclei from hyperplasia of primary lobular elements (epithelium and/or stroma) or from the presence of inflammatory cells alone or in conjunction with the hyperplasia.

In lobules, as in the ducts, the lumina of the ductules or acini are visible in many instances. It is therefore possible, many times, to recognize intraluminal secretions and alterations in thickness of the lining epithelium.

PRELACTATING MAMMARY GLAND

The normal lobules of the breast, in response to hormonal stimulation during pregnancy, become markedly enlarged with prominent acinar structures. Replacement and/or displacement and "invasion" of fat by parenchymal lobules appears to occur during pregnancy.

The pregnant breast can be recognized at the subgross level because of the abundance of lobules, the relative absence of fat, and the scarcity of visible branching ducts. The response in different parts of the same breast is not entirely uniform.

CYSTS

Cystically dilated acini, ductules, and ducts are evident at the subgross level. They occur with surprising frequency, raising a question concerning their significance. All degrees of dilatation are evident. Pathogenesis may be related to the formation of excessive secretion, or to obstruction of ducts.

Cysts may be isolated without obvious duct communication, or they may be attached to a patent duct system. The cyst walls are generally translucent, revealing the luminal contents and the configuration of lining epithelium. The shape is generally spherical, and some cysts appear to be partially collapsed. Epithelial proliferation within the cysts can be easily identified. In most instances it is possible to distinguish between dilated (cystic) ducts and acini at the subgross level.

APOCRINE EPITHELIUM

Characteristically, apocrine epithelium forms *regular*, knobby intraluminal densities in cysts observed at the subgross level. The appearance is sufficiently characteristic so that histologic sections may not always be necessary. Apocrine epithelium may also have another subgross pattern, a smoothly thickened epithelium lacking the regular knobby densities. In this case it is not possible at the subgross level to establish whether or not the thickening is due to apocrine epithelium or to epitheliosis. In this instance, it would be necessary to examine histologic sections.

SCLEROSING ADENOSIS

The "cockleburr" or stellate duct formation in the subgross preparations appears to be specific for the histclogic diagnosis of sclerosing adenosis. Ingleby *et al.* (55) illustrate subgross formations of sclerosing adenosis similar to the ones shown in this atlas. However, sclerosing adenosis may assume other subgross forms. Certainly, less severe lobular fibrosis has a different subgross appearance (Figures 96, 97, and 281). The correlation between the subgross formation and the predicted histologic appearance is generally good.

FIBROADENOMA

Fibroadenomas have a characteristic appearance in the subgross preparations. The lesions are generally limited to localized nodules of fibrous tissue containing distorted, flattened ducts.

Little insight is gained concerning the pathogenesis of fibroadenomas after three dimensional observations of tissue using the dissecting microscope. It is difficult to imagine fibrous tissue causing "pressure indentations" of duct walls, thus giving rise to the intracanalicular fibroadenoma. Rather, in agreement with Parks (84), the ducts appear to be growing in a flattened manner and may be determining stromal activity via some regulator mechanism. This idea is based on observations of early duct buds which are flat initially rather than cylindroid.

DUCT ECTASIA

In mammary duct ectasia periductal haziness is secondary to inflammatory cells infiltrating the stroma.

PAPILLOMAS AND PAPILLOMATOSIS

Because duct lumina are clearly visible in most instances, the characteristic stalked intraluminal projections of papillomas are clearly visible. Whether it is a solitary papilloma or multiple papillomata (papillomatosis) can be easily determined, because the entire breast is available for examination.

Papillomatosis at times is difficult to recognize unless seen on cross-section, where obvious intraluminal papillomas can be identified. Various associated patterns are illustrated in Figures 198 through 228. A given subgross pattern possibly related to papillomatosis does not necessarily suggest a specific epithelial change. Therefore, it is important to recognize the "bubble-like" luminal translucencies and section them, confirming the condition of the epithelium by histologic examination.

EPITHELIOSIS

Most authors consider epitheliosis as the most likely preneoplastic lesion in the human mammary gland. Epitheliosis often exhibits several of the following changes, all dealing with the appearance of duct or ductule walls: 1) duct dilatation in relation to surrounding ducts; 2) focal or fusiform duct enlargement; 3) increased duct wall thickness

with a) a ragged or frayed luminal border, b) irregular luminal densities, or c) smooth regular thickening; 4) cribriform pattern occurring as such on cross-section or as "bubble-like" translucencies sagitally; or 5) total occlusion of the duct lumen by nuclei.

When the outer borders of the ducts remain sharply delineated, the epithelial change remains in-situ. Some authors believe the only significant epitheliosis occurs in large ducts. If that is the case, the change can be identified consistently at the subgross level. The examples given in the atlas (e.g., Figure 250) illustrate the ease of identifying duct wall changes in the large ducts. Smaller ducts pose more of a problem, although it is usually possible to identify duct wall changes or at least be suspicious of changes in ducts having epitheliosis.

INFILTRATING DUCTAL CARCINOMA

Infiltrating neoplasm is characterized by large, dense, irregular shapes, all with the hazy border signifying the advancing edge of the infiltrating tumor. Many times the malignant cells infiltrate between fat cells, causing the fat cells to stand out in silhouette. The differential diagnosis of such a subgross pattern includes hemorrhage, inflammation, and an occasional unusual lobular pattern.

UNUSUAL BREAST STRUCTURES

The significance of the lymphoid nodules described in the present study is not clear. They may be intimately associated with the lymphatic system of the breast. Since they do not occur with great frequency,

they could be the result of a specific stimulus, possibly of immunologic nature.

A second lesion, previously undescribed, was discovered in 3 of the 27 breasts. The label "lipocyst" has been coined to refer to this lesion, which is localized to the lobules of fat cells. The etiology is questionable. They may be artefactual, secondary to some phase of the processing, or they may be real, possibly secondary to trauma. The lipocyst does not appear to be related to significant mammary pathology.

The calcified bodies in Figures 324 through 327 are variants of mammilolithiasis as described by Sandison (90).

The lesion in Figures 328 and 329 is included because of its peculiar subgross appearance and the totally fibrous nature on histopathologic section. The etiology and significance of this structure are unknown.

Finally, the lobule-like object in Figure 330 is interesting in that the histopathology is unusual. The small spaces may represent lymphatic channels, but their origin is uncertain.

CONCLUSION

A method is presented which permits examination of the entire human breast at the subgross level. The full range of subgross structure in a group of human female breasts is described in this study. Subgross appearances are identified for all the usual lesions of the classical histopathology of mammary dysplasia. Many of the subgross structural configurations are sufficiently characteristic to allow accurate prediction of the corresponding histopathology. Therefore, this atlas suffices as a first step toward future quantitation and statistical study of human mammary dysplasia and its relation to preneoplasia and neoplasia.

REFERENCES

1. Anderson, W. A. D. Pathology, Volume II. St. Louis: C. V. Mosby Co., 1966. pp 1206-1230.

2. Anderson, W. Boyd's Pathology for the Surgeon. Philadelphia and London: Saunders, 8th edition, 1967. pp 478-505.

3. Antonius, J. I., and Jones, H. W. Significance of certain types of epithelial proliferation occurring in female mammary gland. Bull. Mason Clin. 17: 17-26, 1963.

4. Bloodgood, J. C. The pathology of chronic cystic mastitis of female breast. Arch. Surg. 3: 445, 1921.

5. Bloom, W., and Fawcett, D. W. A Textbook of Histology. Philadelphia, London, and Toronto: Saunders, 9th edition, 1968. pp 767-775.

6. Bonser, G. M., and Jull, J. W. Hormonal factors in breast cancer. IN Recent Advances in Pathology (edited by C. V. Harrison). London: Churchill, 7th edition, 1960. pp 384, 415-423.

7. Boyd, W. Surgical Pathology. Philadelphia and London: Saunders, 5th edition, 1945. pp 513-548.

8. British Medical Journal. Natural history of breast cancer. Brit. Med. J. 5476: 1450, 18 Dec., 1965.

9. Cappell, D. F. Miur's Textbook of Pathology. London: Arnold, 8th edition, 1965. pp 761-776.

10. Charteris, A. A. On changes in mammary gland preceding carcinoma. J. Path. Bact. 33: 101-117, 1930.

11. Cheatle, G. L. Hyperplasia of epithelial and connective tissues in breast, its relation to fibro-adenoma and other pathological conditions. Brit. J. Surg. 10: 436-455, 1923.

12. Cheatle, G. L. Desquamative and dysgenetic epithelial hyperplasias in the breast; their situation and characteristics; their likeness to lesions induced by tar. Brit. J. Surg. 13: 509-532, 1926.

13. Cheatle, G. L., and Cutler, M. Tumours of the breast: Their pathology, symptoms, diagnosis and treatment. London: Arnold, ca. 1931. p 596.

14. Clagett, O. T., Plimpton, N. C., and Root, G. T. Lesions of breast; relationship of benign lesions to carcinoma. Surgery 15: 413-419, 1944.

15. Cohen, R. B. Glucose-6-phosphate dehydrogenase activity in hyperplastic and neoplastic lesions of the breast. Cancer 17: 1067-1072, 1964.

16. Cole, W. H., and Rossiter, L. J. Benign parenchymatous hyperplasia. Ann. Surg. 119: 573-590, 1944.

17. Cooper, A. P. The Anatomy and Diseases of the Breast. Philadelphia: Lea and Blanchard, 1845. pp 45-46.

18. Cooper, R. A. Personal communication. 1968.

19. Copeland, M. M. Mammary dysplasia; diagnosis and treatment. Texas J. Med. 55: 801-805, 1959.

20. Cowie, A. T. IN Milk: The Mammary Gland and Its Secretion (edited by S. Kon and A. T. Cowie), Volume I. New York and London: Academic Press, 1961. pp 191-198.

21. Davis, H. H., Simons, M., and Davis, J. B. Cystic disease of the breast: Relationship to carcinoma. Cancer 17: 957-978, 1964.

22. Dawson, E. K. Sweat gland carcinoma of the breast; morpho-histological study. Edinburgh Med. J. 39: 409-438, 1932.

23. Dawson, E. K. Carcinoma in mammary lobule and its origin. Edinburgh Med. J. 40: 57-82, 1933.

24. Dawson, E. K. Histological study of normal mamma in relation to tumour growth; early development to maturity. Edinburgh Med. J. 41: 653-682, 1934.

25. Dawson, E. K. Histologic study of normal mamma in relation to tumour growth; mature gland in pregnancy and lactation. Edinburgh Med. J. 42: 569, Nov.; 633, Dec., 1935.

26. Dawson, E. K. Mammary cancer and menopause (Honyman Gillespie Lecture). Edinburgh Med. J. 50: 721-736, 1943.

27. Dawson, E. K. Genesis and spread of mammary cancer. Ann. Roy. Coll. Surg. England 2: 241-247, 1948.

28. Dawson, E. K. Fibrosing adenosis; little recognized mammary picture. Edinburgh Med. J. 61: 391-401, 1954.

29. Dawson, E. K. Breast. IN Cancer (edited by R. W. Raven), Volume II. London: Butterworth, 1958. pp 269-297.

30. Dawson, E. K. Sarcoma of the breast: Some observations on their origin, evolution and metaplasia. IN Cancer Progress (edited by R. W. Raven. London: Butterworth, 1960. pp 59-64.

31. DeOme, K. B. The role of the mammary tumor virus in mouse mammary noduligenesis and tumorigenesis. IN Viruses, Nucleic Acids, and Cancers. Baltimore: Williams and Wilkins, 1963. pp 498-507.

32. DeOme, K. B. Formal discussion of: Multiple factors in mouse mammary tumorigenesis. Cancer Res. 25: 1348-1351, 1965.

33. DeOme, K. B. Personal communication. 1968.

34. Dunn, J. E. Formal discussion of: Multiple etiologic factors in neoplastic development. Cancer Res. 25: 1352-1355, 1965.

35. Ewing, J. Neoplastic Diseases: A Treatise on Tumours. Philadelphia and London: Saunders, 4th edition, 1940. p 1160.

36. Fallis, B. D. Textbook of Pathology. New York, Toronto, and London: McGraw-Hill, 1964. pp 556-567.

37. Foote, F. W., Jr., and Stewart, F. W. Lobular carcinoma in situ; rare form of mammary cancer. Am. J. Path. 17: 491-496, 1941.

38. Foote, F. W., and Stewart, F. W. Comparative studies of cancerous versus non-cancerous breasts. Ann. Surg. 121: 6, Jan.; 197, Feb., 1945.

39. Foulds, L. Multiple etiologic factors in neoplastic development. Cancer Res. 25: 1339-1346, 1965.

40. Frantz, V. K., Pickren, J. W., Melcher, G. W., and Auchincloss, H., Jr. Incidence of chronic cystic disease in so-called "normal breasts"; study based on 225 postmortem examinations. Cancer 4: 762-783, 1951.

41. Geschickter, C. F. Diseases of the Breast: Diagnosis: Pathology: Treatment. Philadelphia, London, and Montreal: Lippincott, 2nd edition, 1945. p 826.

42. Haagensen, C. D. Mammary duct ectasia; disease that may simulate carcinoma. Cancer 4: 749-761, 1951.

43. Haagensen, C. D. Diseases of the Breast. Philadelphia: Saunders, 1956. p 751.

44. Hadfield, G. Dormant cancer cell (Kettle Memorial Lecture). Brit. Med. J. 2: 607-610, 1954.

45. Hadfield, G., and Stretton-Young, J. The controlling influence of the pituitary on the growth of the normal breast. Brit. J. Surg. 46: 265, 1958.

46. Hirst, E., Glen, D. L., and Rawle, R. M. The lactating nodule. Aust. New Zeal. J. Surg. 31: 17-24, 1961.

47. Hodge, J., Surver, J., and Aponte, G. G. The relationship of fibrocystic disease to carcinoma of the breast; a study based on 876 cases. AMA Arch. Surg. 79: 670-678, 1959.

48. Humphrey, J., and Swerdlow, M. Relationship to benign breast disease to carcinoma of the breast. Surgery 52: 841-846, 1962.

49. Humphrey, L. J., and Swerdlow, M. Histologic changes in clinically normal breasts at postmortem examination. Arch. Surg. (Chicago) 92: 192-193, 1966.

50. Ihnen, M., and Perez-Tamayo, R. Breast stroma; morphological and histochemical study. AMA Arch. Path. 56: 46-67, 1953.

51. Ingleby, H. Development of carcinoma of breast; report of case. Arch. Path. 8: 653-660, 1929.

52. Ingleby, H. Relation of fibro-adenoma and chronic mastitis to sexual cycle changes in breast. Arch. Path. 14: 21-41, 1932.

53. Ingleby, H. Normal and pathological proliferation in the breast with special reference to cystic disease. Arch. Path. 33: 573-588, 1942.

54. Ingleby, H., and Gershon-Cohen, J. Adenosis of the female breast. Surg. Gynec. Obst. 99: 199-206, 1954.

55. Ingleby, H., and Gershon-Cohen, J. Comparative Anatomy, Pathology, and Roentgenology of the Breast. Philadelphia: University of Pennsylvania Press, 1960. p 13.

56. Ingleby, H., and Holly, C. A method for the preparation of serial slices of the breast. Bull. Int. Ass. Med. Mus. 19: 93-96, 1939.

57. Ingleby, H., Rodman, J., and Moore, L. The relation of types of breast to the structure of mammary carcinoma. J. A. Einstein Med. Cent. 4: 9-16, 1955.

58. Jackson, J. G., and Orr, J. W. The ducts of carcinomatous breasts with particular reference to connective-tissue changes. J. Path. Bact. 74: 265-273, 1957.

59. Kaplan, S. D., and Acheson, R. M. A single etiologic hypothesis for breast cancer? J. Chronic Dis. 19: 1221-1230, 1966.

60. Karpas, C. M., Leis, H. P., Oppenheim, A., and Mersheimer, W. L. Relationship of fibrocystic disease to carcinoma of the breast. Ann. Surg. 162: 1-8, 1965.

61. Keynes, G. Chronic mastitis. Brit. J. Surg. 11: 89-121, 1923.

62. Kier, L. C., Hickey, R. C., Keettel, W. C., and Womach, N. A. Endocrine relationships in benign lesions of the breast. Ann. Surg. 135: 782-785, 1952.

63. Kuzma, J. F. Myoepithelial proliferations in human breast. Am. J. Path. 19: 473-489, 1943.

64. Langman, J. Medical Embryology; Human Development--Normal and Abnormal. Baltimore: Williams and Wilkins, 1st edition, 1963. pp 315-316.

65. Layton, J. M. Precancerous breast lesions. Proc. Nat. Cancer Conf. 5: 151-153, 1964.

66. Lendrum, A. C. On "pink" epithelium of cystic breast and staining of its granules. J. Path. Bact. 57: 267-270, 1945.

67. Lepper, E. H., and Weaver, M. O. Generalized distention of the ducts of the breast by fatty secretion. J. Path. Bact. 45: 465-467, 1937.

68. Lewison, E. F., and Lyons, J. G., Jr. Relationship between benign breast disease and cancer. Arch. Surg. 66: 94-114, 1953.

69. Lewison, E. F. The relationship between breast carcinoma and benign breast disease. Am. Surg. 25: 571-574, 1959.

70. Louis, C. J. Tumours of the breast; a study employing a histochemical technique. Brit. J. Surg. 46: 147-155, 1958.

71. Marcum, R. G., and Wellings, S. R. Subgross pathology of the human breast: Method and initial observations. J. Nat. Cancer Inst. 42: 115-121, 1969.

72. Marcuse, P. M. Fibrocystic disease of the breast. Correlation of morphologic features with the clinical course. Amer. J. Surg. 103: 428-431, 1962.

73. Massie, F. M., and McClellan, J. T. An analysis of 1500 breast biopsies. Amer. Surg. 26: 509-515, 1960.

74. Mayer, G. IN Milk: The Mammary Gland and Its Secretion (edited by S. K. Kon and A. T. Cowie), volume I. New York and London: Academic Press, 1961. pp 79-81.

75. McLaughlin, C. W., Schenker, J. R., and Tamisiea, J. X. A study of precancerous epithelial hyperplasia and noninvasive papillary carcinoma of the breast. Ann. Surg. 153: 735-744, 1961.

76. Muir, R. Further observations on Paget's disease of the nipple. J. Path. Bact. 49: 299-312, 1939.

77. Muir, R. The evolution of carcinoma of the mamma. J. Path. Bact. 52: 155-172, 1941.

78. Muir, R. Textbook of Pathology. London: Arnold, 8th edition, 1965. pp 761-776.

79. Mulligan, R. M. Syllabus of Human Neoplasms. Philadelphia: Lea and Febiger, 1951. pp 12 and 227-242.

80. Nathanson, I. T. Relationship of hormones to diseases of breast. Surgery 16: 108-140, 1944.

81. Nelsen, O. E. Comparative Embryology of the Vertebrates. New York, Toronto: Blakiston, 1953. pp 587-590.

82. Ochsner, A. Cystic disease of the breast. Postgrad. Med. 33: 133-138, 1963.

83. Parks, A. G. Stereoscopic micro-anatomy. Brit. J. Surg. 44: 209-214, 1956.

84. Parks, A. G. The micro-anatomy of the breast. Ann. Roy. Coll. Surg. England 25: 235-251, 1959.

85. Patey, D. H. Chronic cystic mastitis and carcinoma; collective review. Internat. Abstr. Surg. 68: 575-579, 1939.

86. Raynaud, A. IN Milk: The Mammary Gland and Its Secretion (edited by S. K. Kon and A. T. Cowie), Volume I. New York and London: Academic Press, 1961. pp 15-22.

87. Reynolds, E. L., and Wines, J. V. Individual differences in physical changes associated with adolescent girls. Am. J. Dis. Child. 75: 329-350, 1948.

88. Rodman, J. S., and Ingleby, H. Plasma cell mastitis. Ann. Surg. 109: 921-930, 1939.

89. Rosenburg, A. Zu der Arbeit Dieckmanns "Ueber die Histologie der Brustdrüse bei gestörtem und ungestörtem Menstruationsablauf." Virchow's Arch. f. path. Anat. 262: 298-303, 1926 [Bemerkungen Von H. Dieckmann, 304].

90. Ryan, J. A., and Coady, C. J. Intraductal epithelial proliferation in the human breast - a comparative study. Canad. J. Surg. 5: 12-19, 1962.

91. Sandison, A. T. A study of surgically removed specimens of breast with special reference to sclerosing adenosis. J. Clin. Path. 11: 101-109, 1958.

92. Sandison, A. T. An autopsy study of the adult human breast with special reference to proliferative epithelial changes of importance in the pathology of the breast. Nat. Cancer Inst. Monogr. 4: 1-145, 1962.

93. Sloss, P. T., Bennett, W. A., and Clagett, O. T. Incidence in normal breasts of features associated with chronic cystic mastitis. Am. J. Path. 33: 1181-1191, 1957.

94. Sternberg, W. H. IN Current Concepts in Breast Cancer (edited by A. Segaloff, K. K. Meyer, and S. DeBakey). Baltimore: Williams and Wilkins, 1967. pp 19-30.

95. Stewart, F. W. Tumors of the breast. Atlas of Tumor Pathology. Armed Forces Institute of Pathology, section IX, fascicle 34, pp 1-114, 1950.

96. Stewart, F. W. The problem of the precancerous lesion. Postgraduate Med. 27: 317-323, 1960.

97. Swerdlow, M., and Humphrey, L. J. Fibrocystic disease and carcinoma of the breast. Arch. Surg. 87: 457-460, 1963.

98. Swyer, G. I. M. Some recent advances in endocrinology. Brit. Med. J. 2: 5-10, 1956.

99. Taylor, H. C., and Waltman, C. A. Hyperplasia of the mammary gland in the human being and in the mouse. Arch. Surg. 40: 733-820, 1940.

100. Tellum, M., Prive, L., and Merange, D. R. Four-quadrant study of breasts removed for carcinoma. Cancer 15: 10-17, 1962.

101. Urban, J. A., and Adair, F. E. Sclerosing adenosis. Cancer 2: 625-634, 1949.

102. Vassar, P. S., and Culling, C. F. Fibrosis of the breast. Arch. Path. 67: 128-133, 1959.

103. Wanebo, C. K., Johnson, K. G., Sato, K., and Thorslund, T. W. Breast cancer after exposure to the atomic bombings of Hiroshima and Nagasaki. N. Eng. J. Med. 279: 667-671, 1968.

104. Warren, S. The relation of chronic mastitis to carcinoma of the breast. Surg. Gynec. Obstet. 71: 257-273, 1940.

105. Warren, S. Prognosis of benign lesions of the female breast. Surgery 19: 32-39, 1946.

106. Wellings, S. R. Personal communication. 1968.

107. Willis, R. A. Pathology of Tumours. London: Butterworths, 4th edition, 1967. pp 46-48, 204, and 208-256.

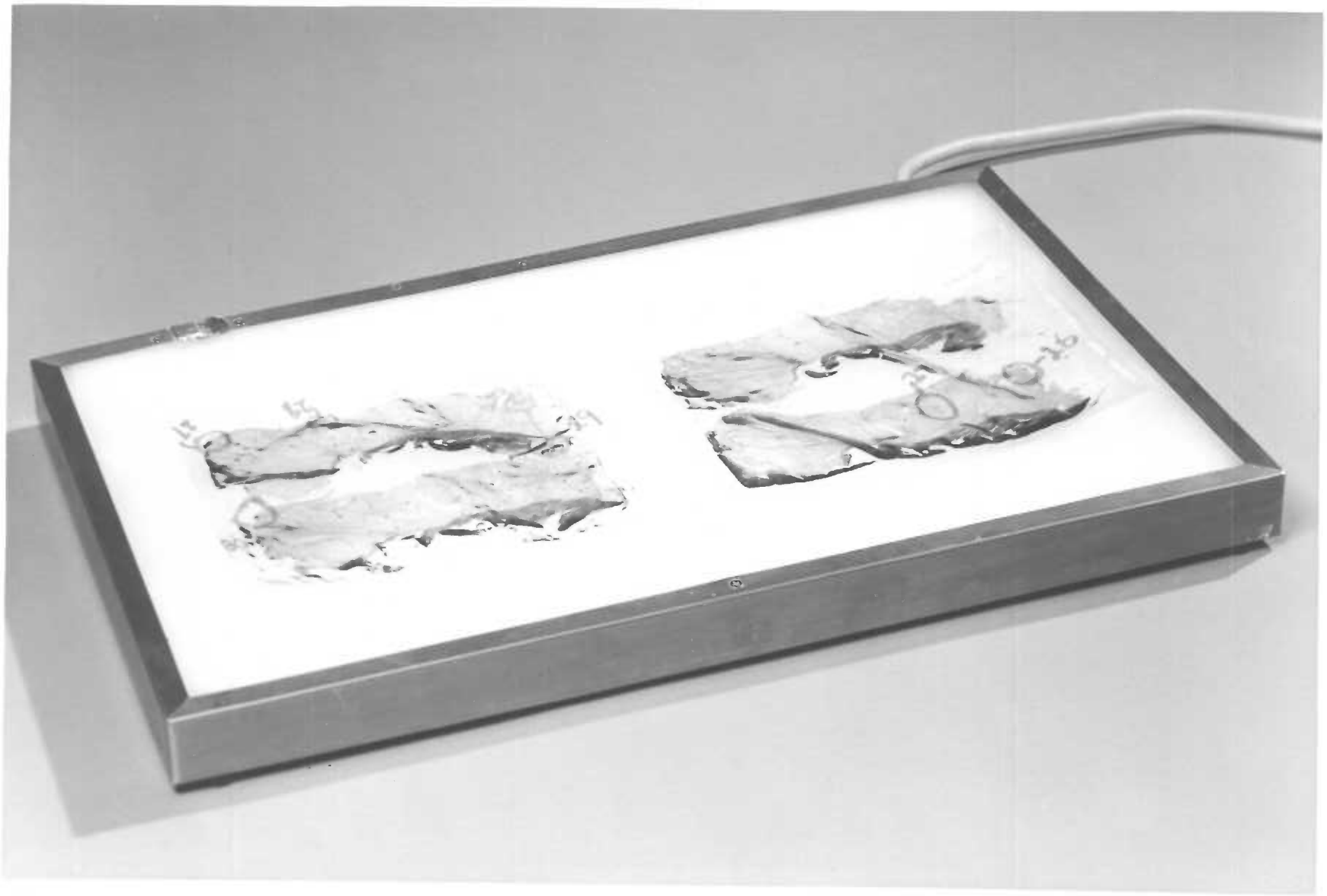
108. Womack, N. A. Endocrine relationships between chronic cystic mastitis and cancer of the breast. Am. Surg. 24: 618-629, 1958.

109. Zeppa, R., and Womack, N. A. The role of histamine release in chronic cystic mastitis. Surgery 52: 195-202, 1962.

FIGURES

Figure 3:

Bagged tissue specimens on the view box, ready for examination with the dissecting microscope.



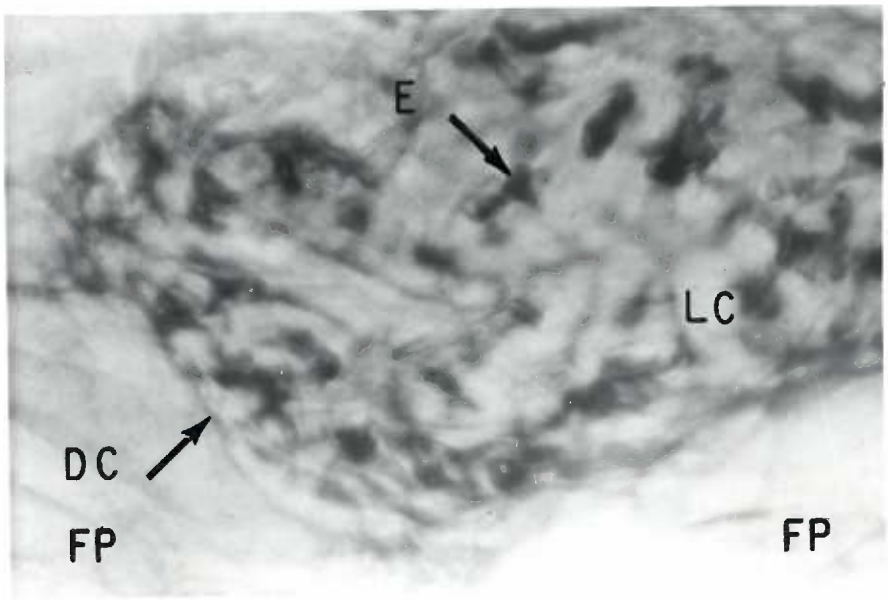
NORMAL DUCTS

Figure 4:

Female, stillborn, infantile breast (M-66-16). Subgross. This is the early duct system located immediately below the nipple and areola. Epithelial layer (E) is dark, and is surrounded by layers of loose connective tissue (LC) and dense connective tissue (DC). Surrounding fat pad (FP). Hematoxylin. 10X.

Figure 5:

Corresponding histology of Figure 4. Note the numerous ducts, absence of lobules, and the more cellular stroma surrounding the ducts, as compared with the fat pad. Epithelium (E), loose connective tissue (LC), dense connective tissue (DC), and fat pad (FP). Hematoxylin and eosin. 10X.



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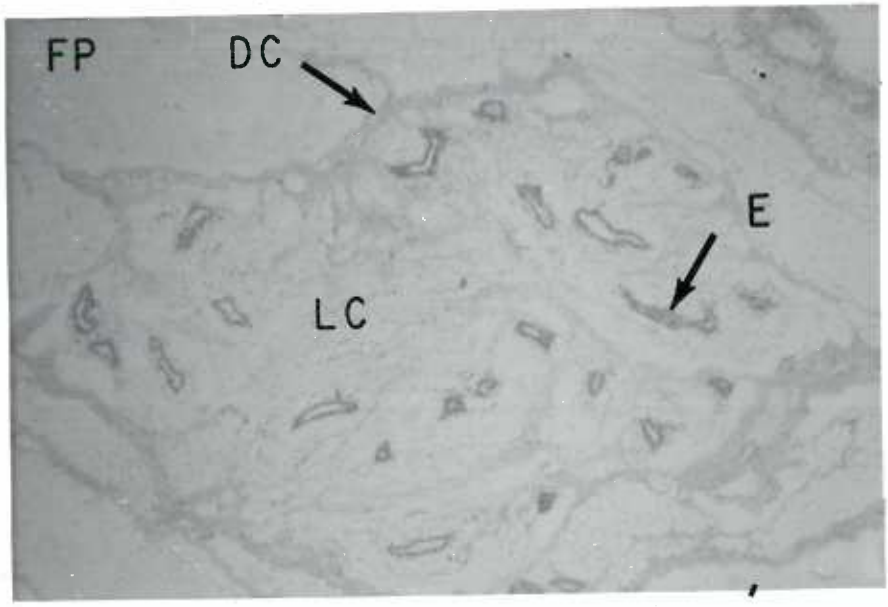

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Figure 6:

Corresponding histology of Figure 4. The ductal epithelium is several cell layers thick and surrounded by loose connective tissue. Amorphous material in the duct lumen (L) may be secretion or exfoliated debris. No mitoses are noted. Hematoxylin and eosin. 160X.

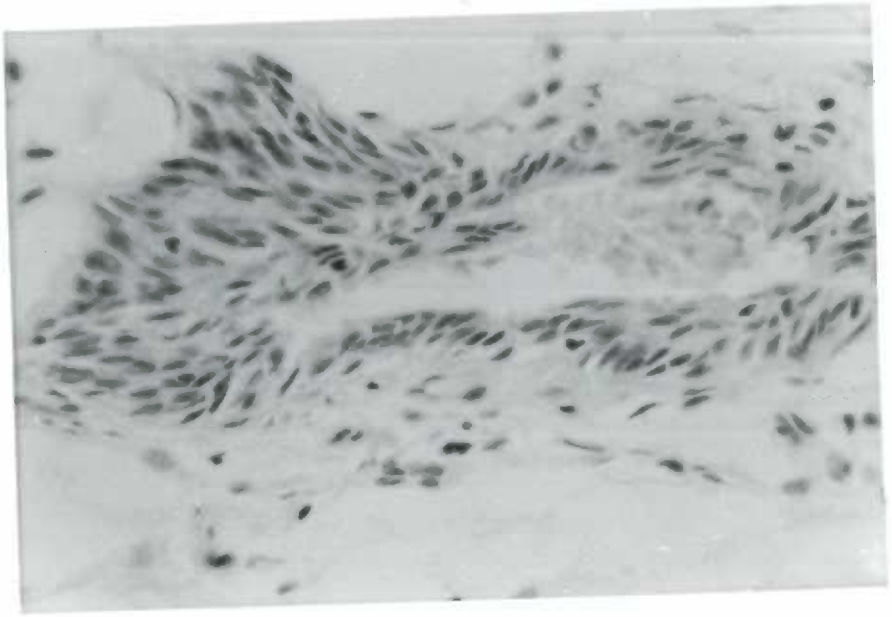

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Figure 7:

Female, 2 months, infantile breast (M-67-1). Subgross. The duct structure is larger and more fully developed than in Figure 4. The duct wall is represented by the dark lines. Note duct buds (arrow). The lumen appears empty. Hematoxylin. 10X.

Figure 8:

Corresponding histology of Figure 7. The ductal epithelium is several cell layers thick and normal in appearance. The periductal stroma (PS) is more cellular and compact than the interductal stroma (IS). A small amount of amorphous material is seen in the duct lumen. Hematoxylin and eosin. 40X.

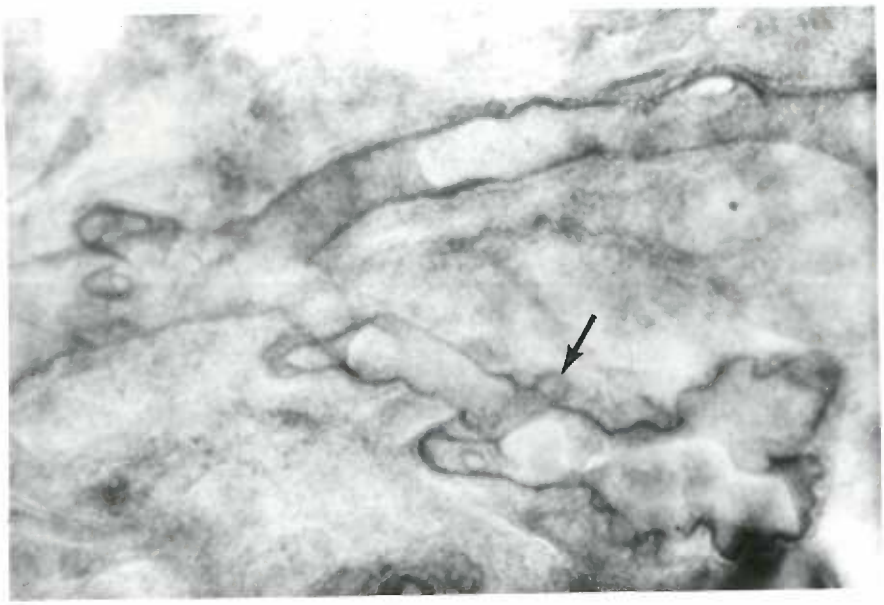

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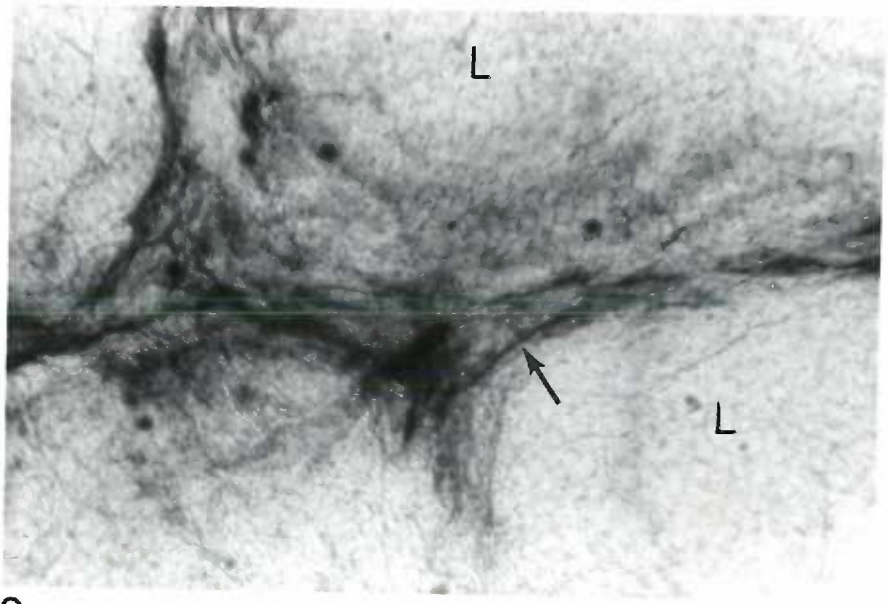
Figure 9:

Female, 17 years, normal breast (M-66-23). Subgross. The indistinct, dark bands represent the connective tissue bands coursing through the fat lobules (L). A duct system is in the fibrous connective tissue (arrows). Hematoxylin. 10X.

Figure 10:

Corresponding histology of Figure 9. A small duct with normal double-layered epithelium, empty lumen, and dense periductal connective tissue is visible. Hematoxylin and eosin. 160X.



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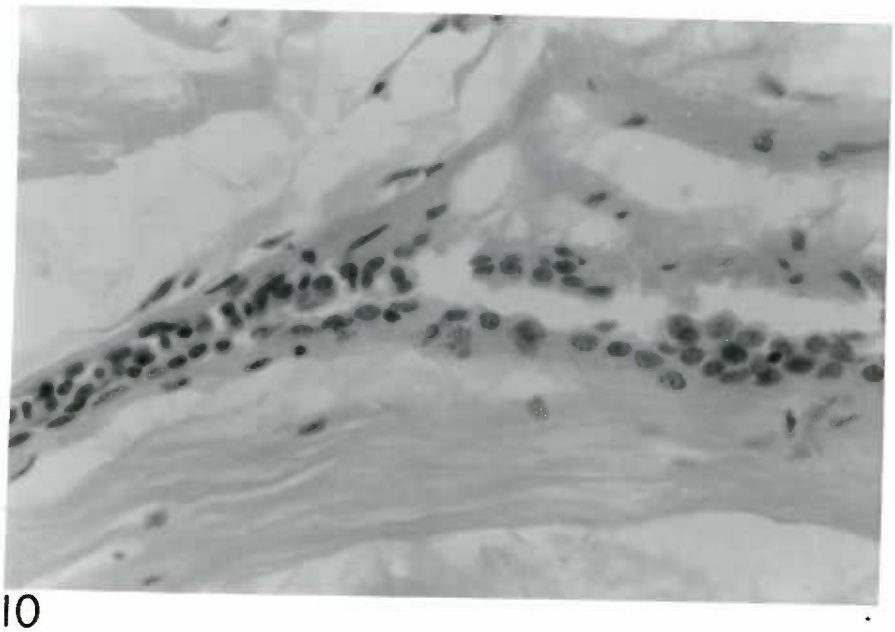

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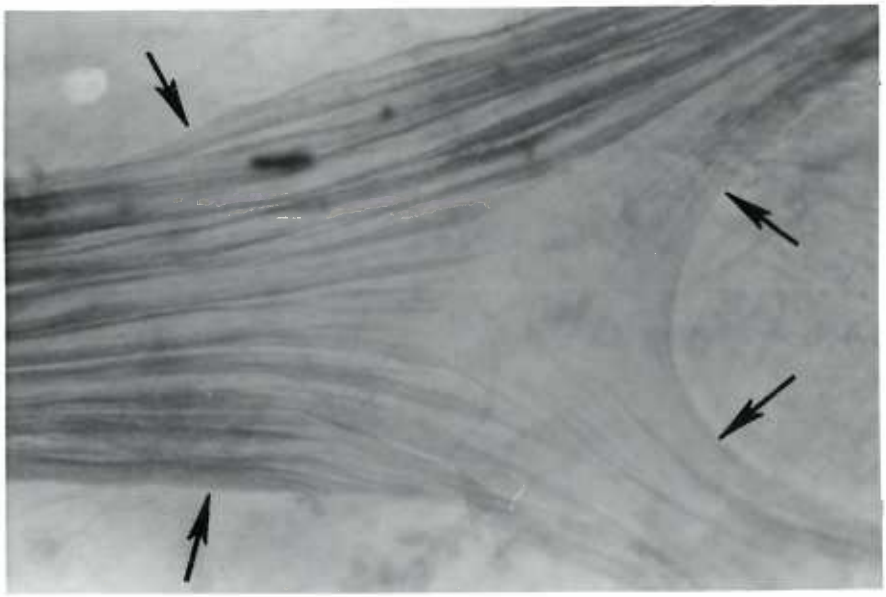
Figure 11:

Female, 19 years, normal breast (M-66-8). Subgross. This is a large, branching duct, the limits of which are indicated by the arrows. The wall appears to be wrinkled, or collapsed, and on cross-section would be scalloped in configuration. The lumen appears empty. Hematoxylin. 10X.

Figure 12:

Corresponding histology of Figure 11. Oblique cut of duct illustrating the folds. The apparent thickening of the epithelium is an artefact due to the tangential nature of the section. Hematoxylin and eosin. 10X.



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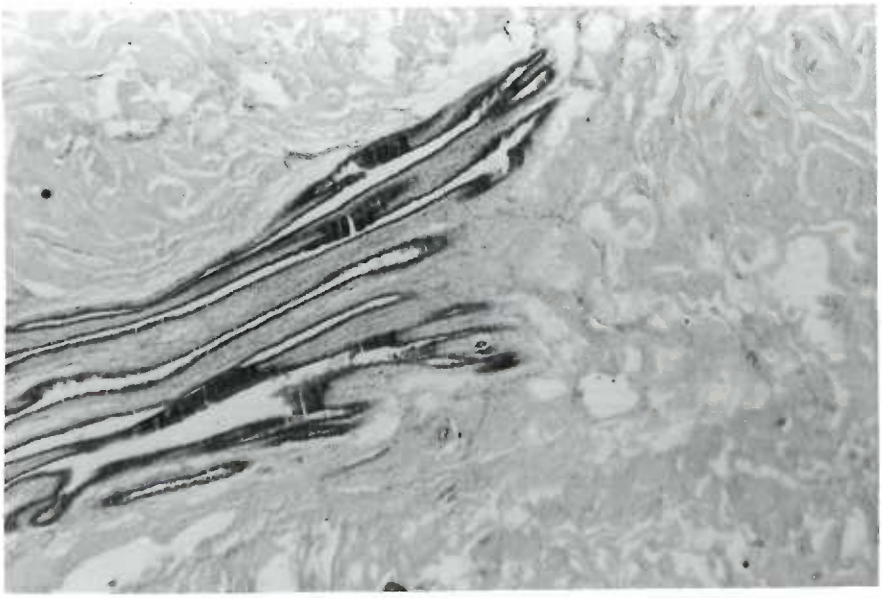

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Figure 13:

Female, 19 years, normal breast (M-66-20). Subgross. Normal duct, cut obliquely, and with scalloped outline. The lumen appears empty. Hematoxylin. 10X.

Figure 14:

Corresponding histology of Figure 13. The scalloped appearance seen in the subgross preparation is represented in section by invaginations of stromal connective tissue surfaced by epithelium. Hematoxylin and eosin. 40X.

13

14

Figure 15:

Female, 19 years, normal breast (M-66-20). Subgross. A branching duct with several longitudinal folds, represented by alternating light and dark lines oriented in the long axis of the duct. The approximate outer limits of the duct are marked by arrows. Nothing is visible in the lumen. Hematoxylin. 10X.

Figure 16:

Corresponding histology of Figure 15. Normal duct histology is shown. Hematoxylin and eosin. 40X.

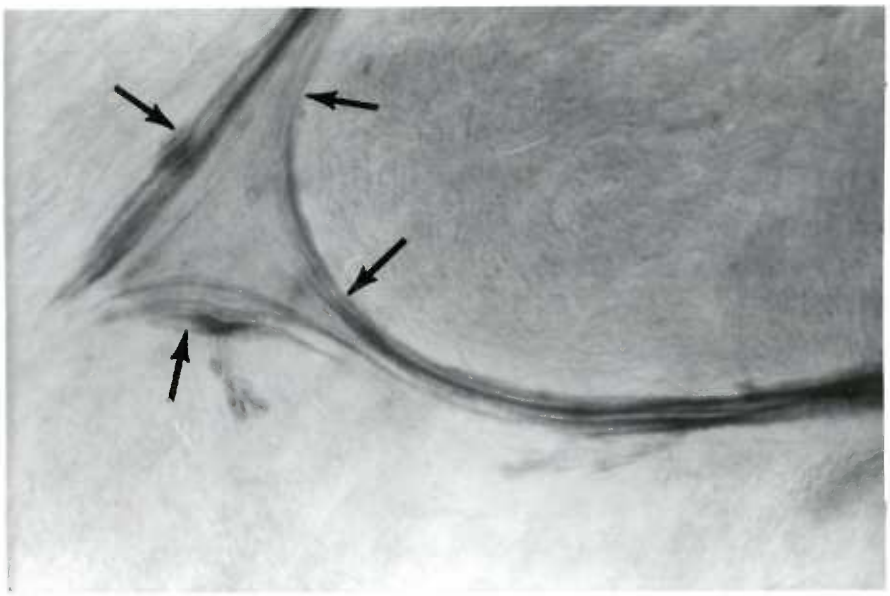

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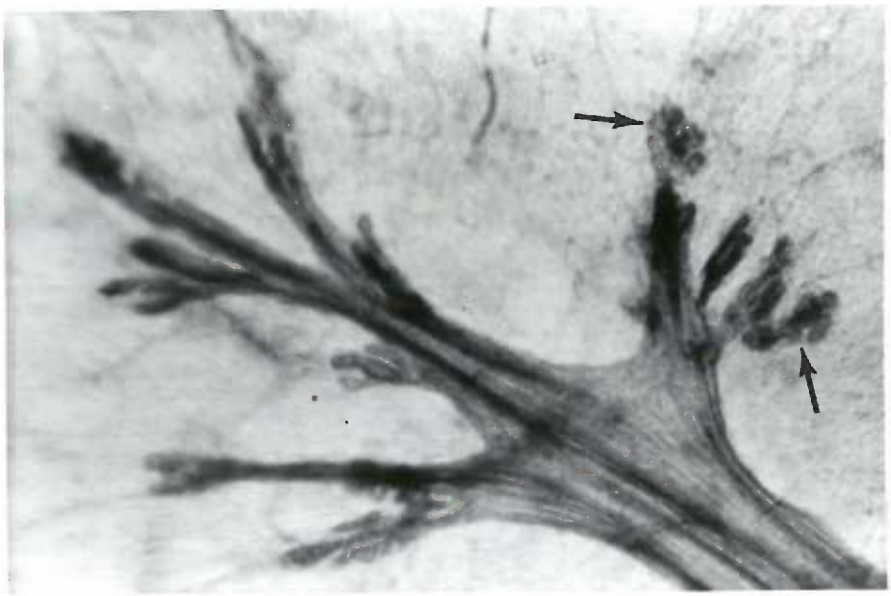
Figure 17:

Female, 19 years, normal breast (M-66-20). Subgross. Larger duct (entering from the upper left) branches into smaller ducts, at least three of which terminate in small lobules (arrows). Hematoxylin. 10X.

Figure 18:

Corresponding histology of Figure 17. A flattened duct with small duct buds and normal epithelial and stromal components is illustrated. Hematoxylin and eosin. 10X.



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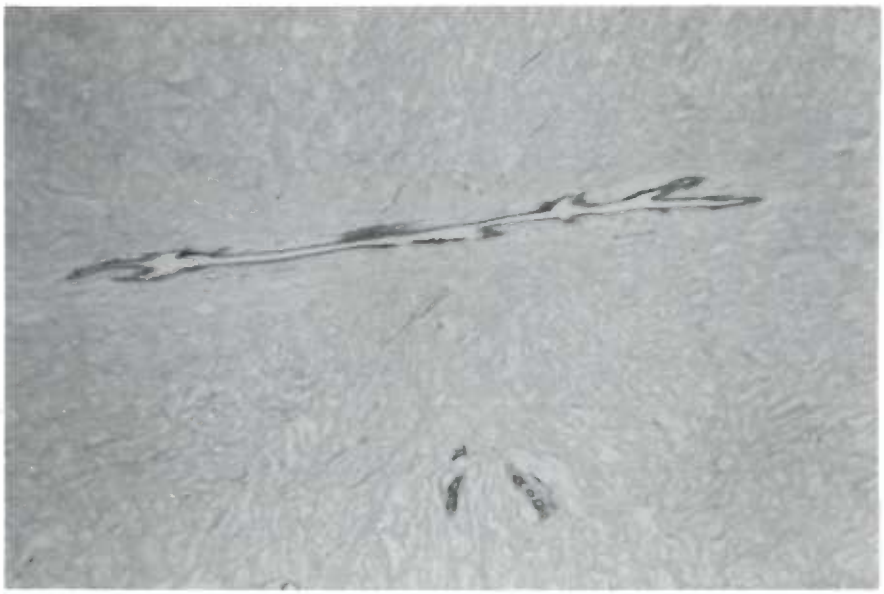

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Figure 19:

Female, 19 years, normal breast (M-66-20). Subgross. The delicate dark lines represent fine ducts, some of which may be organized into lobules (arrow). (This delicate duct network is seen frequently.) Hematoxylin. 10X.

Figure 20:

Corresponding histology of Figure 19. Small ducts are projecting into the loose periductal stroma. The epithelium and stroma are normal. Hematoxylin and eosin. 40X.

19

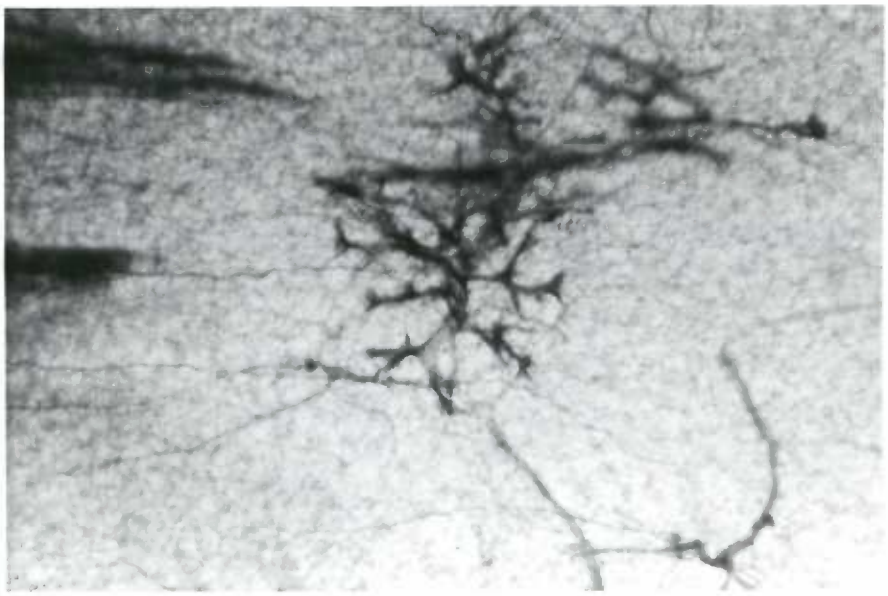
20

Figure 21:

Female, 55 years, normal breast (M-66-19). Subgross. A delicate duct system arborizes among the fat cells of a lobule of fat. (This location is unusual in that mammary ductal and lobular components are more commonly localized to the fibrous bands between the lobules of fat, rather than within the lobules of fat.) The fat cells give the background the appearance of "chicken wire". A duct lumen is visible (arrow) with the majority of ducts appearing as small solid cords. Hematoxylin. 10X.

Figure 22:

Corresponding histology of Figure 21. The small ducts have very thin investing sheaths of fibrous tissue separating the epithelial component from surrounding fat. Hematoxylin and eosin. 40X.



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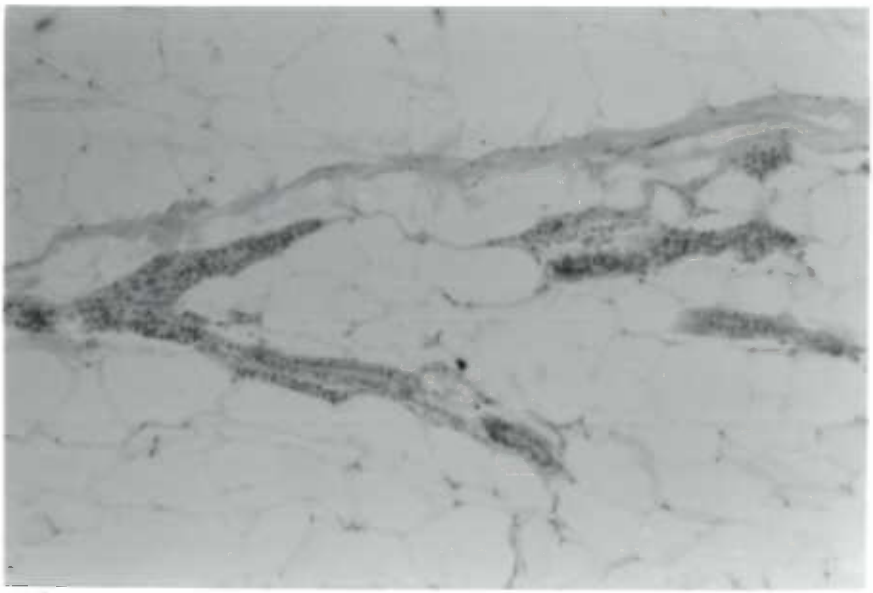

22

Figure 23:

Female, 53 years, normal breast (M-66-21). Subgross. This duct has linear folds or scalloping represented by the alternating dark and light lines in the long axis of the duct. A large branch (lower field of picture) terminates in small duct branches. Hematoxylin. 10X.

Figure 24:

Corresponding histology of Figure 23. The focal epithelial thickening of the duct is an artefact secondary to the tangential cut of the section. The epithelium and stroma are normal. Hematoxylin and eosin. 40X.

23

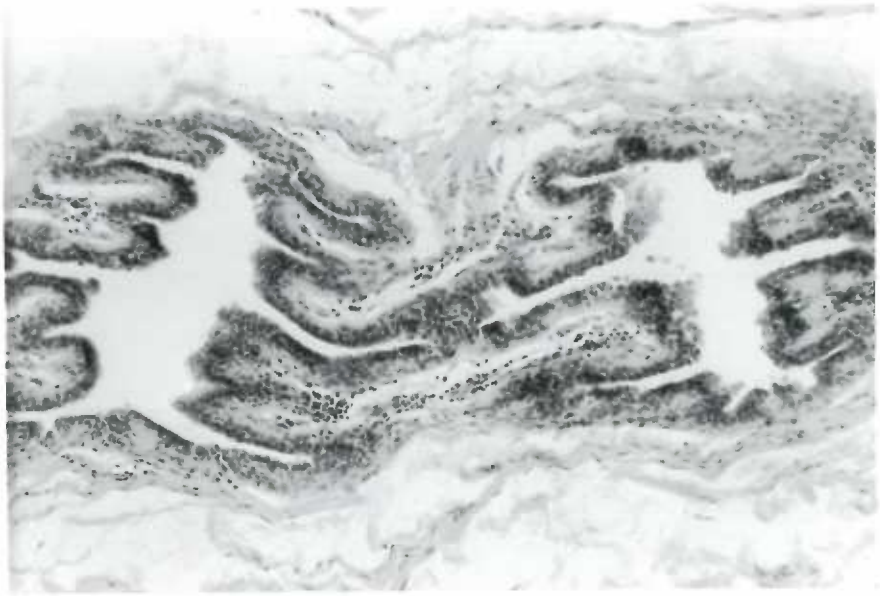

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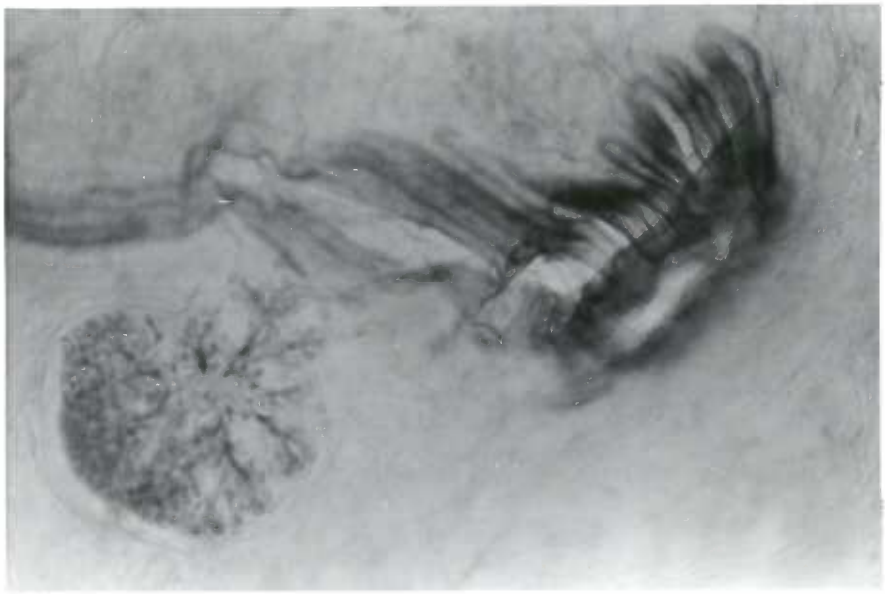
Figure 25:

Female, 19 years, normal breast (M-66-8). Subgross. A large duct, scalloped on cross-section, has an apparently empty lumen, and a well formed adjacent lobule. Hematoxylin. 10X.

Figure 26:

Corresponding histology of Figure 25. The epithelium and surrounding stroma appear normal. Luminal material containing exfoliated cells is noted. The scalloped appearance in the subgross preparation is represented by the numerous, broad stromal invaginations covered by duct epithelium. Hematoxylin and eosin. 40X.



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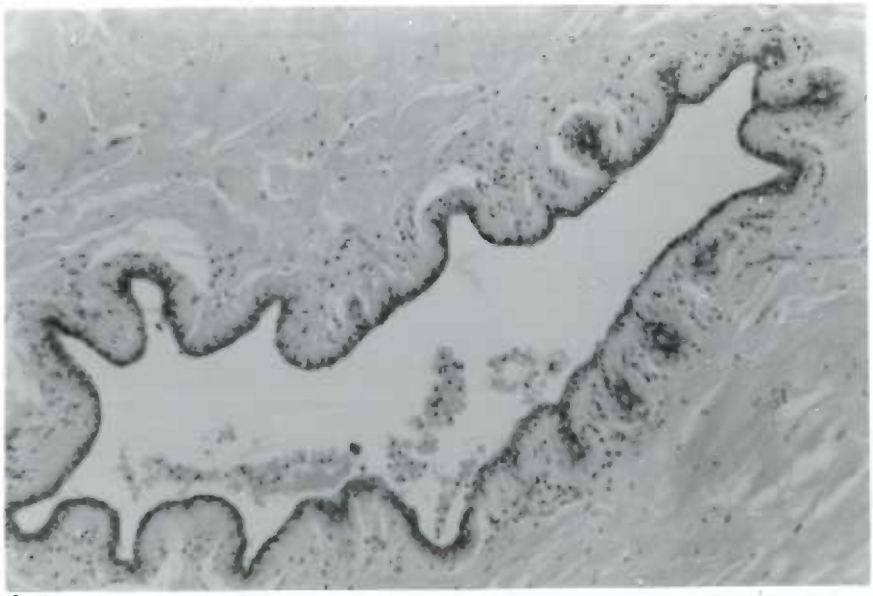

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Figure 27:

Female, 19 years, normal breast (M-66-8). Subgross. A large duct has a dense thickened wall (arrow). A smaller duct branches to a complex lobular formation in the lower right portion of the photograph. Hematoxylin. 10X.

Figure 28:

Corresponding histology of Figure 27. The large duct with portions of the smaller duct is seen (arrow). Note the more dense intralobular connective tissue present in the lobules in the lower right portion of the photograph. Hematoxylin and eosin. 10X.

27

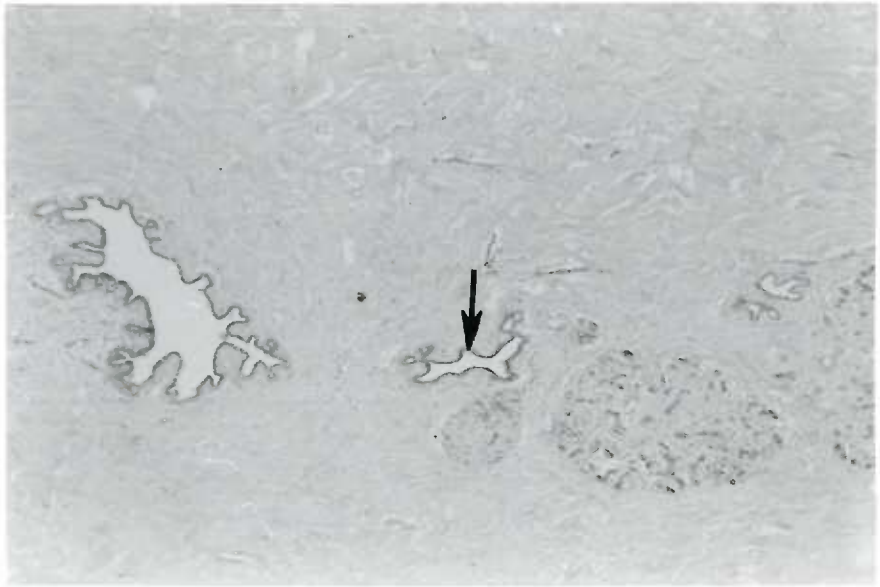

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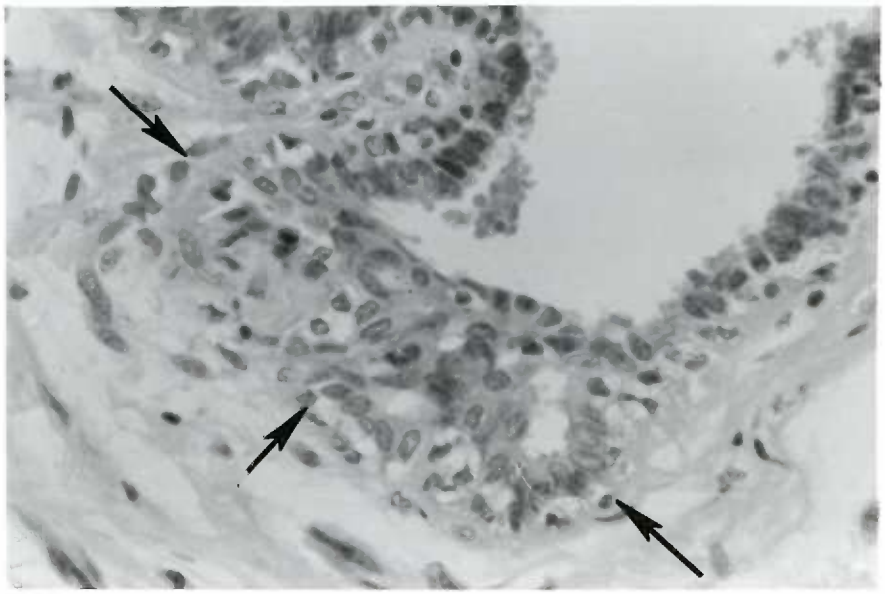
Figure 29:

Corresponding histology of Figure 27. The dense, thickened appearance of the duct shown at the arrow in Figure 27 is apparently due to cellularity resulting from epithelial evaginations along the duct wall. One of the evaginations is indicated here by arrows whose tips touch the basement membrane. Hematoxylin and eosin. 160X.



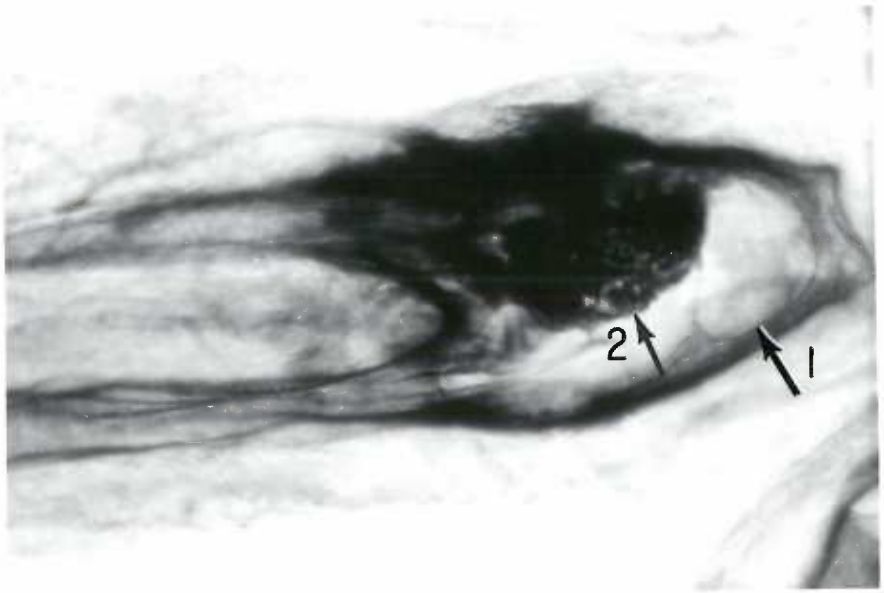
29

Figure 30:

Female, 57 years, normal breast (M-66-22). Subgross. Note intraluminal material in the large duct (arrow 1). A large dense mass originating from the duct wall is protruding into surrounding stroma (arrow 2). Both of these features are easily viewed in three dimensions by means of a dissecting microscope. Hematoxylin. 10X.

Figure 31:

Corresponding histology of Figure 30. Intraluminal secretion (lower left). The epithelial lining forms a tortuous formation extending from the upper left corner of the photograph to the lower right. Outpouchings or evaginations of duct wall are evident. A few lymphocytes are visible in the loose connective tissue of the duct wall. Hematoxylin and eosin. 40X.



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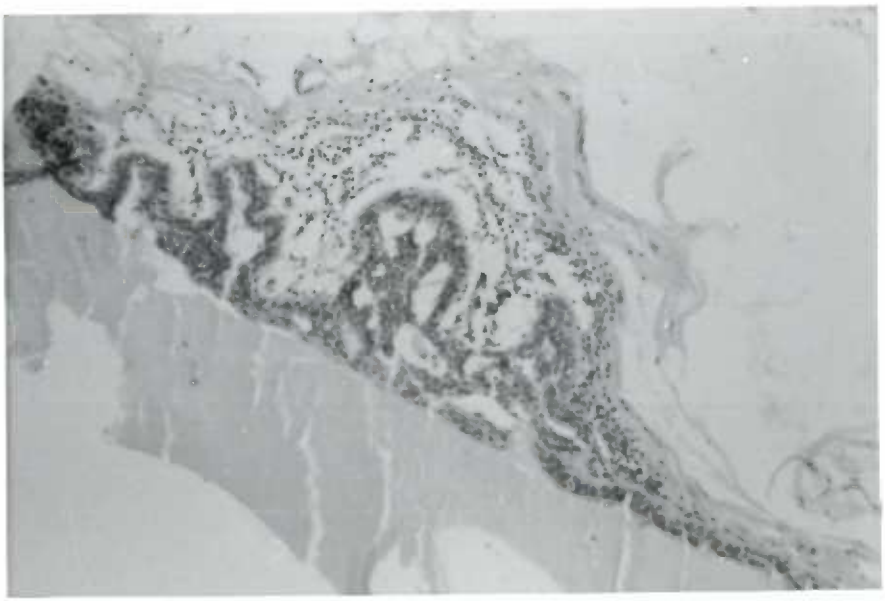


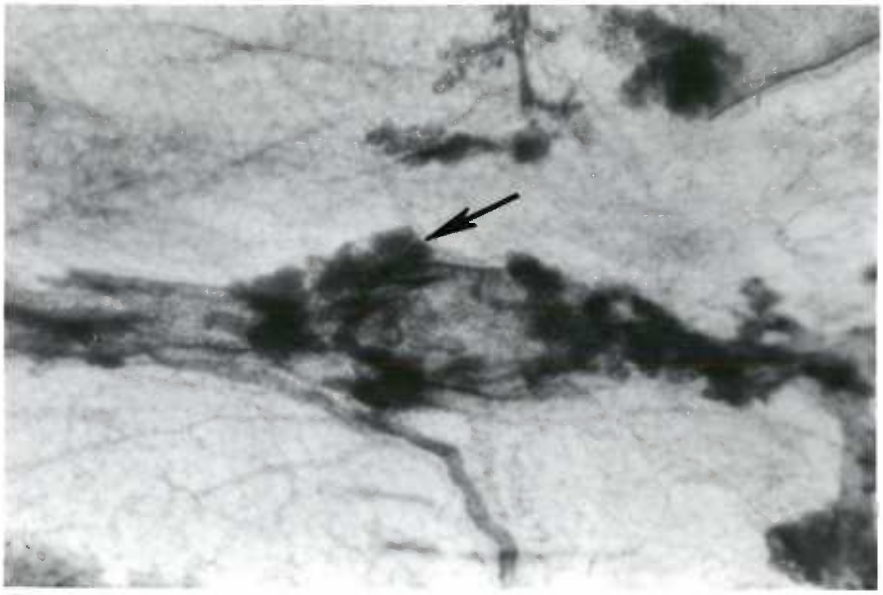
31

Figure 32:

Female, 45 years, normal breast (M-66-2). Subgross. Several small, dark masses (arrow) are attached to the wall of a segmentally dilated duct. Hematoxylin. 10X.

Figure 33:

Corresponding histology of Figure 32. Amorphous material is present in the duct lumen. The dark masses referred to in Figure 32 are apparently duct buds (arrow) associated with the large duct. The duct buds are poorly defined due to the cellularity and mild inflammatory infiltrate of the surrounding stroma. The epithelium and stroma are apparently normal. Hematoxylin and eosin. 40X.



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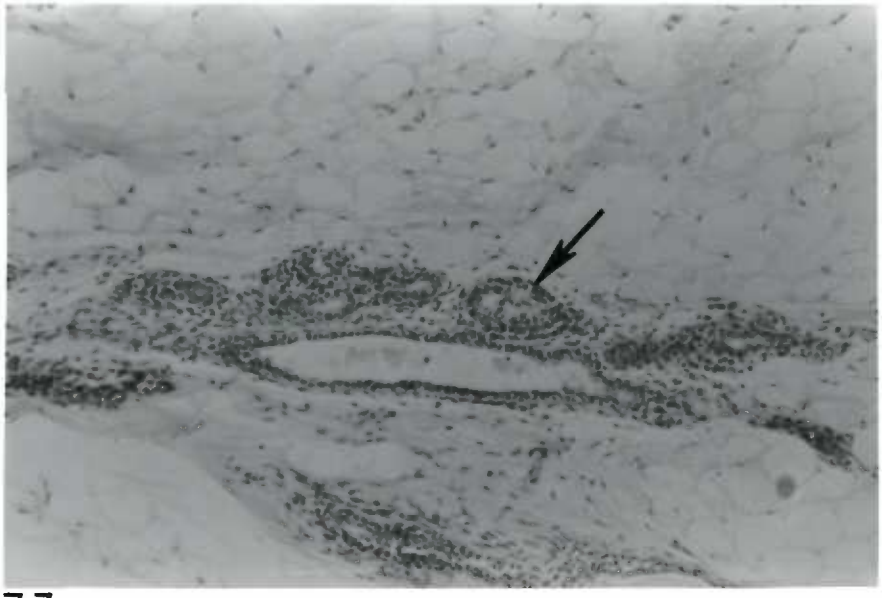

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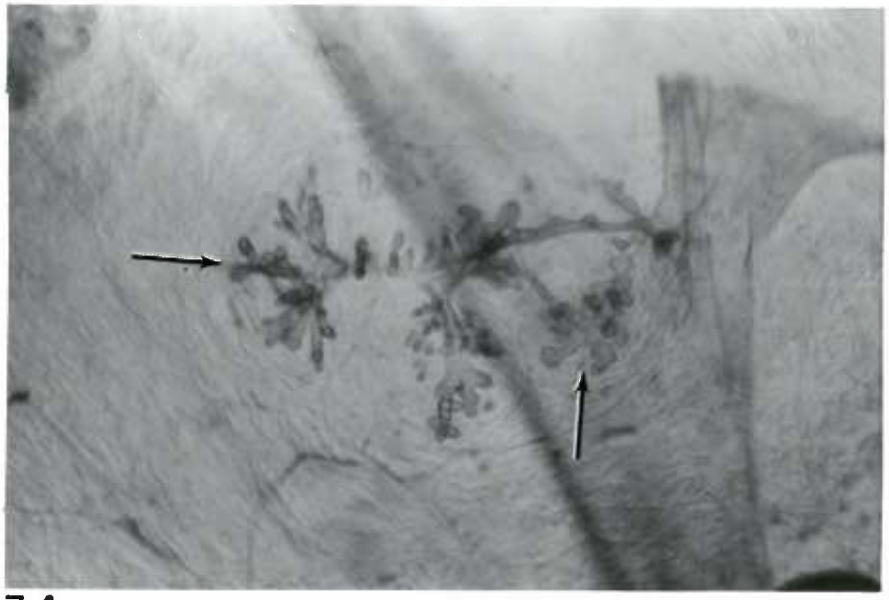
Figure 34:

Female, 19 years, normal breast (M-66-8). Subgross. Several small, blunt ductules branching from a single duct appear to be grouped in lobule-like array (arrows). Hematoxylin. 10X.

Figure 35:

Corresponding histology of Figure 34. Normal ducts are closely invested by stroma which is more dense than surrounding tissue. The ducts are grouped into lobule-like formations (upper left and lower right). Hematoxylin and eosin. 10X.



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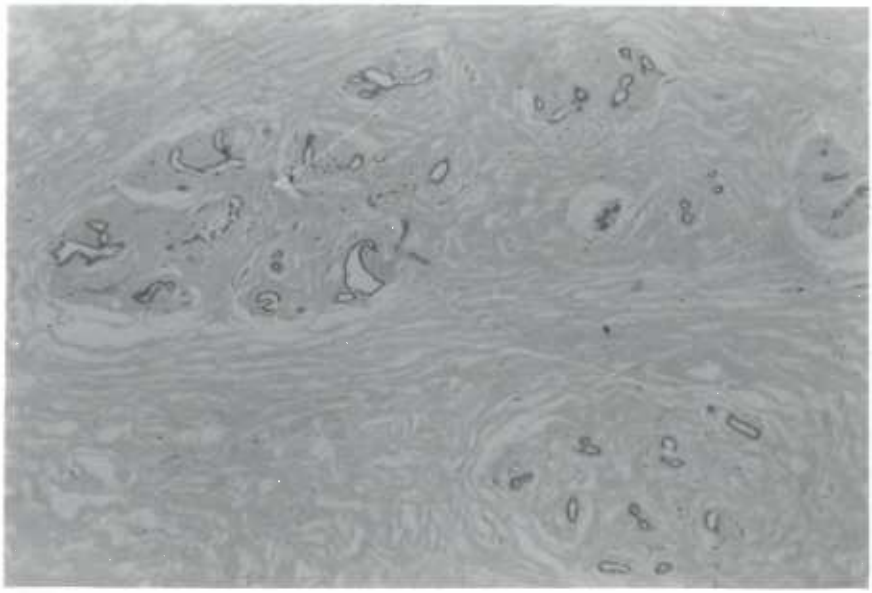


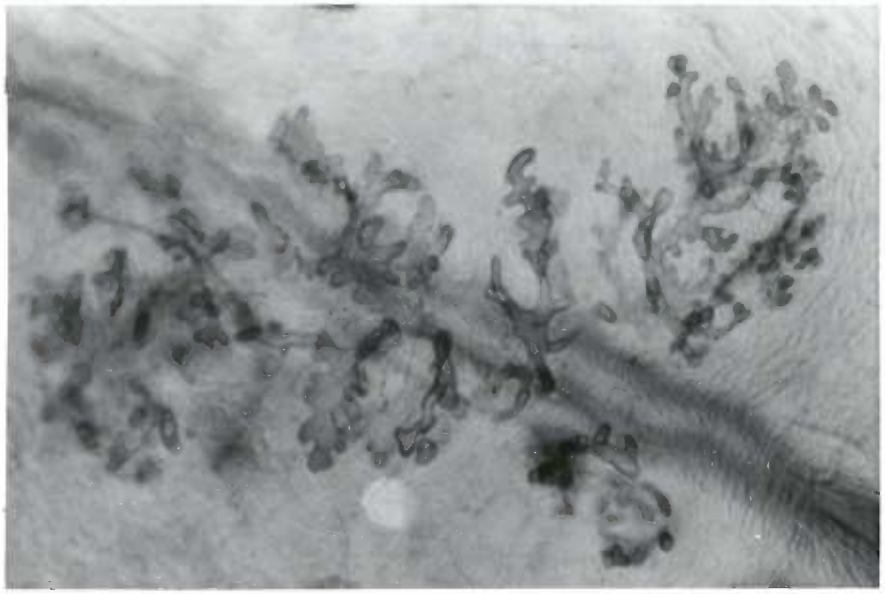
35

Figure 36:

Female, 19 years, normal breast (M-66-8). Subgross. A complex pattern of blunt ductules is seen. Lumina appear empty. Hematoxylin. 10X.

Figure 37:

Corresponding histology of Figure 36. The ductules have empty lumina and normal epithelium. Hematoxylin and eosin. 40X.



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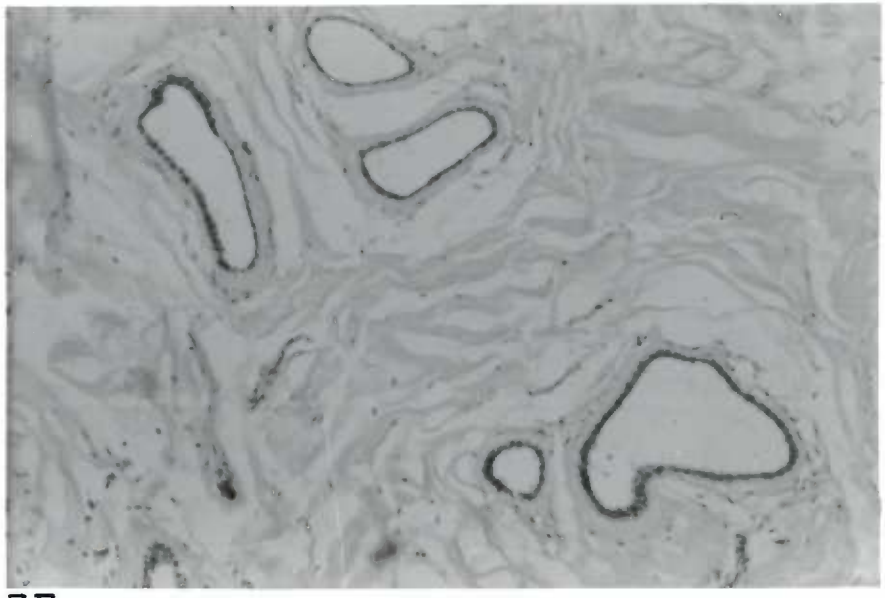

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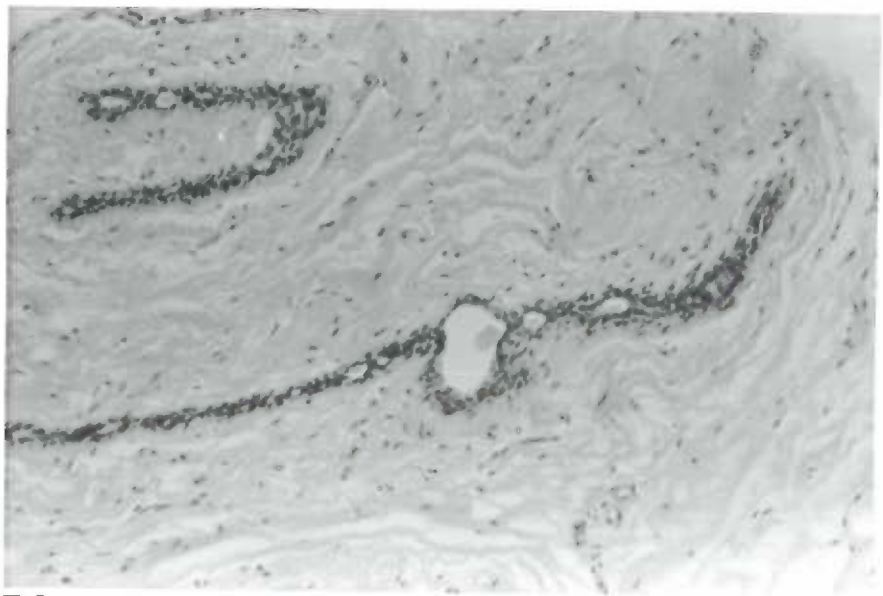
Figure 38:

Female, 45 years, normal breast (M-66-2). Subgross. The larger ducts are flat and have delicate lobular formations arising from their smaller branches. Lumina of many ductules are visible. Hematoxylin. 10X.

Figure 39:

Corresponding histology of Figure 38. The larger ducts in Figure 38, here seen in cross-section, are flattened so that very little lumen remains. Amorphous material is noted in lumina. Hematoxylin and eosin. 40X.

38



39

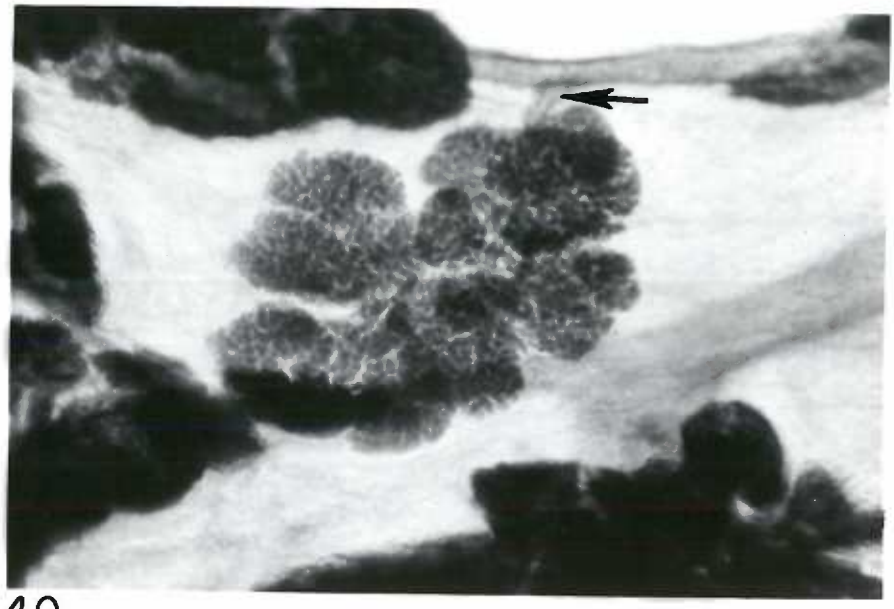
LOBULES

Figure 40:

Female, 48 years, normal breast (M-66-14). Subgross. Clusters of ductules are observed in a normal lobular array (center). The surrounding densities are other lobules which are above or below the plane of focus. Note the communicating duct system (arrow). Hematoxylin. 10X.

Figure 41:

Corresponding histology of Figure 40. The lobule has loose intralobular stroma separating ductules lined by normal epithelium. Hematoxylin and eosin. 40X.



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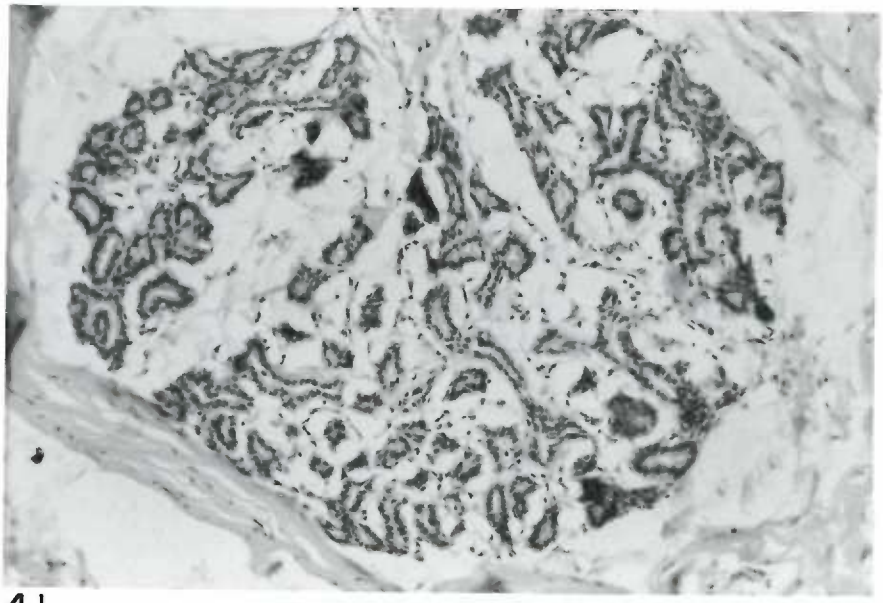

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Figure 42:

Female, 48 years, normal breast (M-66-14). Subgross. A normal lobule of closely approximated small dense ductules arises from a communicating duct (arrow). Hematoxylin. 10X.

Figure 43:

Corresponding histology of Figure 42. A normal lobule is noted. It has loose intralobular connective tissue and normal ductules. Hematoxylin and eosin. 40X.

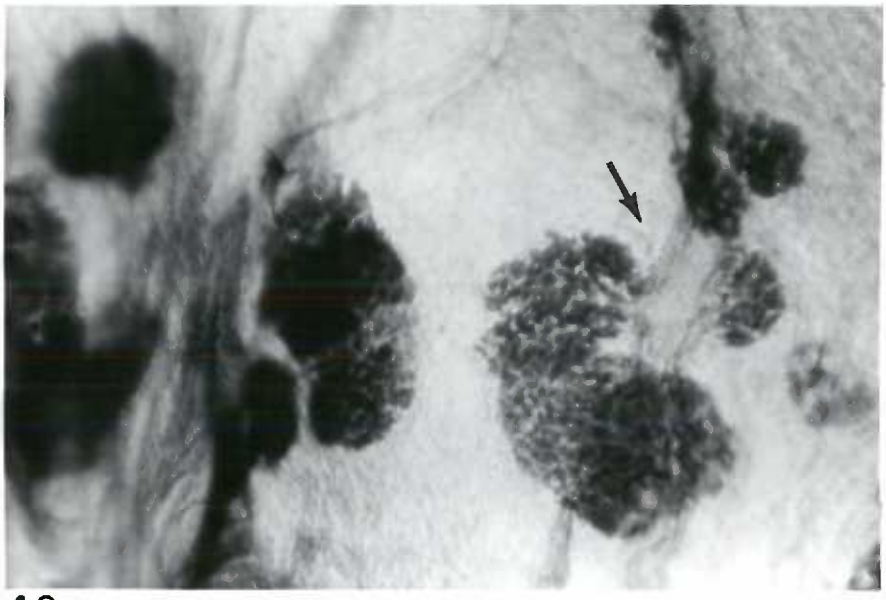

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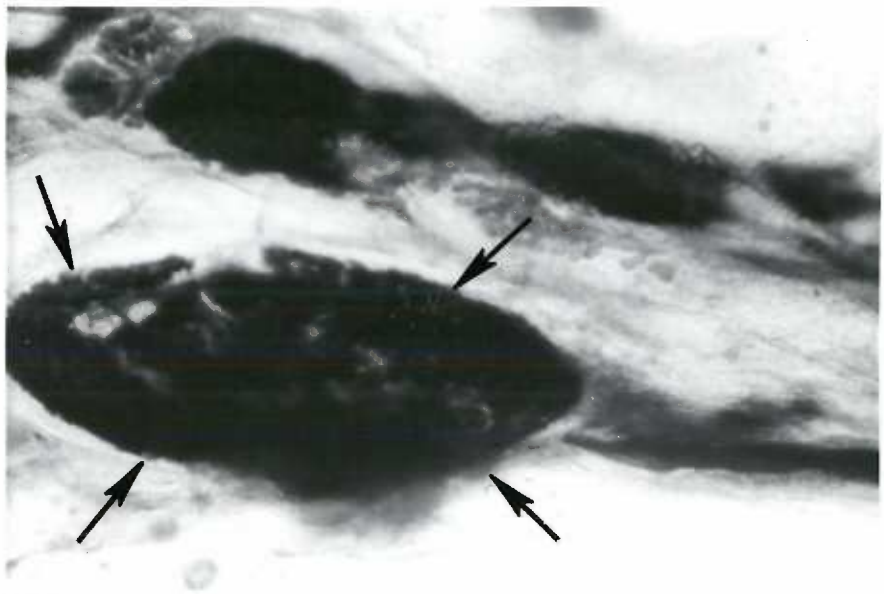
Figure 44:

Female, 48 years, normal breast (M-66-14). Subgross. Note the large, sharply circumscribed dark lobule, the limits of which are indicated by four arrows. Irregular light areas within the large lobule suggest it is not solid. Hematoxylin. 10X.

Figure 45:

Corresponding histology of Figure 44. This is a normal lobule with normal stroma and ductules. The more compact distribution of ductules at the periphery of the lobule may account for the darkness of the lobule in the subgross preparation (Fig. 44). Hematoxylin and eosin. 40X.



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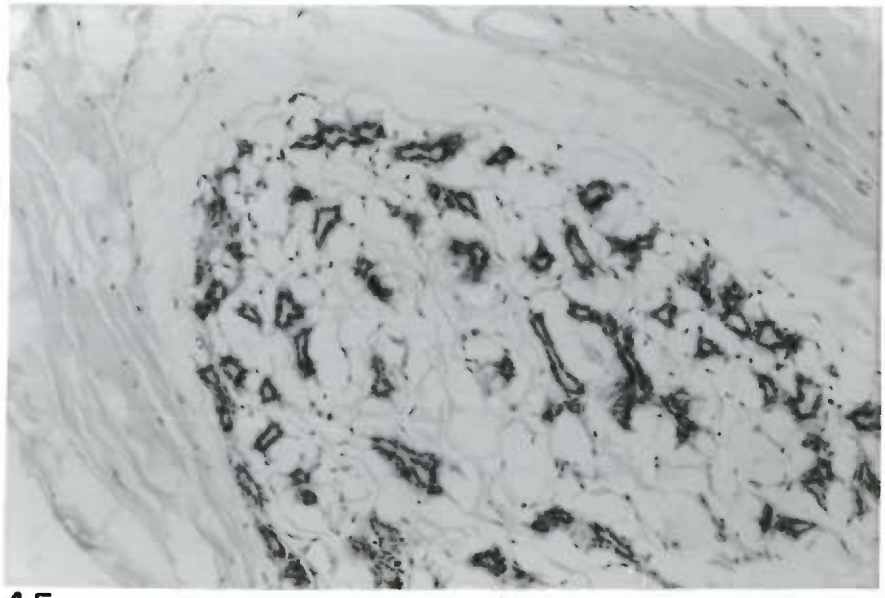

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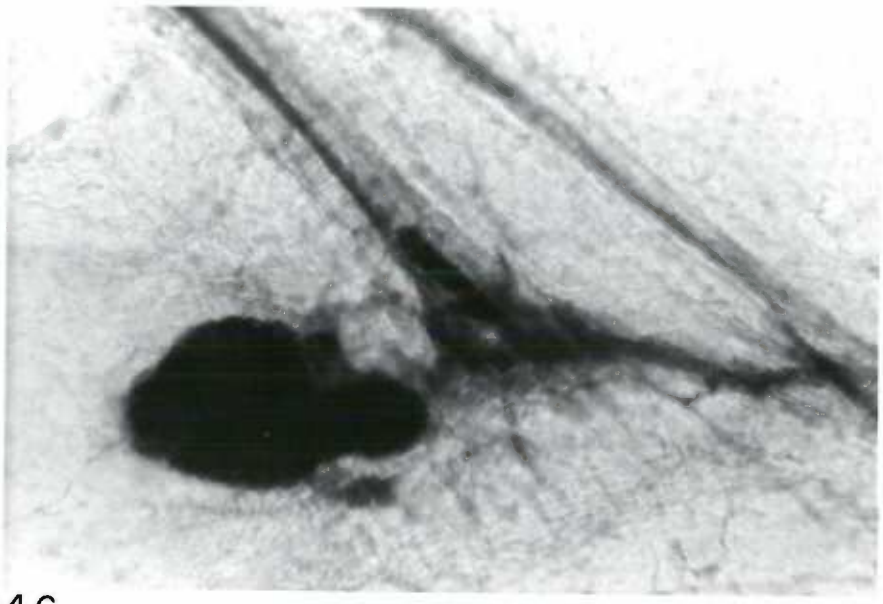
Figure 46:

Female, 28 years, normal breast (M-66-24). Subgross. A well-defined, ovoid lobule similar to that of Figure 44 has a communicating duct system. Hematoxylin. 10X.

Figure 47:

Corresponding histology of Figure 46. The lobule is composed of normal ductules and a cellular stroma with a mild chronic inflammatory cell infiltrate. The cellularity of the entire structure accounts for the solid appearance at the subgross level. Hematoxylin and eosin. 40X.



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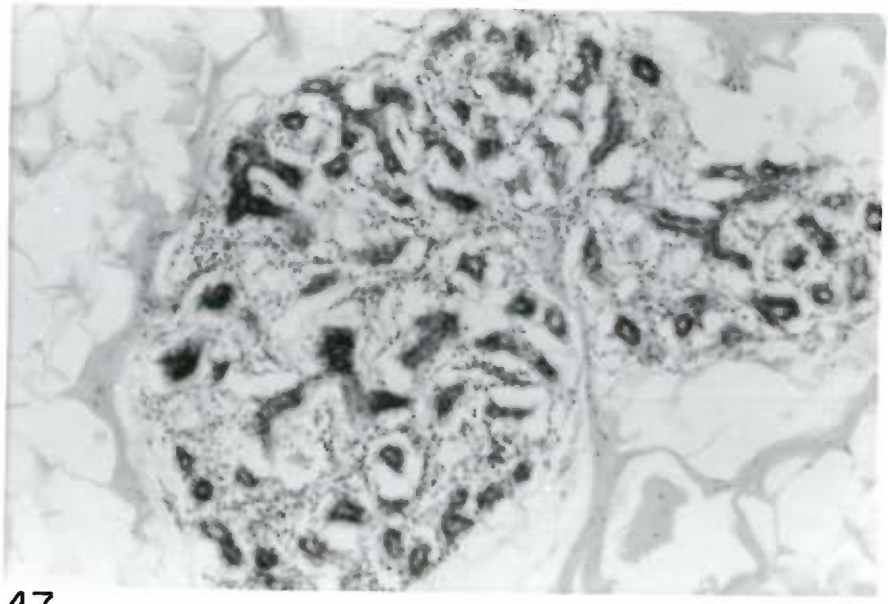

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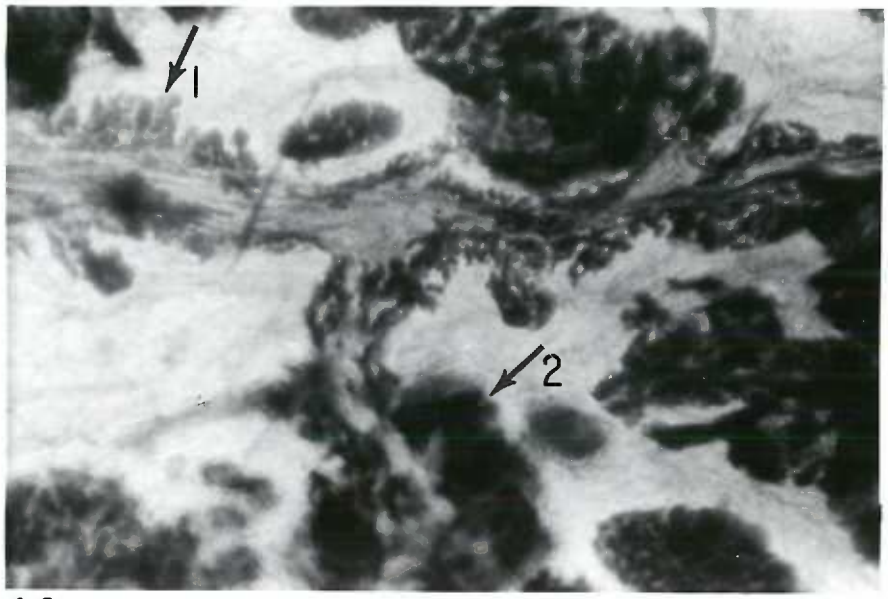
Figure 48:

Female, 48 years, normal breast (M-66-14). Subgross. Numerous irregular, feathery densities (arrow 1) are distributed along the duct wall. Lobule-like structures are also present (arrow 2). Hematoxylin. 10X.

Figure 49:

Corresponding histology of Figure 48. A central duct has radiating ductules which extend into surrounding loose stroma. The epithelium and stroma are normal. Hematoxylin and eosin. 40X.



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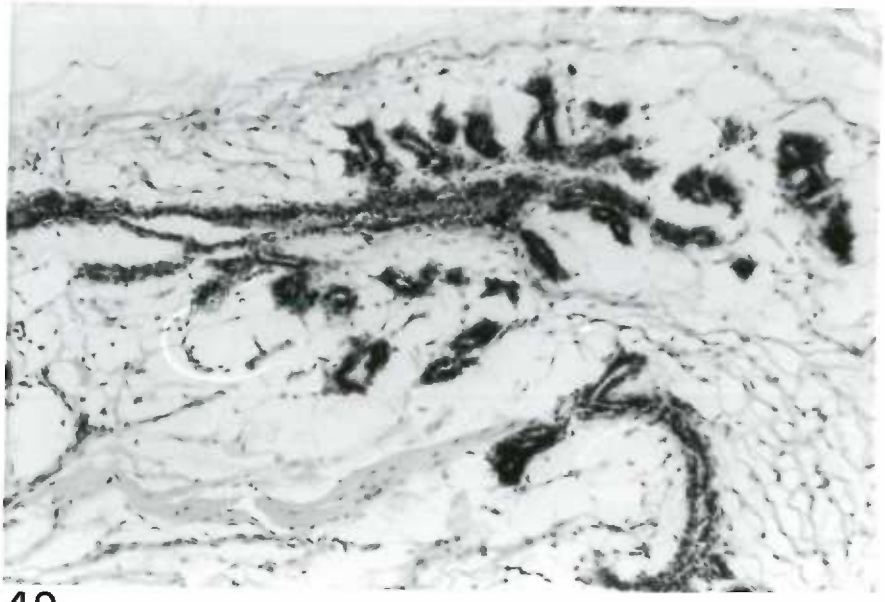

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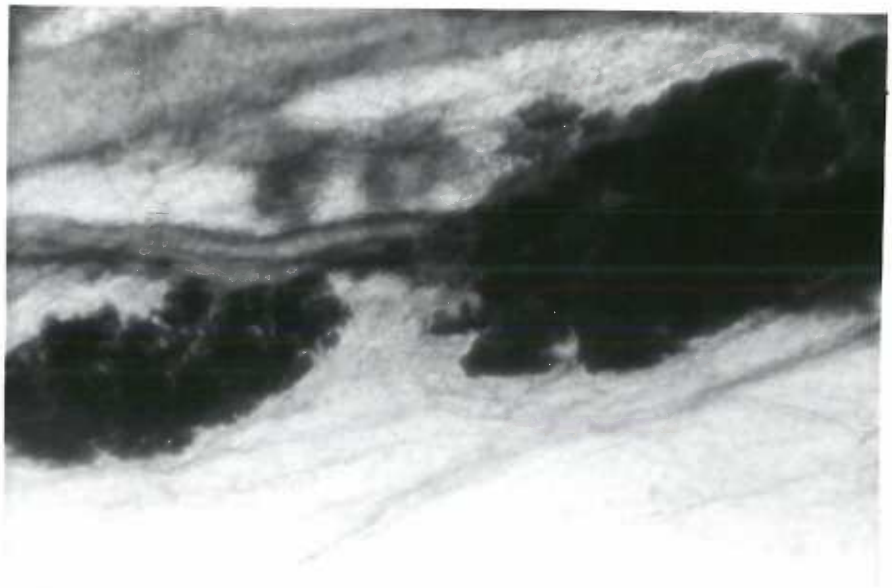
Figure 50:

Female, 48 years, normal breast (M-66-14). Subgross. Two large, dense lobular structures are located near a collecting duct. The lobule to the left shows within its interior the typical paleness characteristic of normal lobules, and not of more solid pathological formations, such as cancerous tissue. Hematoxylin. 10X.

Figure 51:

Corresponding histology of Figure 50. The ductules comprising the lobule are normal and closely packed in the loose intralobular stroma. The close proximity of individual ductules may explain the density of the lobules in Figure 50. Hematoxylin and eosin. 40X.



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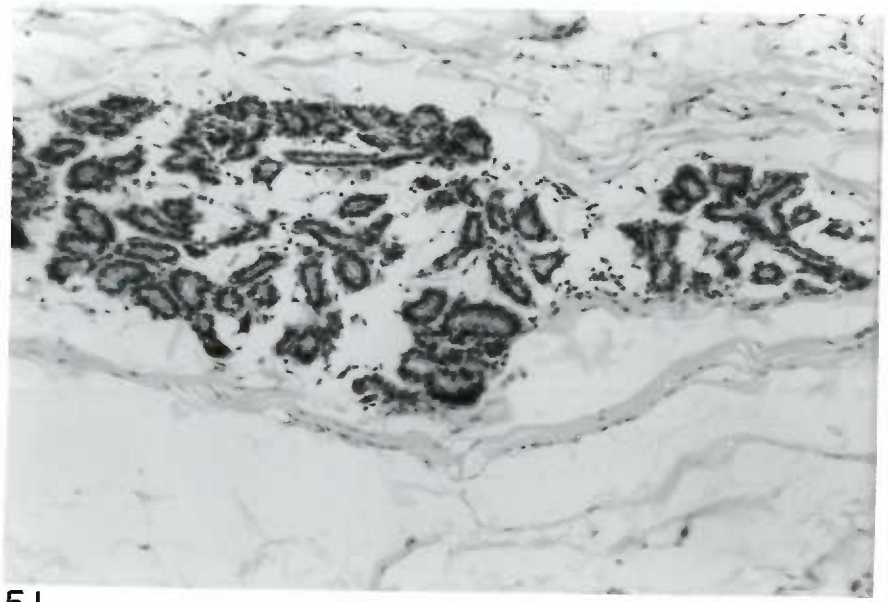

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Figure 52:

Female, 53 years, normal breast (M-66-21). Subgross. In contrast to Figure 50, this lobule (arrow) is very loosely structured, and is therefore more translucent. Ductules arborize among circular profiles, representing stromal fat cells. Hematoxylin. 10X.

Figure 53:

Corresponding histology of Figure 52. The subgross characteristics are represented by sparsely distributed normal ductules coursing through a loose fatty stroma. Hematoxylin and eosin. 10X.

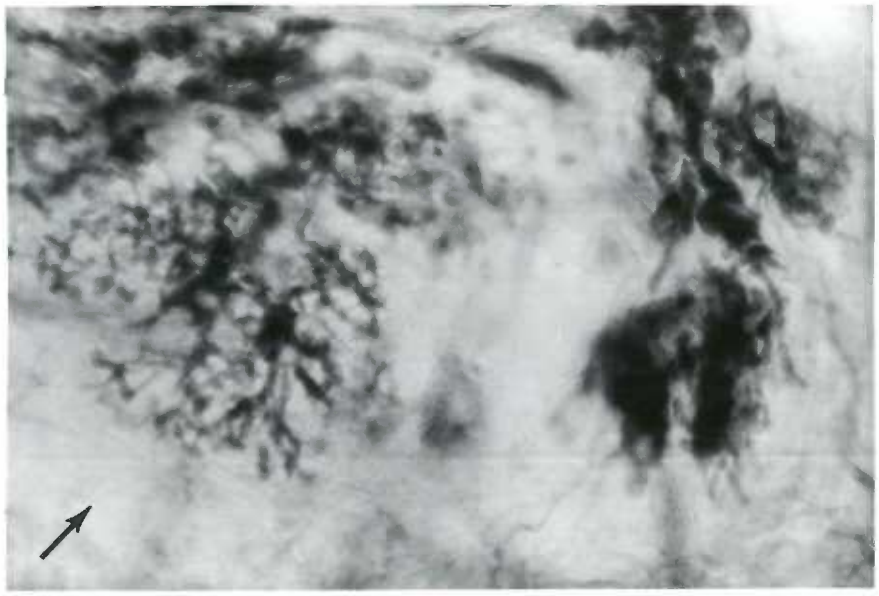

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Figure 54:

Female, 45 years, normal breast (M-66-2). Subgross of a normal lobule (center). The ductules are closer together than those of the lobule in Figure 52, explaining the greater density of this lobule. Hematoxylin. 10X.

Figure 55:

Corresponding histology of Figure 54. The lobule is crescent-shaped in cross-section. Hematoxylin and eosin. 10X.

54

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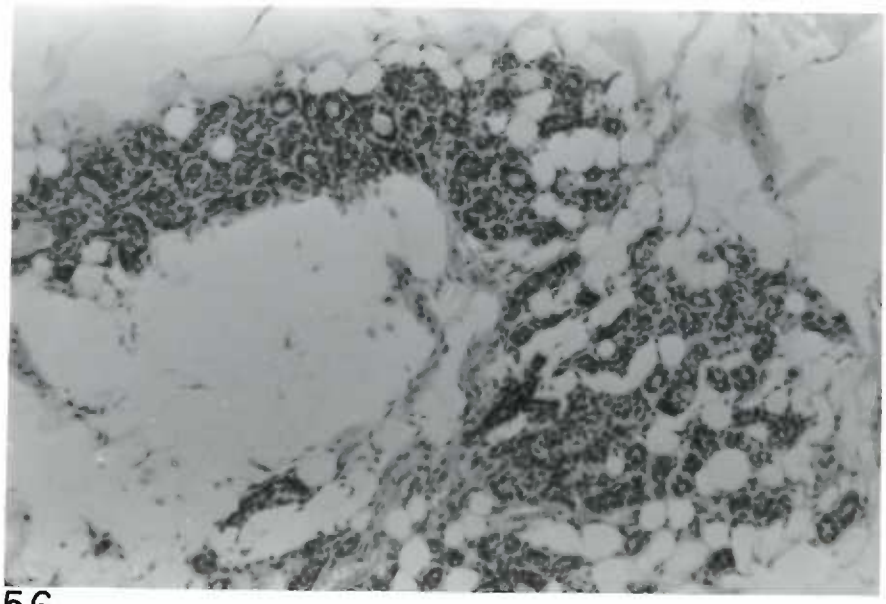
Figure 56:

Corresponding histology of Figure 54. Closely packed normal ductules are separated by dense stroma and fat cells. There is a slight increase in the amount of intralobular fibrous tissue. Hematoxylin and eosin. 40X.



56

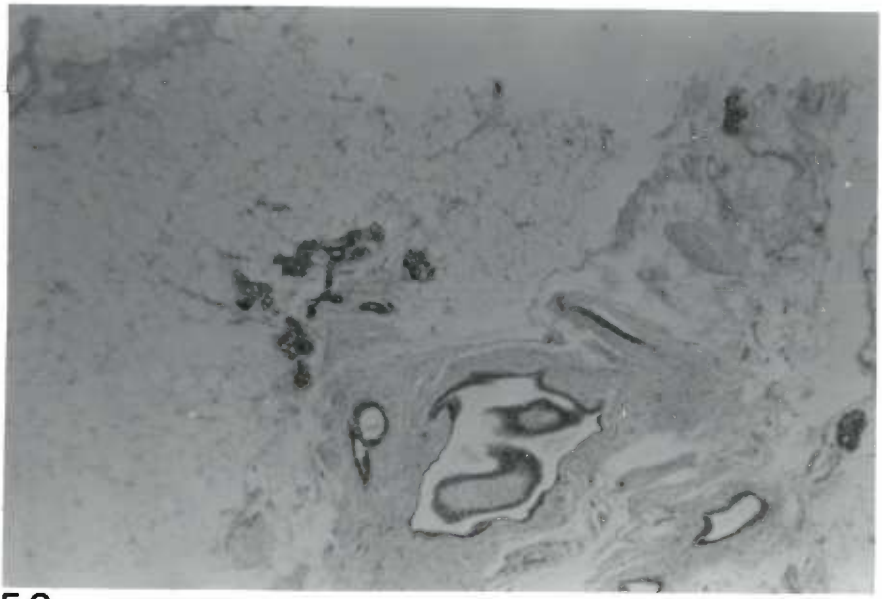
Figure 57:

Female, 45 years, normal breast (M-66-2). Subgross. An arborizing duct system and lobular formation project into a lobule of fat cells. The density at the bottom of the photograph is due to fibrous tissue. Hematoxylin. 10X.

Figure 58:

Corresponding histology of Figure 57 confirms the presence of the duct system in the fat lobule, as well as the presence of fibrous tissue at lower edge of photograph. Hematoxylin and eosin. 10X.

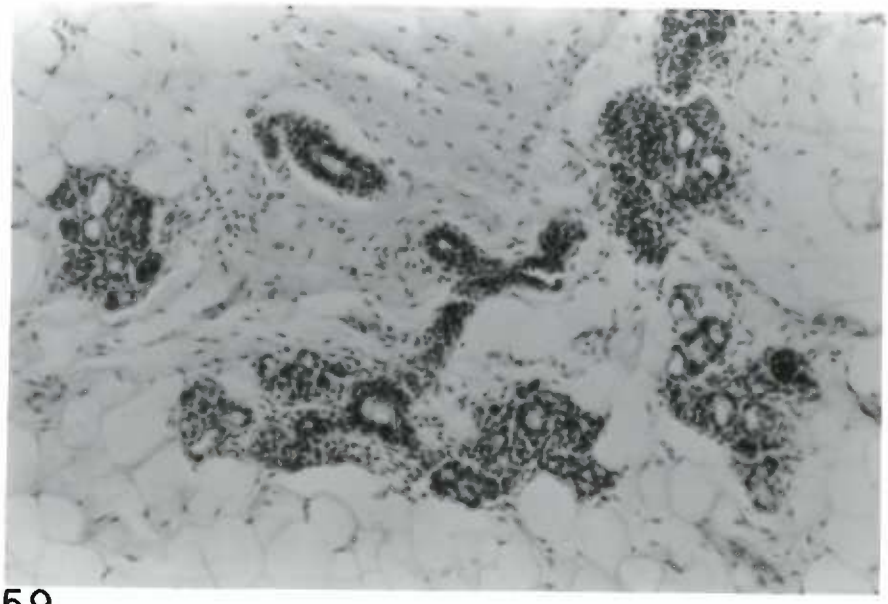
57



58

Figure 59:

Corresponding histology of Figure 57. The normal epithelial structures are thinly invested by fibrous stroma. Hematoxylin and eosin. 40X.



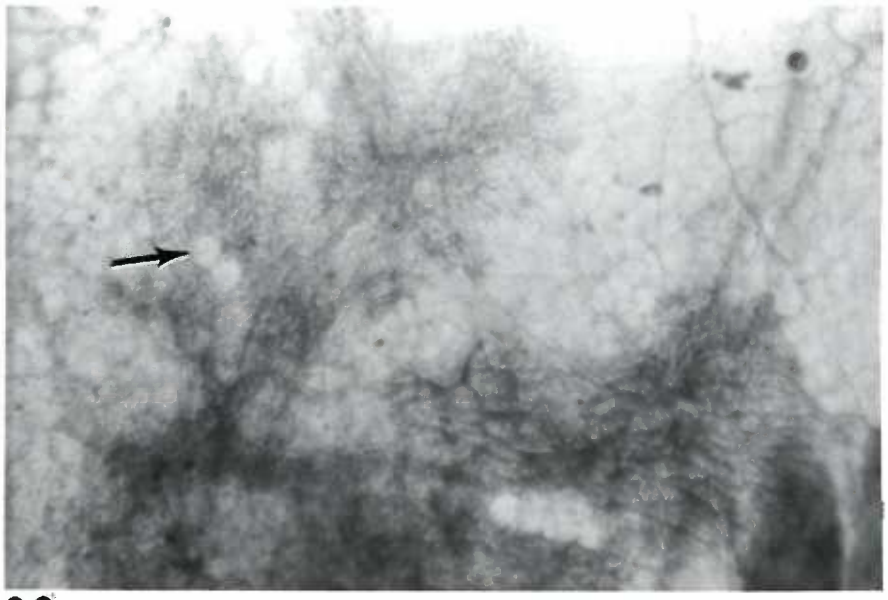
59

Figure 60:

Female, 55 years, normal breast (M-66-19). Subgross. Thin, delicate ductules forming irregular lobules are set in a hazy background. Circular translucent areas (arrow) are due to fat cells located in the lobule. Hematoxylin. 10X.

Figure 61:

Corresponding histology of Figure 60. Normal ductules are surrounded by cellular stroma infiltrated by a few chronic inflammatory cells. The inflammation may explain the periductal haziness in the subgross preparation. Hematoxylin and eosin. 40X.



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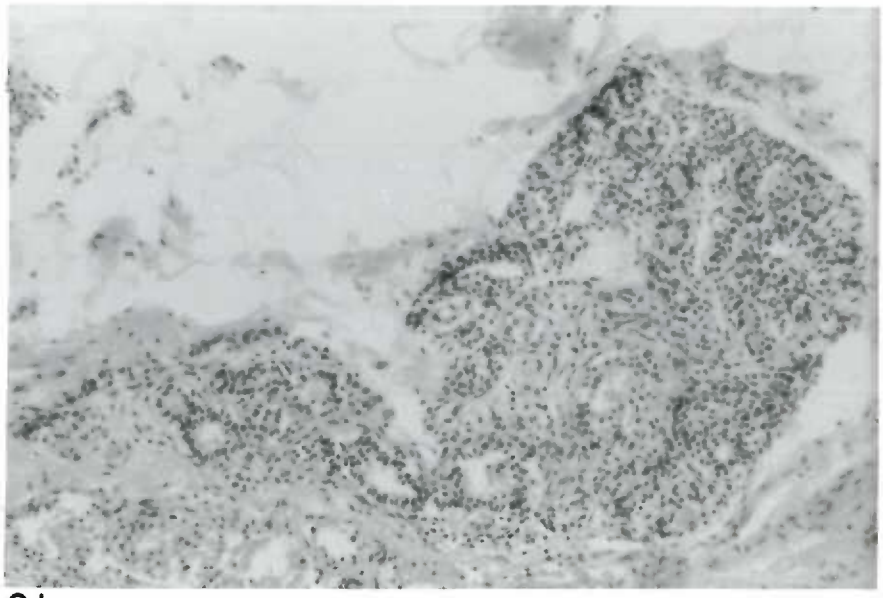


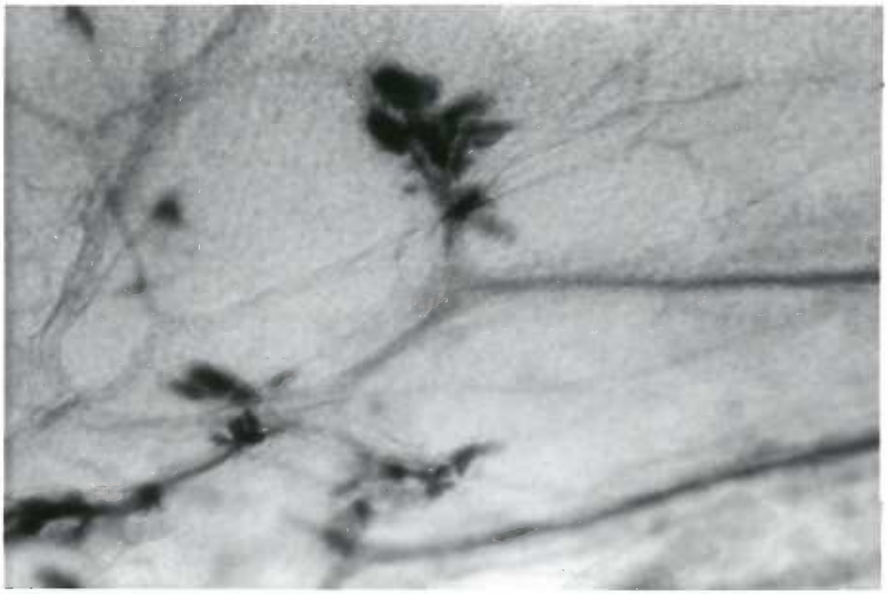
61

Figure 62:

Female, 19 years, normal breast (M-66-20). Subgross. A small, dense lobular formation in the upper center of the photograph has a duct entering from below. Other lobular densities are associated with adjacent ducts. The "chicken-wire" pattern in the background represents lobules of fat cells. Hematoxylin. 10X.

Figure 63:

Corresponding histology of Figure 62. The lobules are primarily cellular fibrous stroma surrounding poorly defined epithelial cells, and correspond to the dense lobular formations in Figure 62. Note the surrounding fat cells. Hematoxylin and eosin. 40X.



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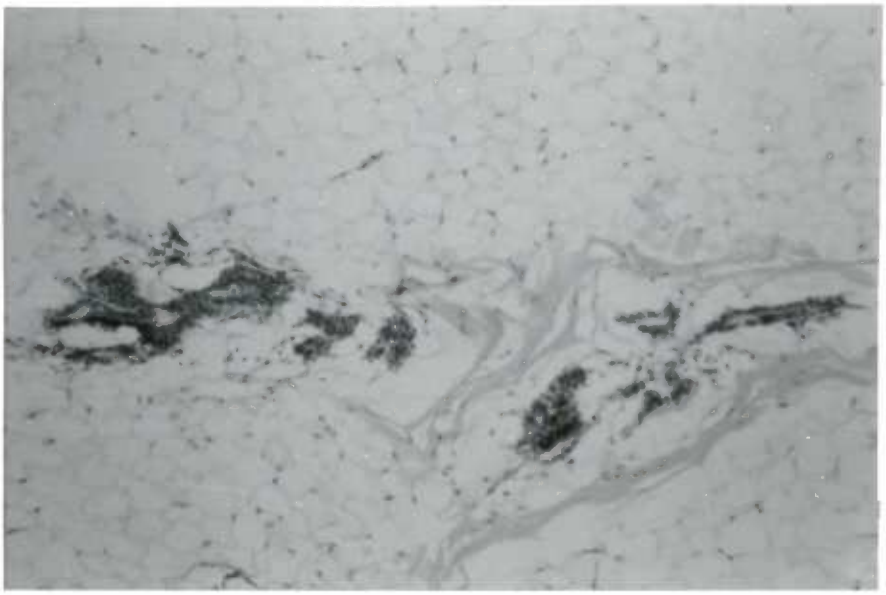


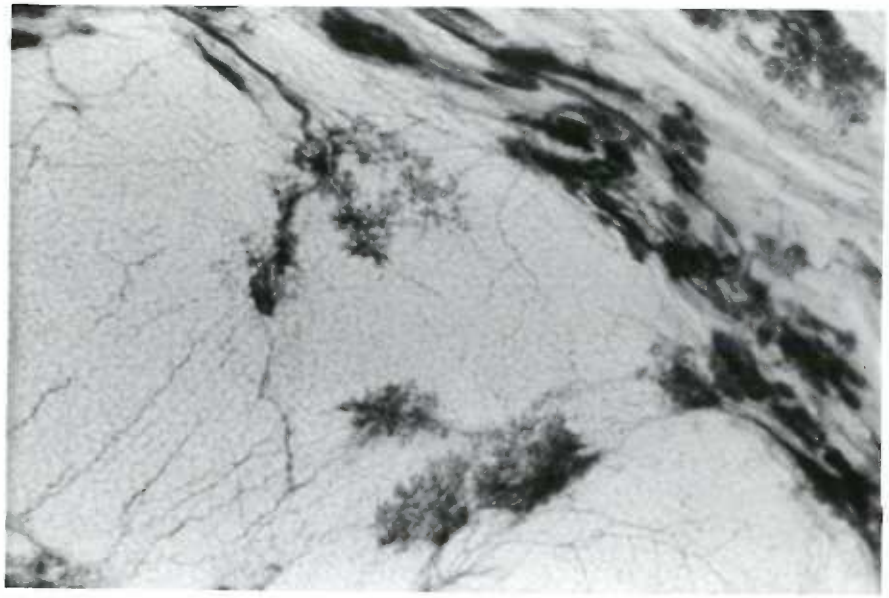
63

Figure 64:

Female, 52 years, normal breast (M-66-3). Subgross. Lobules are embedded in fat (center); and are also observed in the band of fibrous stroma (upper right). Note that the lobules in the fat have sharp, serrated borders, while the lobules in the fibrous band have smooth borders. Hematoxylin. 5X.

Figure 65:

Corresponding histology of Figure 64. Normal ductules with thin periductal fibrous tissue form lobules among fat cells. Hematoxylin and eosin. 40X.



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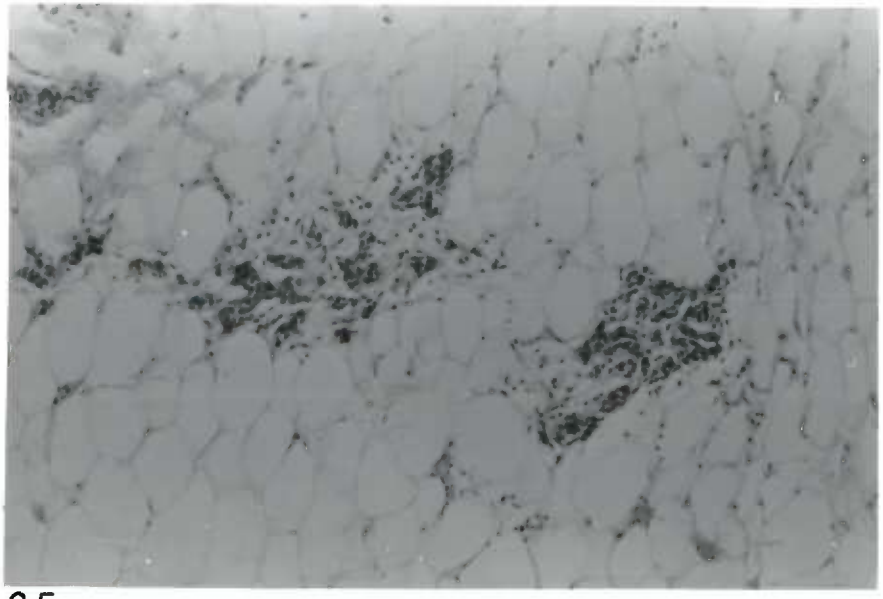


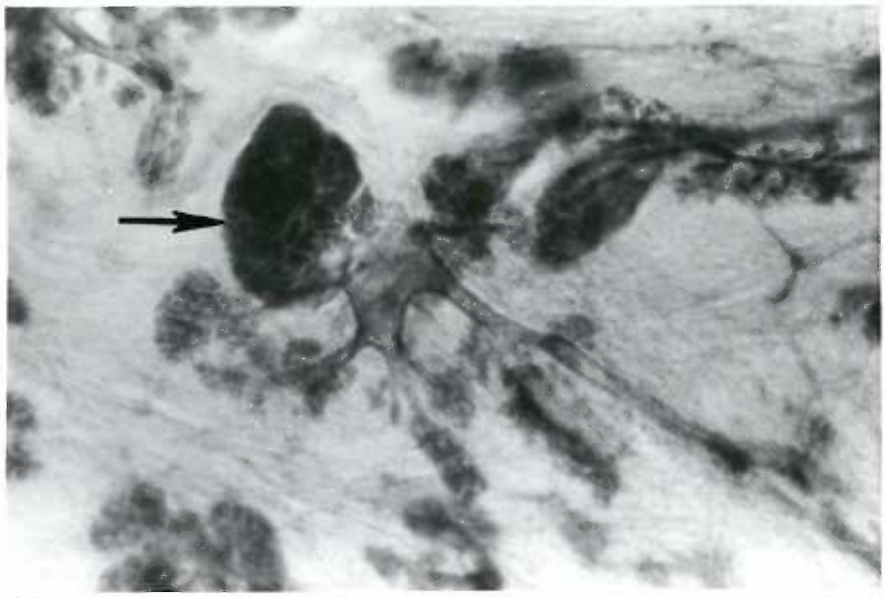
65

Figure 66:

Female, 56 years, breast with mammary dysplasia (M-66-4). Subgross. The unusual lobular formation (arrow) is larger and more dense than surrounding lobules. A large duct enters the base of this lobule as well as several other lobules in adjacent tissue. Hematoxylin. 10X.

Figure 67:

Corresponding histology of Figure 66. Several small ductules, many of which are indistinct, and have atrophic epithelium, are embedded in fibrous tissue. The surrounding stroma is normal. Hematoxylin and eosin. 40X.



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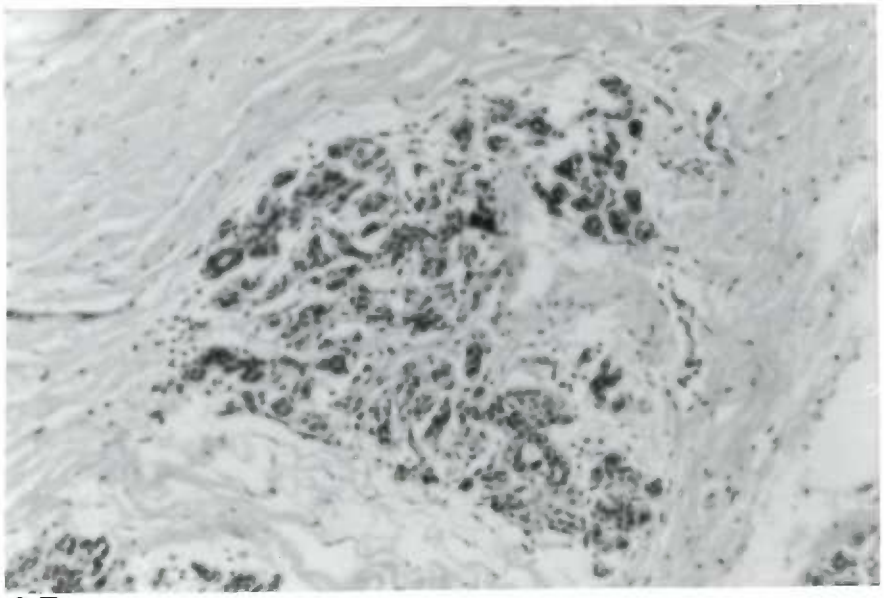


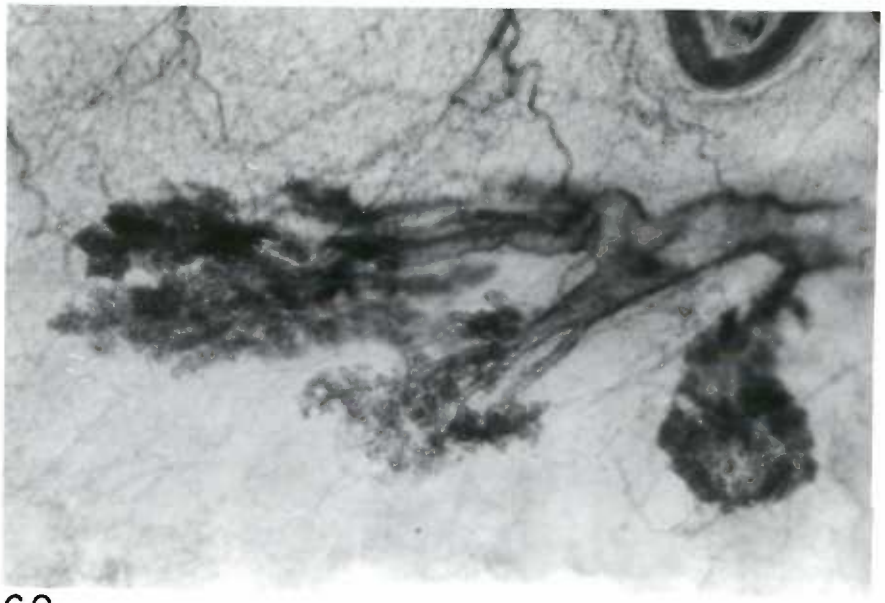
67

Figure 68:

Female, 45 years, normal breast (M-66-2). Subgross. A large duct and its branches enters from the right and terminates in lobular formations. Several thin tortuous dark lines are blood vessels, most obvious in the upper one-third of the photomicrograph. Hematoxylin. 10X.

Figure 69:

Corresponding histology of Figure 68. The microscopic preparation confirms the above. Hematoxylin and eosin. 40X.



68

69

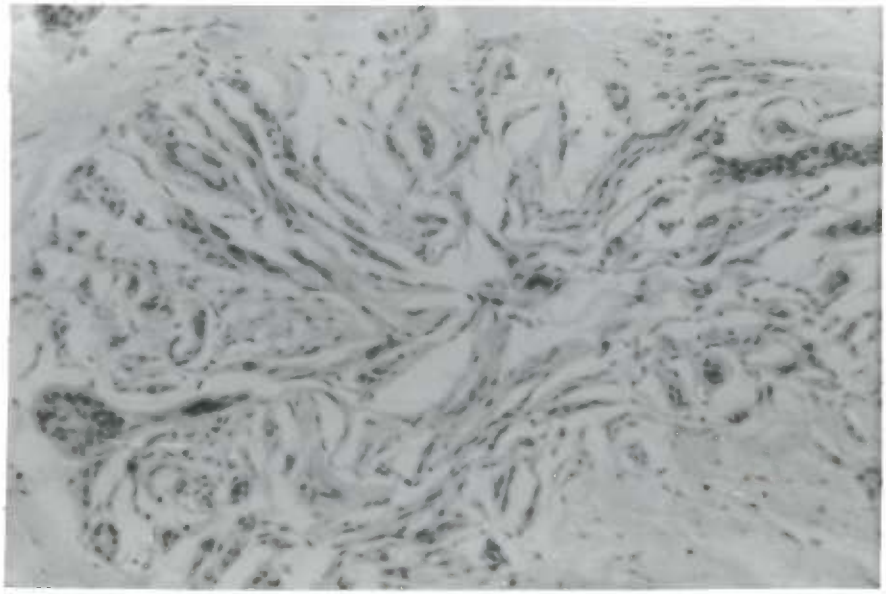
Figure 70:

Female, 56 years, normal breast (M-66-12). Subgross. An unusual lobular pattern in the central portion of the photograph has indistinct borders and a somewhat stellate shape. The formation is composed of circular and linear densities set in a background of fibrous tissue. Hematoxylin. 10X.

Figure 71:

Corresponding histology of Figure 70. Histology shows atrophic ductule epithelium separated by dense fibrous strands containing cleft-like spaces. This is an atrophic lobule. Hematoxylin and eosin. 40X.

70



71

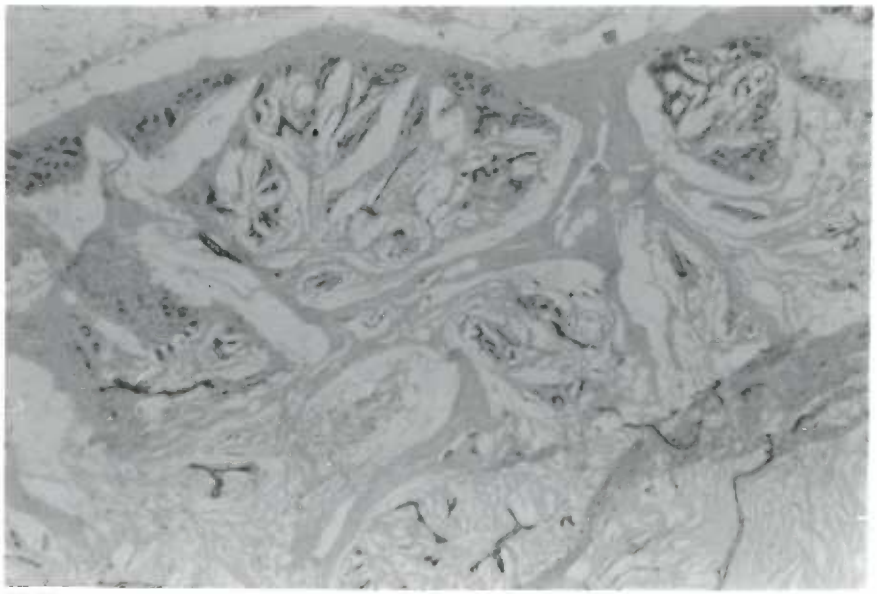
Figure 72:

Female, 19 years, normal breast (M-66-8). Subgross. The lobules are made up of a complex pattern of thin strands of epithelium embedded in intra- and extralobular connective tissue. Hematoxylin. 10X.

Figure 73:

Corresponding histology of Figure 72. Thin ductules, abundant stroma, and cleft-like stromal spaces. Hematoxylin and eosin. 10X.

72



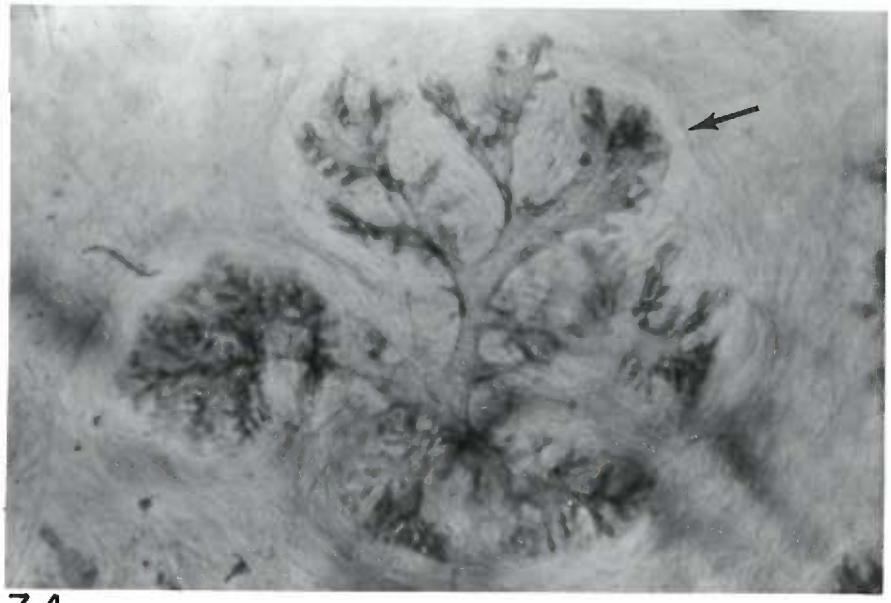
73

Figure 74:

Female, 19 years, normal breast (M-66-8). Subgross. Lobules formed by groups of blunt ductules are easily seen. A border between intra- and extralobular stroma is identified (arrow). Hematoxylin. 10X.

Figure 75:

Corresponding histology of Figure 74. A lobule of normal ductules and dense compact stroma corresponds to the subgross preparation. Note that the intralobular stroma, which is heavily collagenized, forms a layer peripheral to the ductules, as it does in the subgross. Hematoxylin and eosin. 40X.



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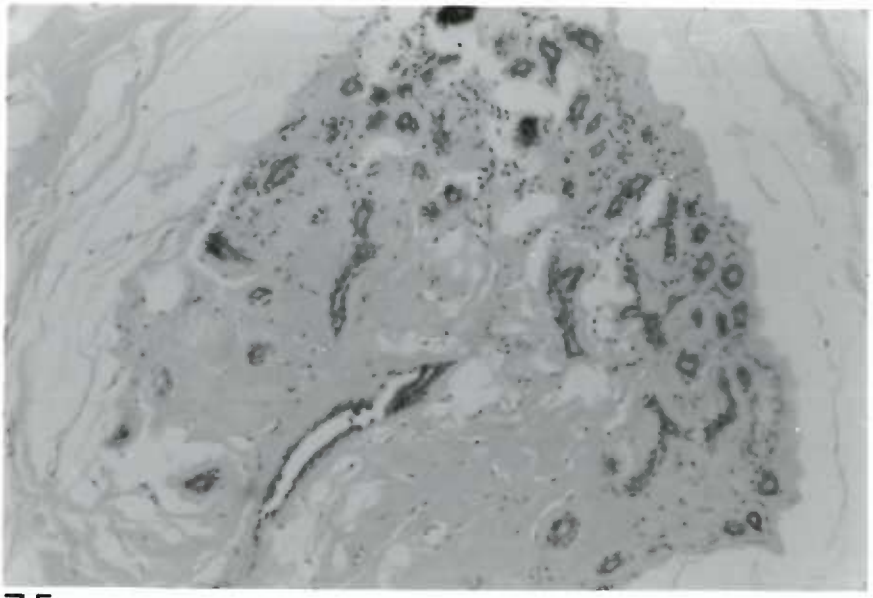


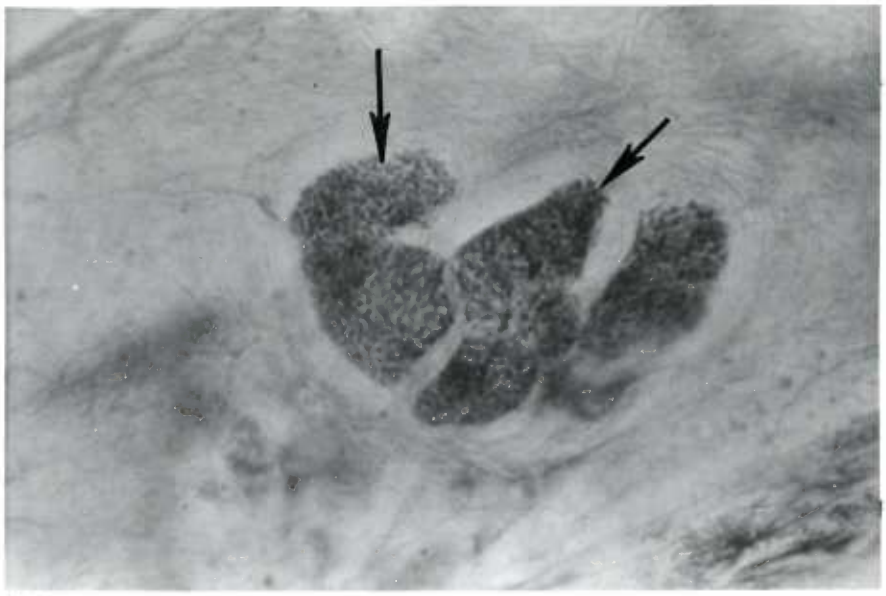
75

Figure 76:

Female, 19 years, normal breast (M-66-8). Subgross. The lobule is composed of closely packed ductules which appear as regularly spaced dense, circular or linear structures. Individual segments of the lobule are separated by bundles of fibrous connective tissue (arrows). Hematoxylin. 10X.

Figure 77:

Corresponding histology of Figure 76. Normal ductules separated by dense intralobular connective tissue. Hematoxylin and eosin. 10X.



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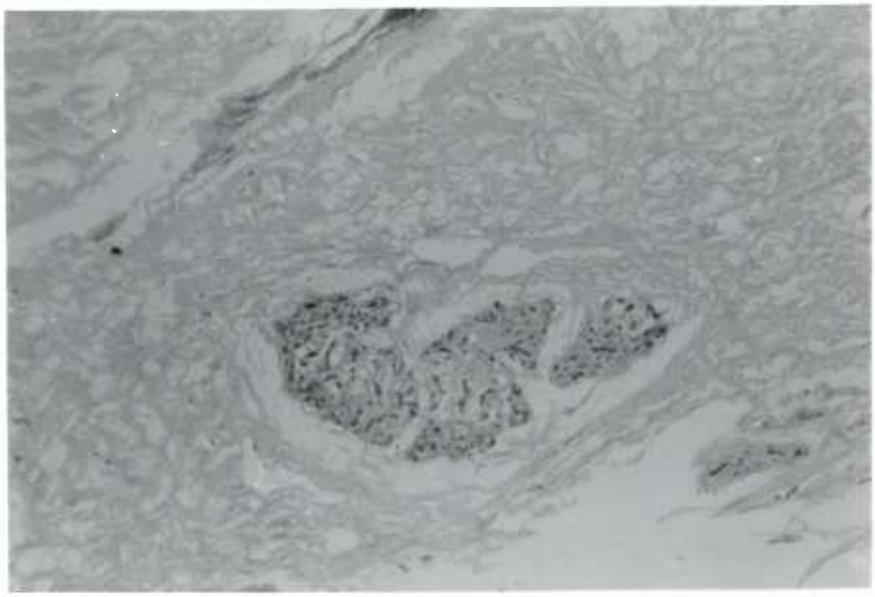


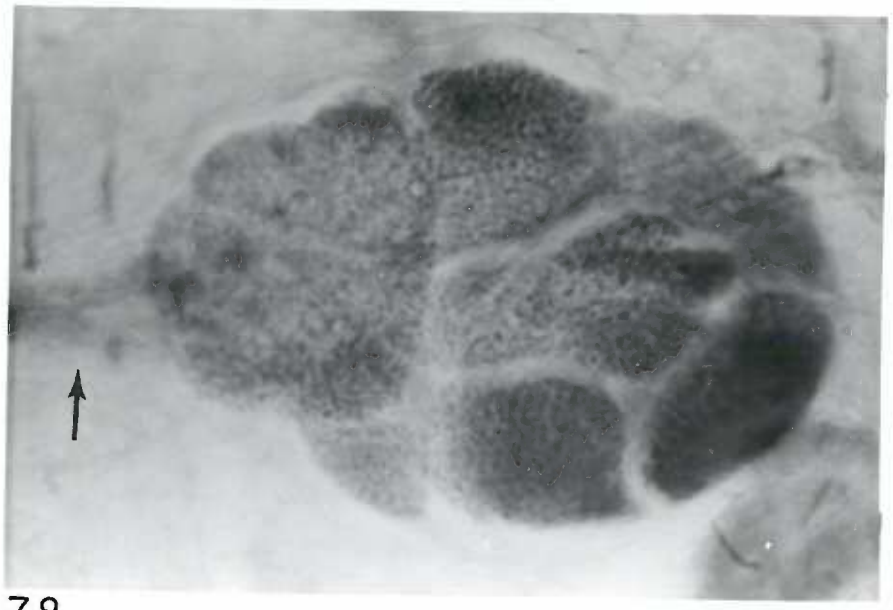
77

Figure 78:

Female, 19 years, normal breast (M-66-8). Subgross. A lobule similar to the one in Figure 76. The pale intersegmental bands in the lobule represent connective tissue. A large duct (arrow) enters the lobule. Hematoxylin. 10X.

Figure 79:

Corresponding histology of Figure 78. Normal ductules with occasional visible lumina are embedded in normal intralobular connective tissue. Several ducts are entering from the side of the microphotograph. Hematoxylin and eosin. 10X.



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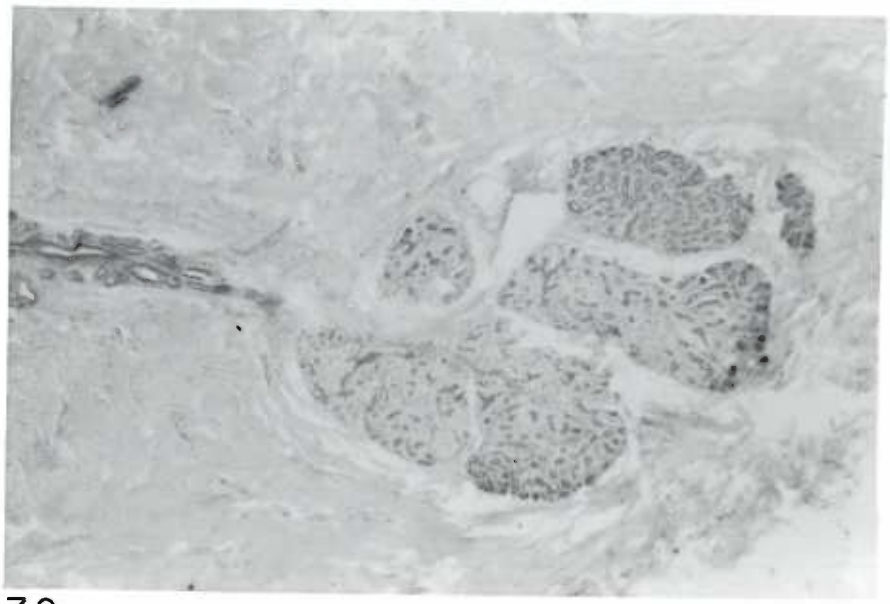


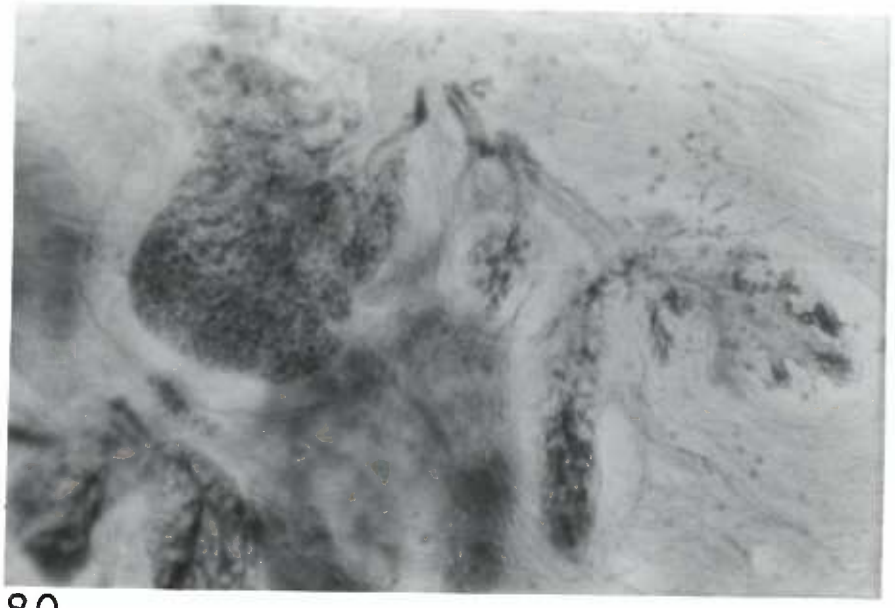
79

Figure 80:

Female, 19 years, normal breast (M-66-8). Subgross. The stippled mass to the right represents ductules grouped into a lobular formation. On the far left, short broad ductules may be forming an early lobule. Hematoxylin. 10X.

Figure 81:

Corresponding histology of Figure 80. The normal, more compact lobule on the right corresponds to the stippled mass in the subgross photograph. Hematoxylin and eosin. 10X.



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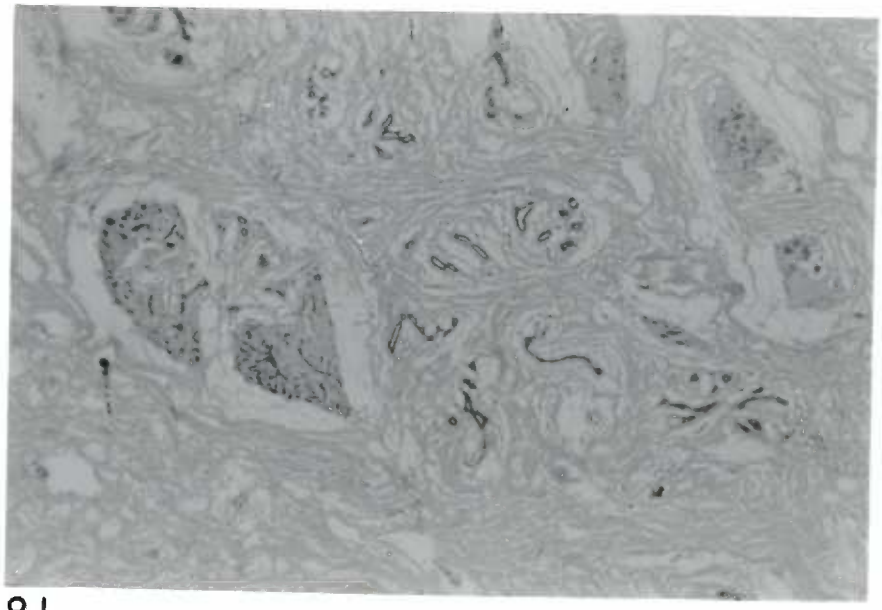
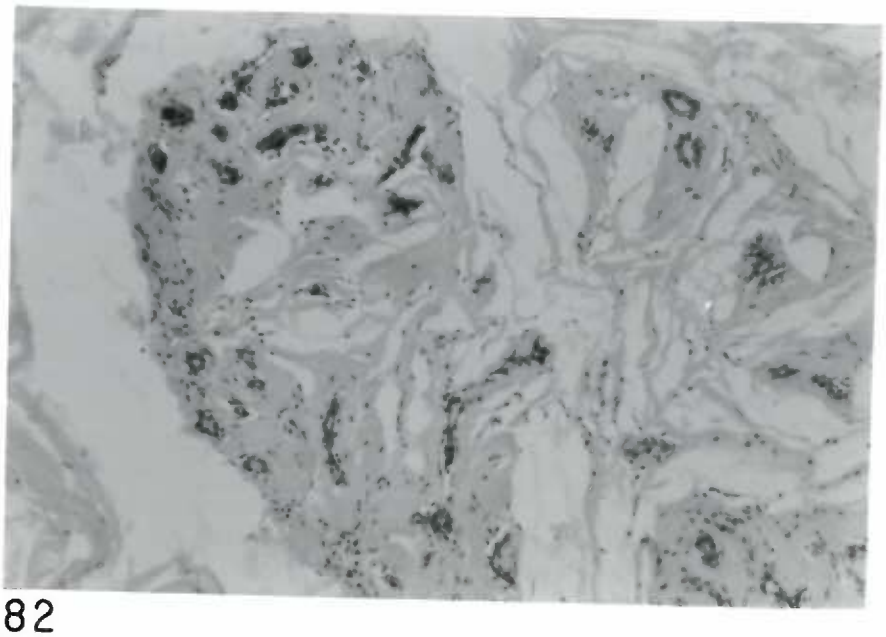


81

Figure 82:

Corresponding histology of Figure 80. The stippled mass has relatively acellular, but dense intralobular connective tissue. Several empty spaces in the connective tissue may be artefactual. Hematoxylin and eosin. 40X.



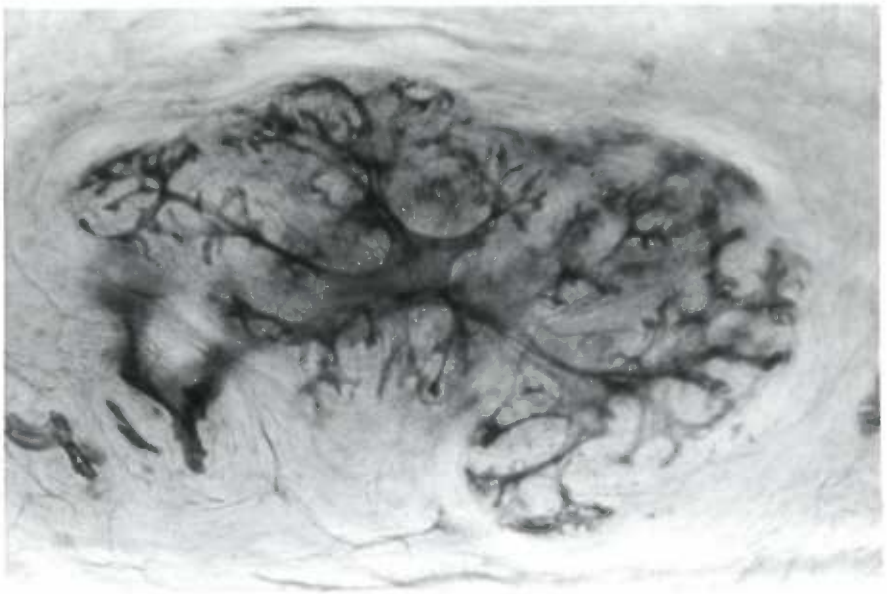
82

Figure 83:

Female, 19 years, normal breast (M-66-8). Subgross. Arborizing, flattened ducts and ductules form a lobule. Hematoxylin. 10X.

Figure 84:

Corresponding histology of Figure 83. Normal ducts with empty lumina are widely separated by lacy, hypocellular fibrous stroma. The nature and abundance of the stroma may account for its translucency in the subgross formation. Hematoxylin and eosin. 40X.



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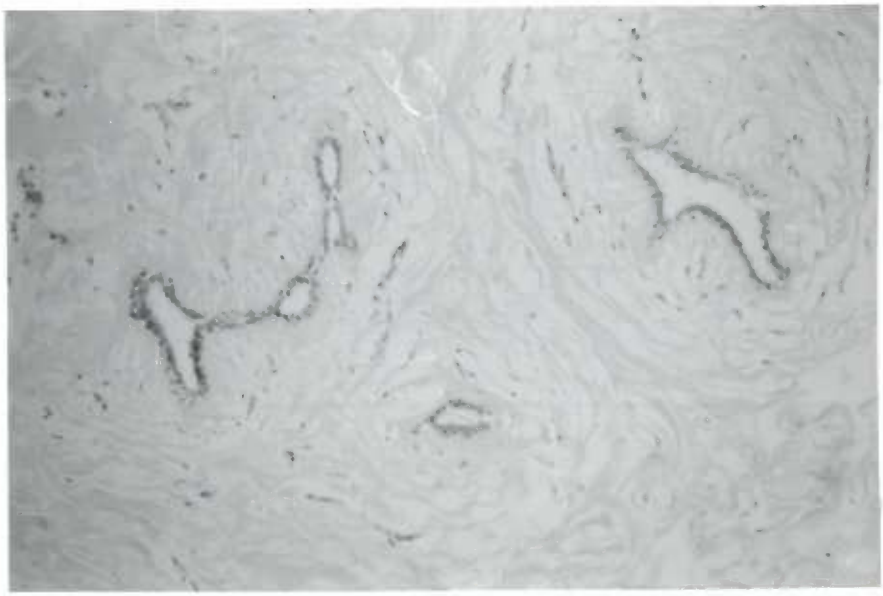


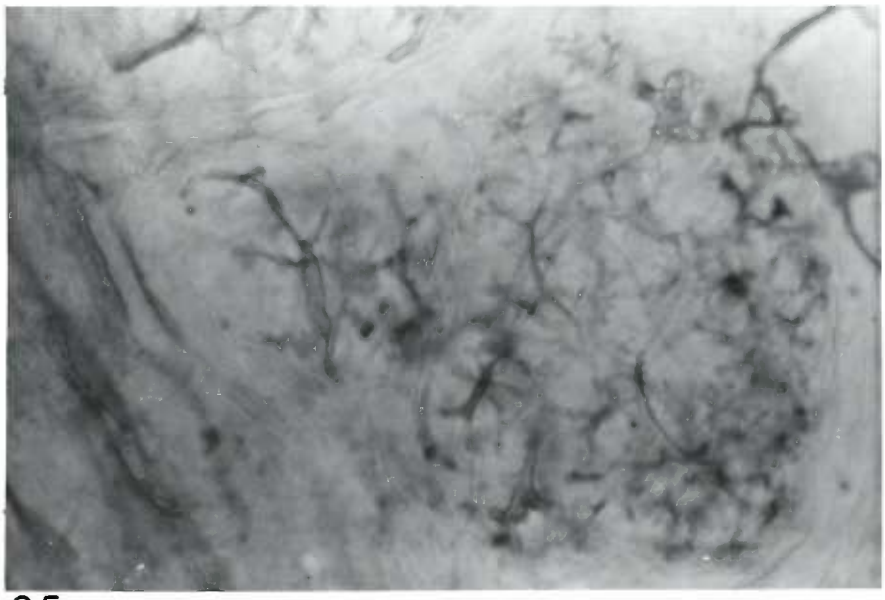
84

Figure 85:

Female, 19 years, normal breast (M-66-8). Subgross. This lobule has several elongated ductules which are loosely woven in abundant lobular stroma. Hematoxylin. 10X.

Figure 86:

Corresponding histology of Figure 85. The normal ductules are separated by dense, compact intralobular stroma. There is a mild inflammatory infiltrate in the lower third of the lobule. Hematoxylin and eosin. 40X.



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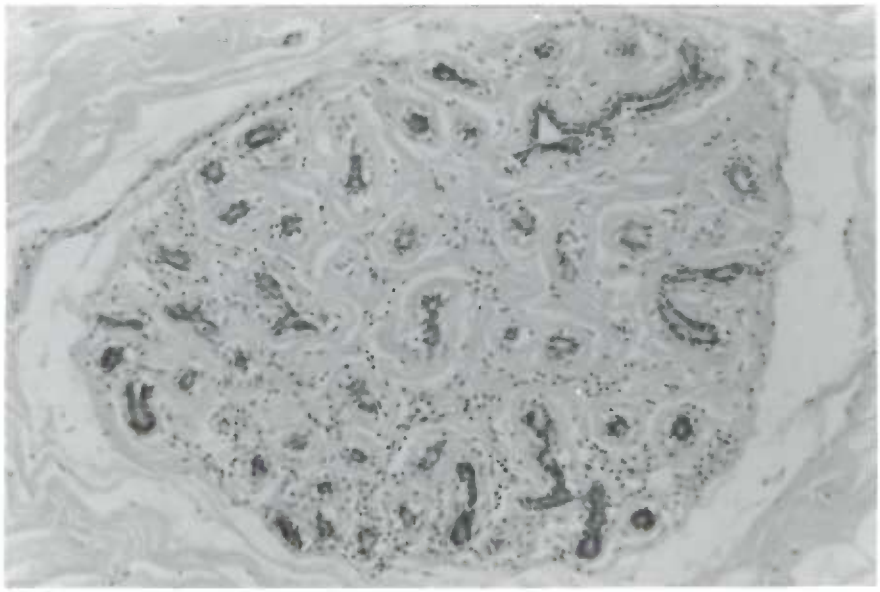


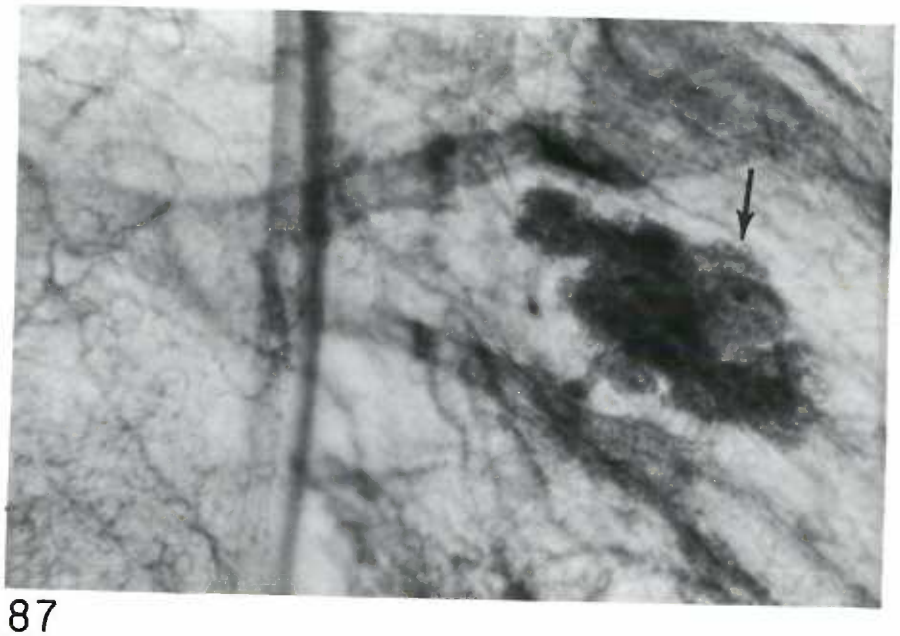
86

Figure 87:

Female, 45 years, normal breast (M-66-2). Subgross. A medium-sized branching duct enters from the left. Dense lobule has a few slightly dilated ductules at its periphery (arrow). Hematoxylin. 10X.

Figure 88:

Corresponding histology of Figure 87. Several dilated ducts and ductules, some of which are peripheral in location, are seen. Occasional acellular intraluminal material is present. The stroma is dense and highly cellular, possibly explaining the homogeneity and dark nature of the subgross structure. This is moderate lobular fibrosis. Hematoxylin and eosin. 40X.



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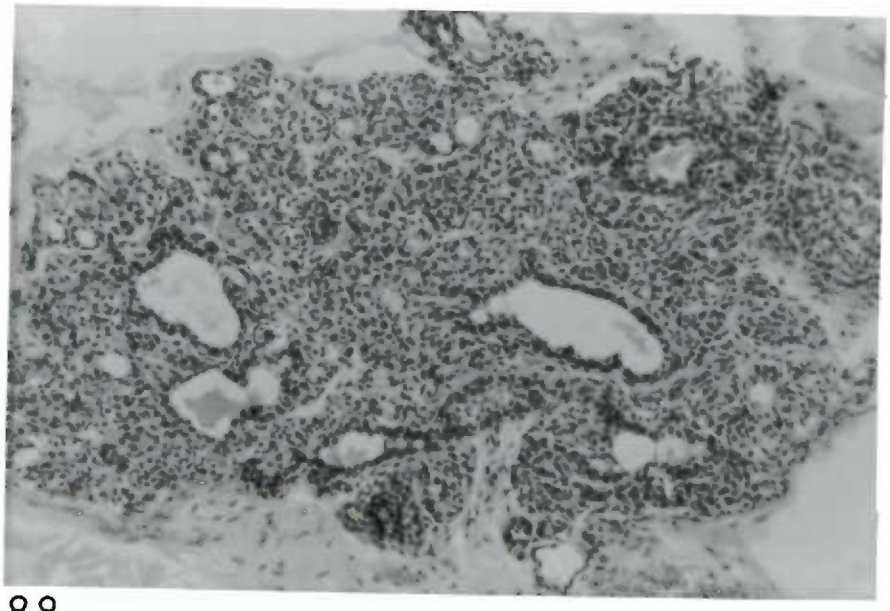


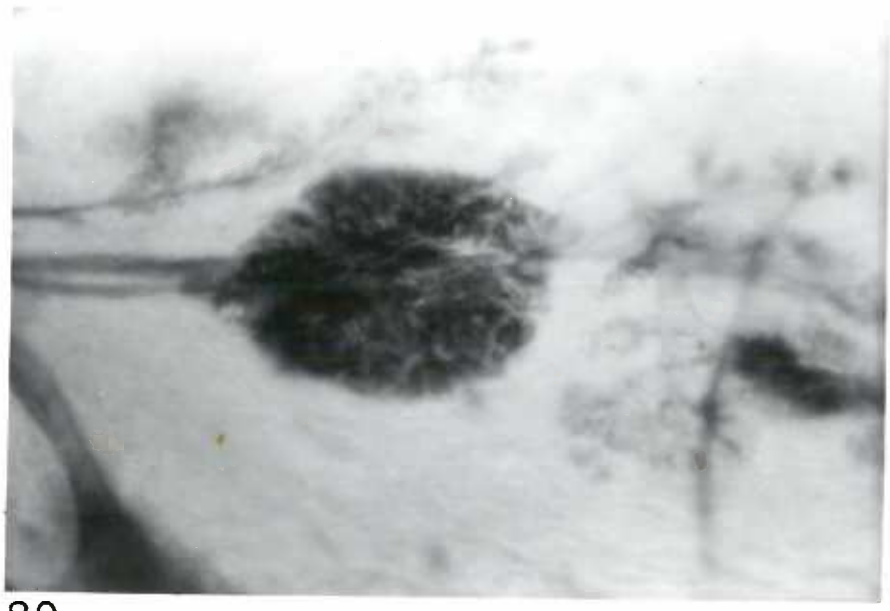
88

Figure 89:

Female, 53 years, normal breast (M-66-21). Subgross. A circumscribed, dense lobule has a duct either entering it, or coursing behind it. The small, light lines within the lobule represent intralobular stroma. Hematoxylin. 10X.

Figure 90:

Corresponding histology of Figure 89. There is loose intralobular stroma and normal, but somewhat atrophic, ductular epithelium. The lumina of many ductules are filled with amorphous material. Hematoxylin and eosin. 40X.



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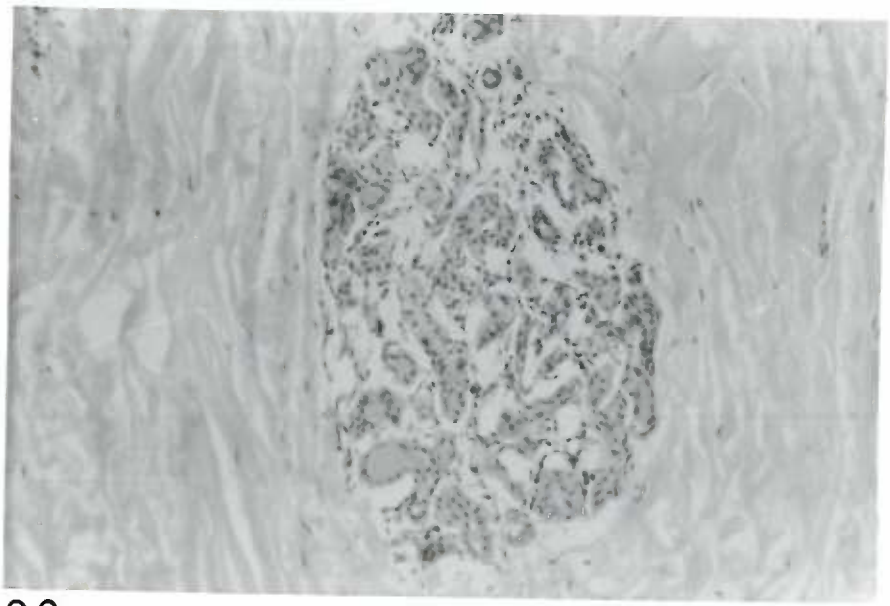

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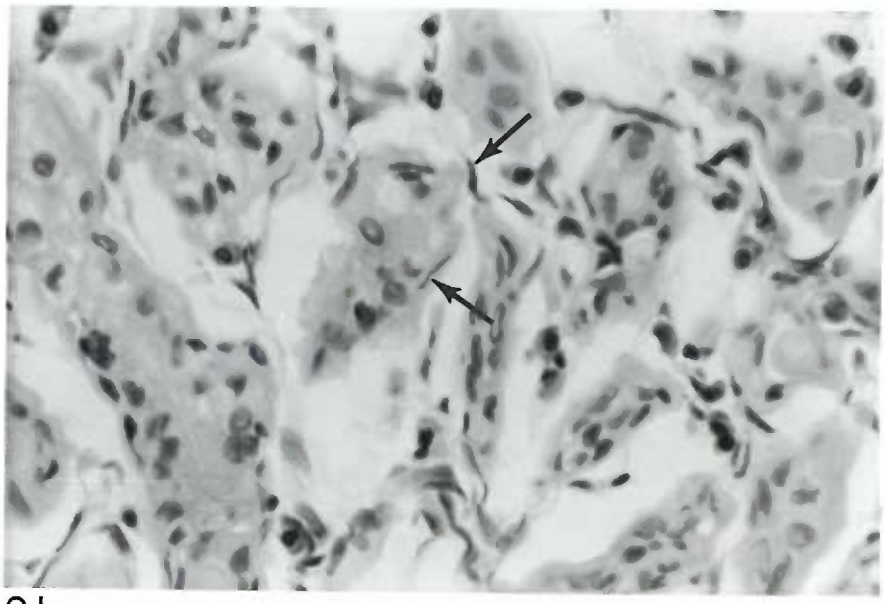
Figure 91:

Corresponding histology of Figure 89. Note the spindle-shaped myoepithelial cells (arrows) surrounding the ductular epithelium. Hematoxylin and eosin. 160X.



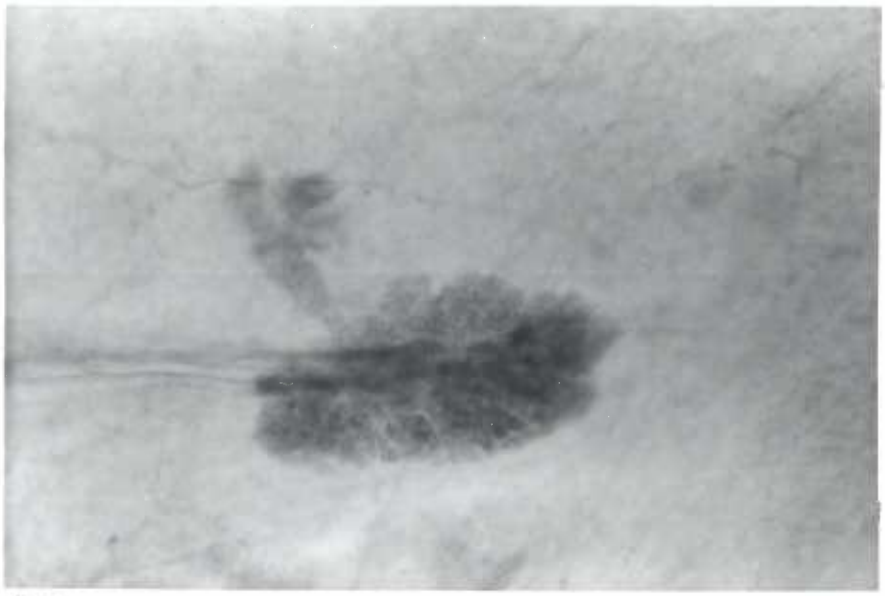
91

Figure 92:

Female, 53 years, normal breast (M-66-21). Subgross. A normal, well defined lobule with its duct. The intralobular stroma is cellular. Therefore, the prominent light lines often observed within the lobule (seen in Fig. 90) are not present. Hematoxylin. 10X.

Figure 93:

Corresponding histology of Figure 92. Dense, cellular, intralobular stroma with normal epithelium. There is moderate lobular fibrosis. Hematoxylin and eosin. 40X.



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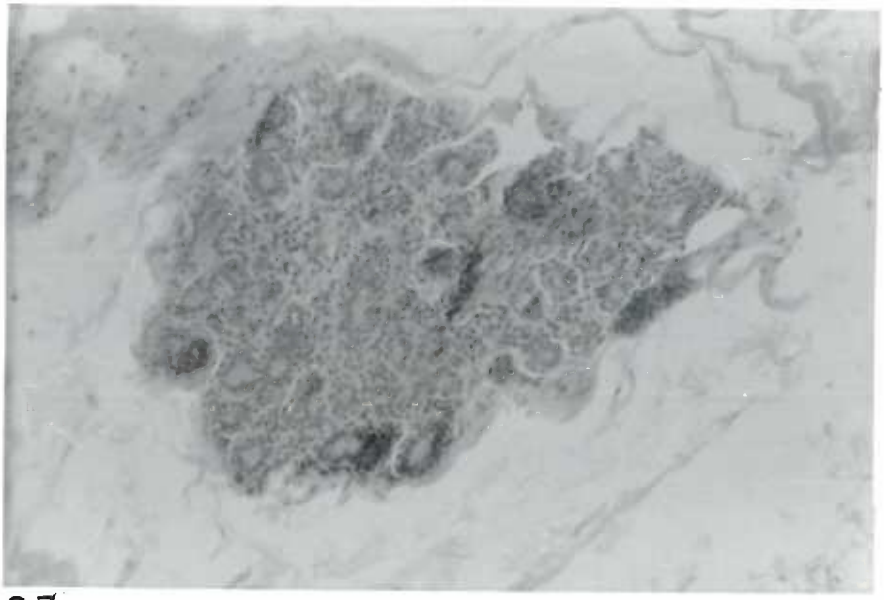


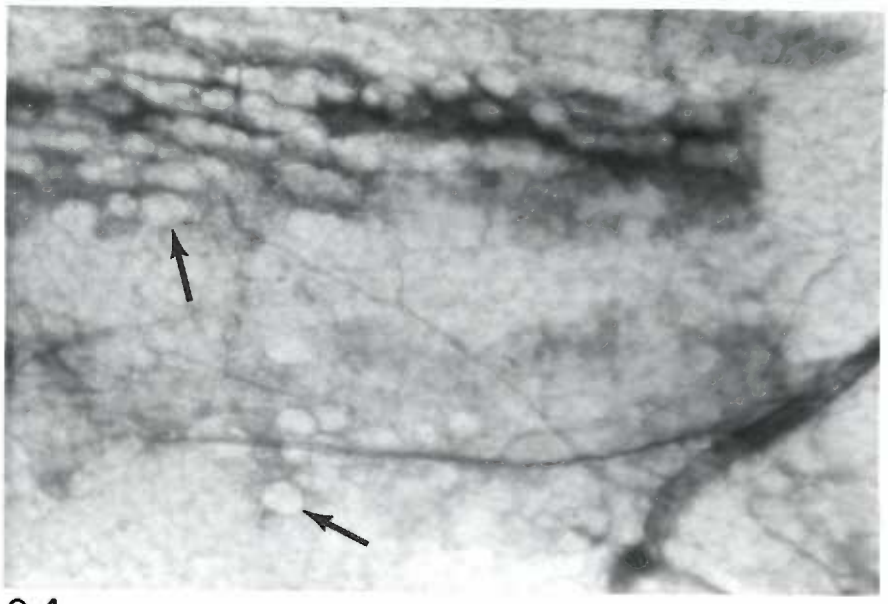
93

Figure 94:

Female, 55 years, normal breast (M-66-19). Subgross. The diffuse densities represent flat, thin lobules. The sharply defined translucent areas are fat cells (arrows) located within the lobules. Hematoxylin. 10X.

Figure 95:

Corresponding histology for Figure 94. The ductules and surrounding stroma are normal. Note the dense cellular stroma which may be responsible for the darker areas in the subgross preparations. Hematoxylin and eosin. 40X.



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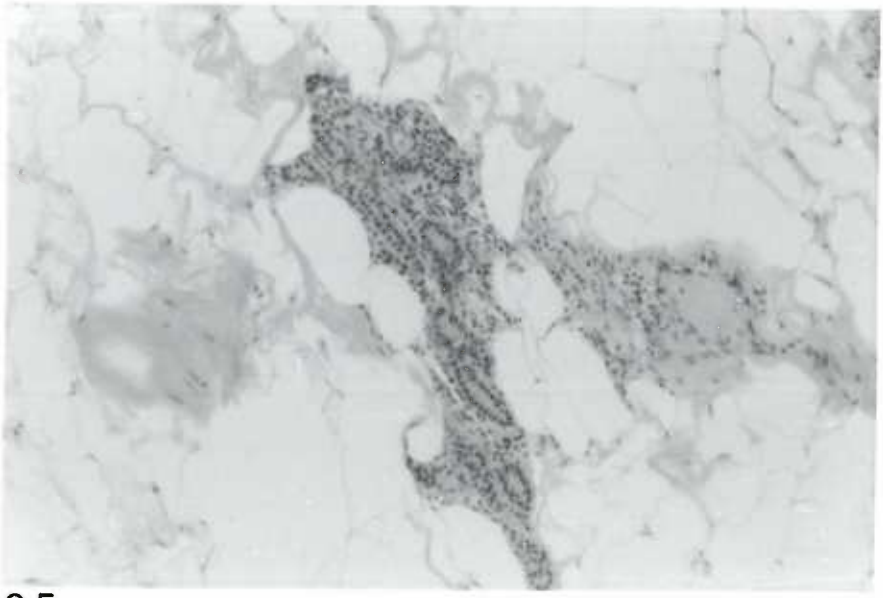


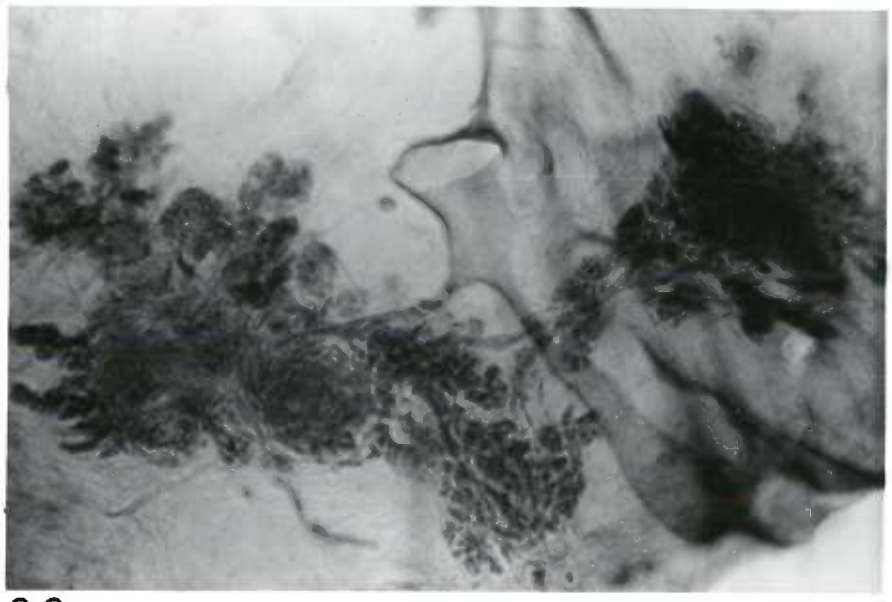
95

Figure 96:

Female, 56 years, normal breast (M-66-12). Subgross. An unusual lobular pattern shows a whorled arrangement of the epithelial components. Entering ducts are easily identified. Hematoxylin. 10X.

Figure 97:

Female, 56 years, normal breast (M-66-12). Subgross. A smaller lobule taken from the same breast has a pattern similar to that seen in Figure 96. Note the entering duct, represented by the poorly defined dark line entering the formation. Hematoxylin. 10X.



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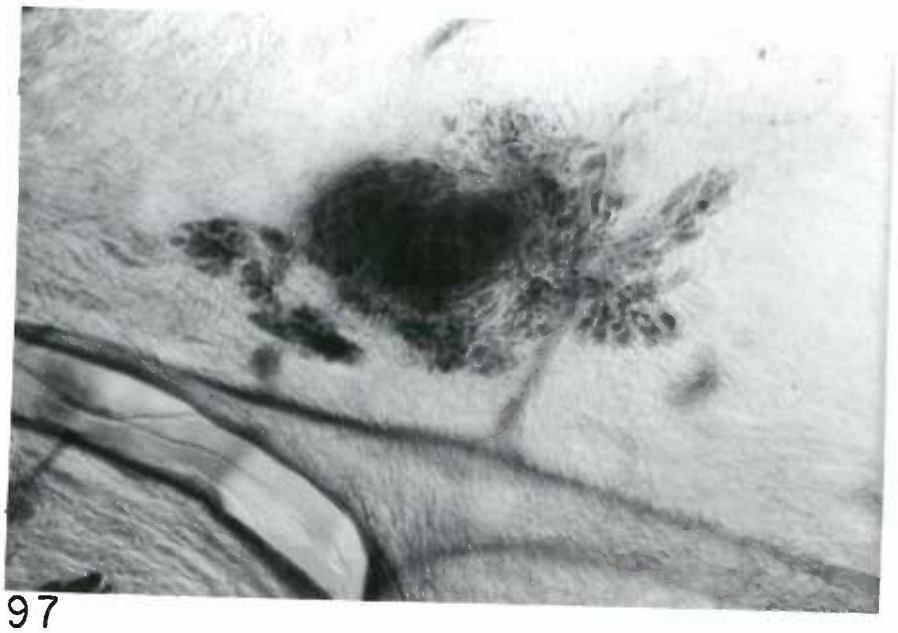
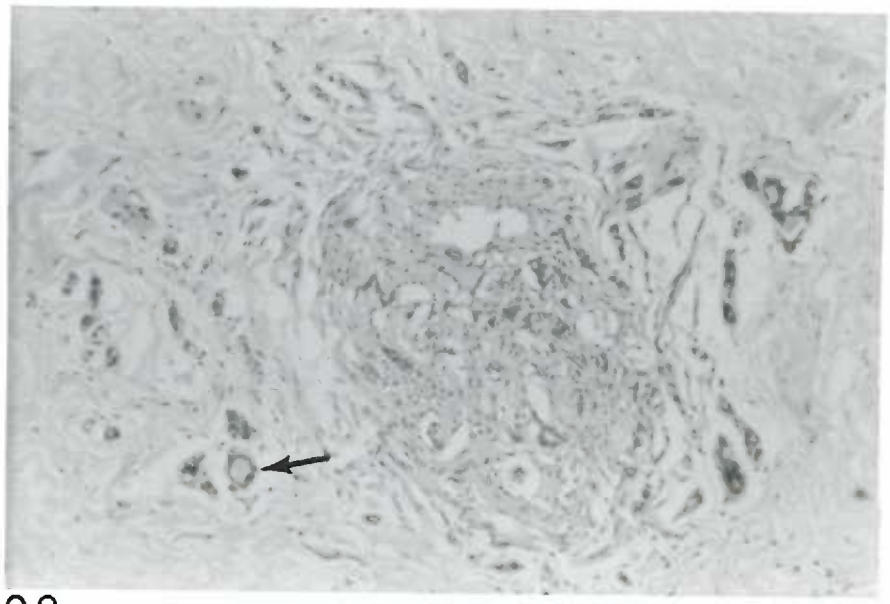


97

Figure 98:

Corresponding histology of Figure 97. The photograph is representative of Figure 96 as well. There is dense intralobular fibrous tissue in an unorganized pattern. The epithelium is moderately atrophic. The border of the lobule is indistinct with some dilated ductules located at the periphery (arrow). This lesion is probably a variation of sclerosing adenosis. Hematoxylin and eosin. 40X.



98

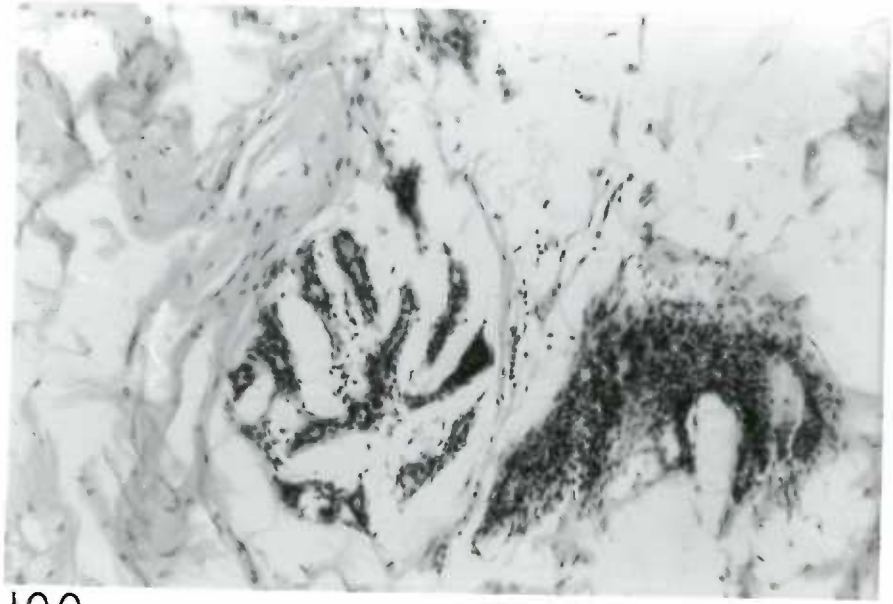
Figure 99:

Female, 48 years, normal breast (M-66-14). Subgross. Several lobules, communicating with a central duct, have a papillary pattern lacking the smooth contours of most lobules. Hematoxylin. 10X.

Figure 100:

Corresponding histology of Figure 99. The loose intralobular stroma allows visualization of individual ductules in Figure 99. Hematoxylin and eosin. 40X.

99



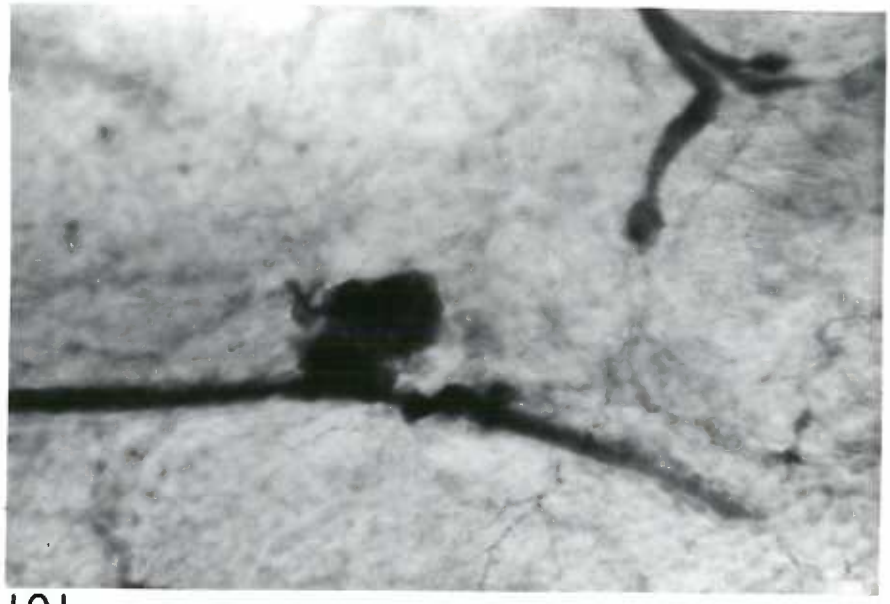
100

Figure 101:

Female, 88 years, normal breast (M-66-15). Subgross. A dense, smoothly contoured mass appears attached directly to a duct without a visible entering duct branch. It is not possible at the subgross level to label this as a lobule. Hematoxylin. 10X.

Figure 102:

Corresponding histology of Figure 101. A lobular pattern is present, with dense cellular intralobular stroma and atrophic epithelium. The adjacent duct is visible. Hematoxylin and eosin. 40X.



101

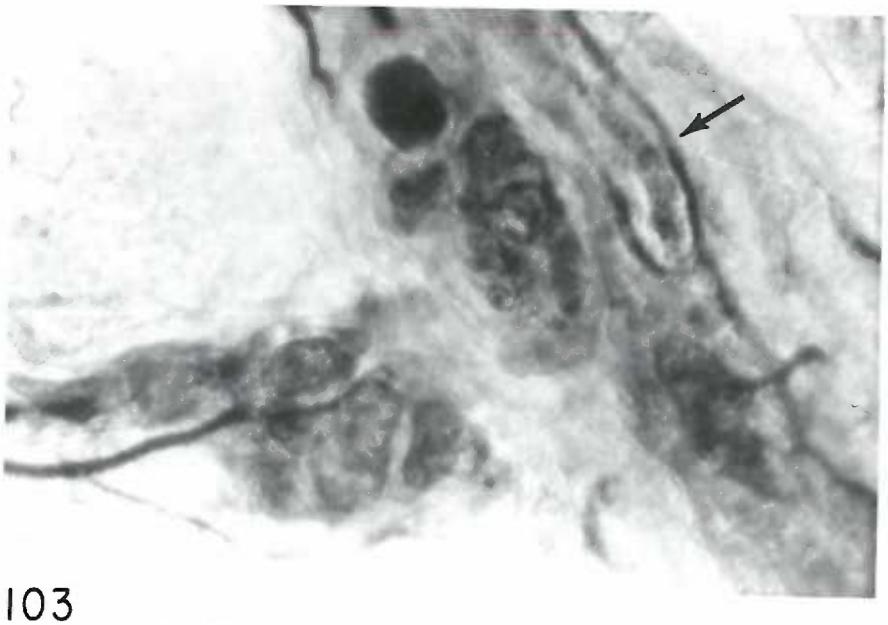
102

Figure 103:

Female, 47 years, normal breast (M-66-28). Subgross. A large duct (arrow) with material in the lumen has several bordering lobules, one of which is more dense. Note the thickness of the duct wall at the arrow. Hematoxylin. 10X.

Figure 104:

Corresponding histology of Figure 103. The dense lobule is represented by the solid group of epithelial cells (left) adjacent to the thick-walled duct. No atypism is noted. Hematoxylin and eosin. 40X.



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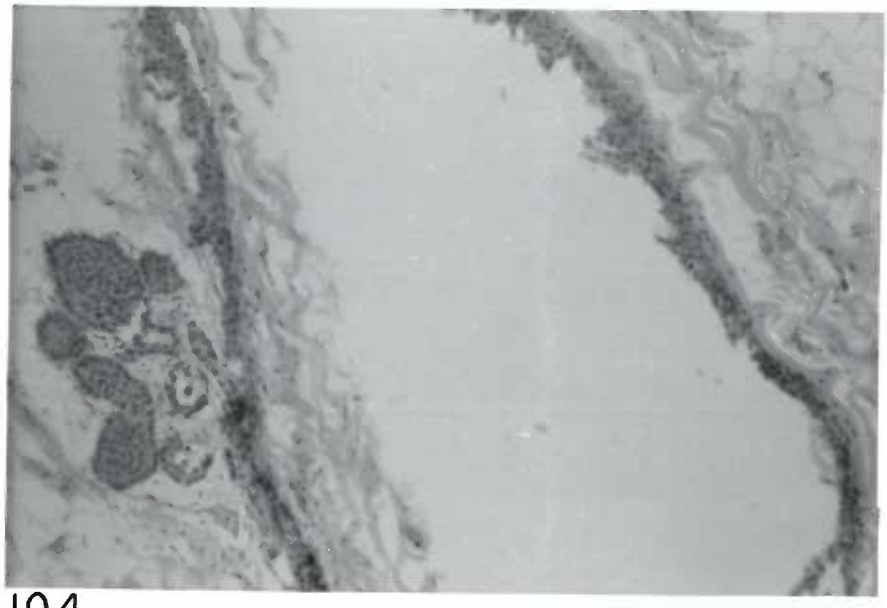


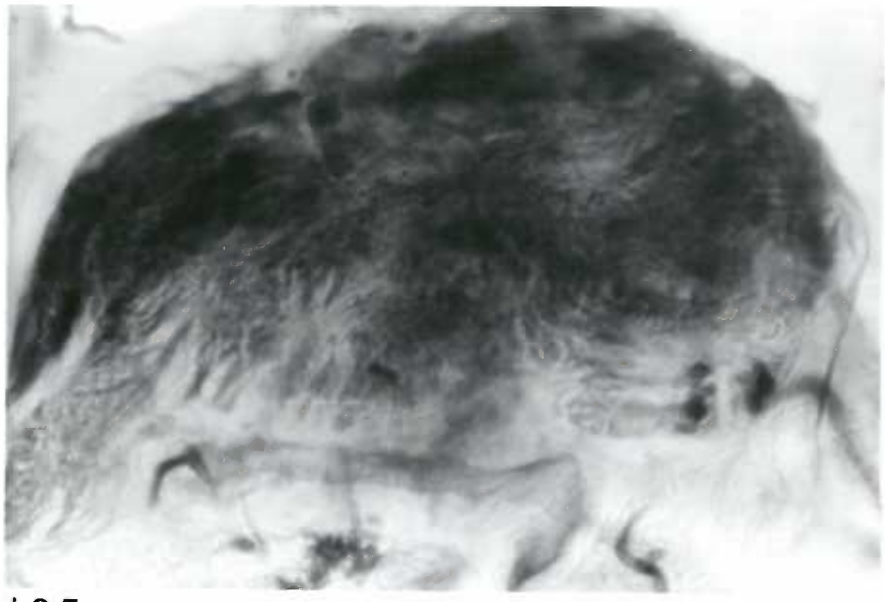
104

Figure 105:

Female, 56 years, normal breast (M-66-12). Subgross. This large lobular formation has an indistinct inferior border and contains few recognizable epithelial elements. Hematoxylin. 10X.

Figure 106:

Corresponding histology of Figure 105. The microscopy is confirmatory, showing mostly fibrous tissue and atrophic epithelium. Hematoxylin and eosin. 40X.



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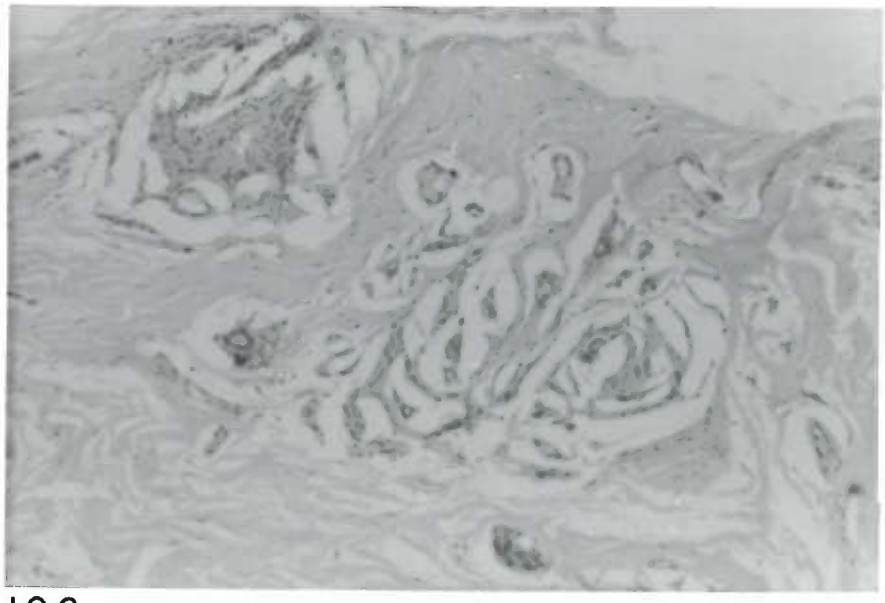


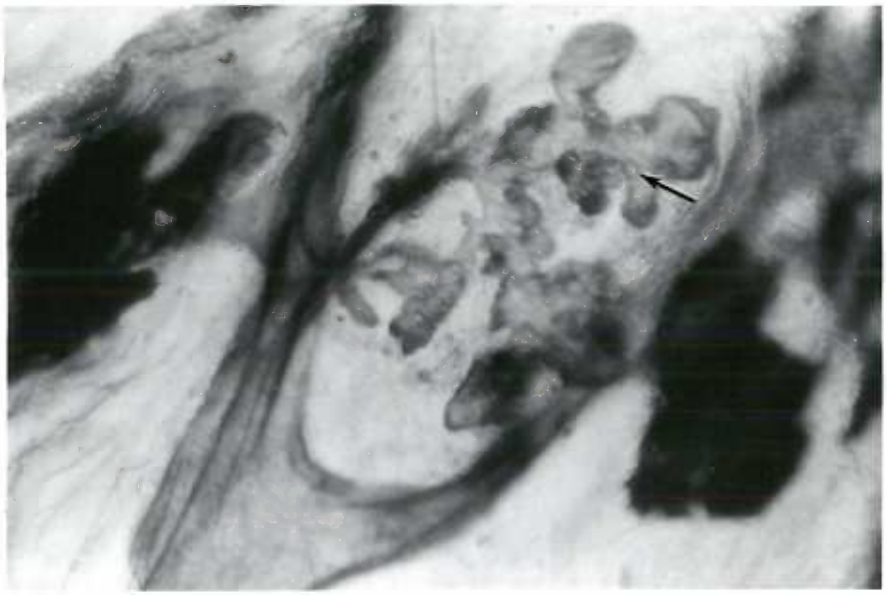
106

Figure 107:

Female, 48 years, normal breast (M-66-14). Subgross. An easily identified duct system leads into a peculiar ductule arrangement. The individual ductules are dilated and have material in the lumina (arrow). Hematoxylin. 10X.

Figure 108:

Corresponding histology of Figure 107. The dilated lumen of a ductule is evident and contains small granules of material which may be calcified. The epithelium is normal and a mild chronic inflammatory infiltrate is noted in surrounding stroma. Hematoxylin and eosin. 40X.



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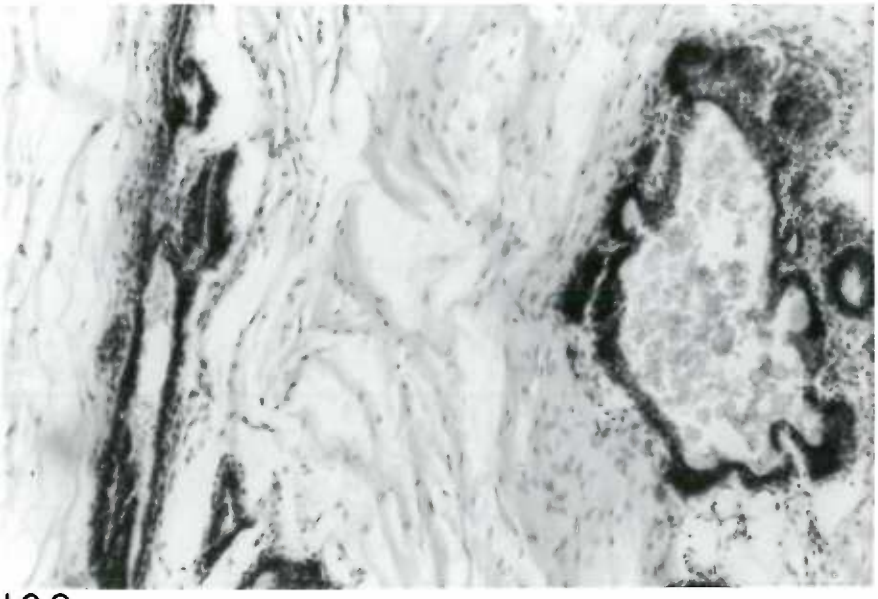


108

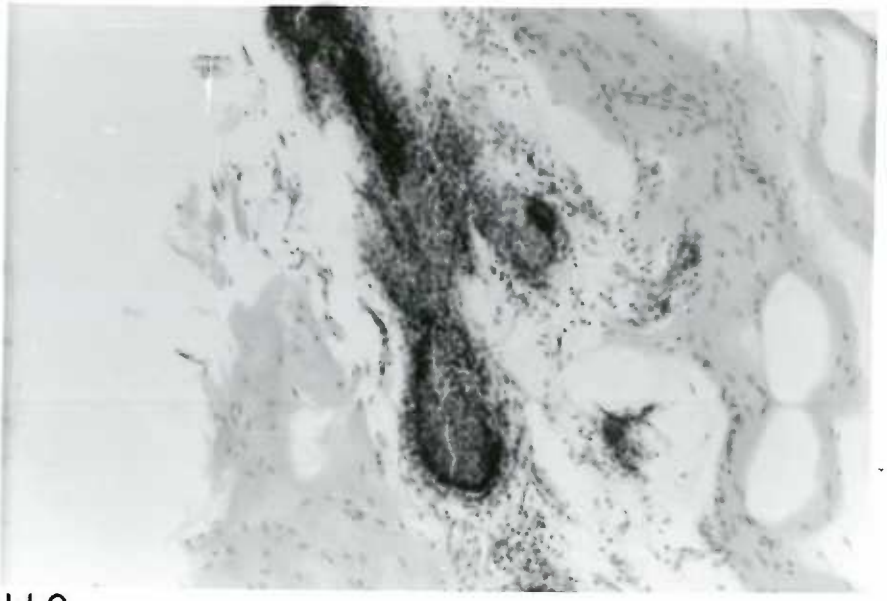
Figure 109:

Female, 28 years, normal breast (M-66-24). Subgross. The lobule (lower right) is composed of "tear-drop shaped" ductules which appear to be dilated. Hematoxylin. 10X.

Figure 110:

Corresponding histology of Figure 109. Two ductules appear to be solidly filled with cells. Hematoxylin and eosin. 40X.

109



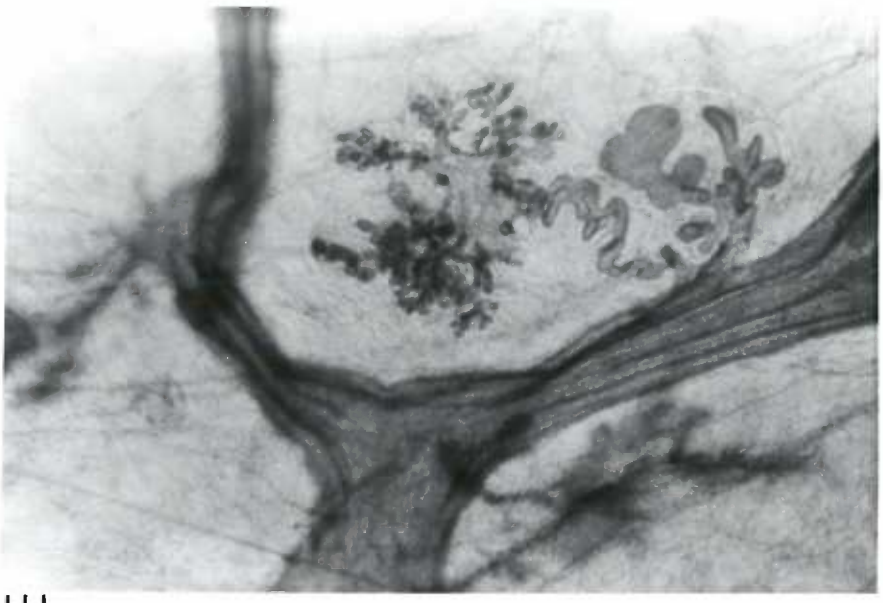
110

Figure 111:

Female, 19 years, normal breast (M-66-8). Subgross. An intricate duct pattern and a small lobule. Hematoxylin. 10X.

Figure 112:

Corresponding histology of Figure 111. Hematoxylin and eosin. 10X.



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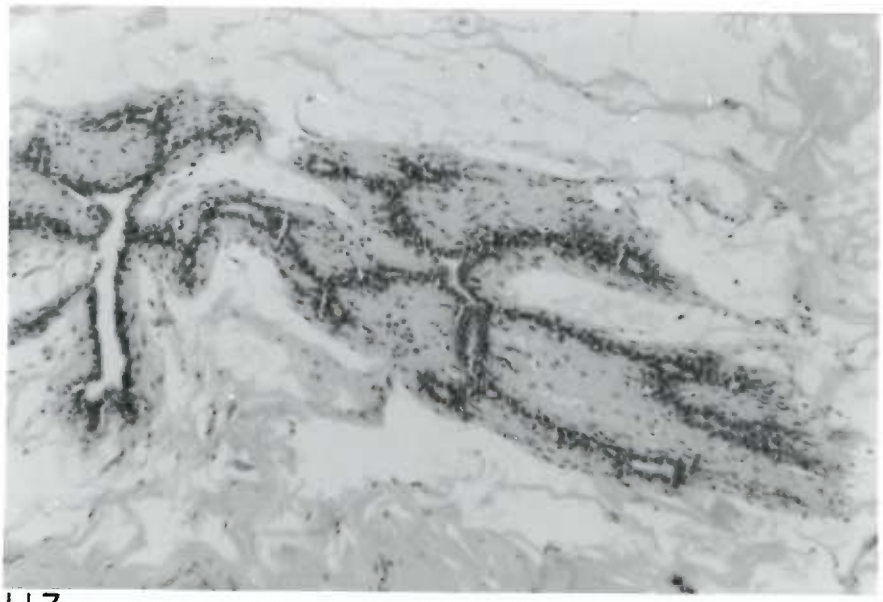
112

Figure 113:

Corresponding histology of the lobule of Figure 111. A higher power exhibits normal epithelium and periductal connective tissue. Hematoxylin and eosin. 40X.



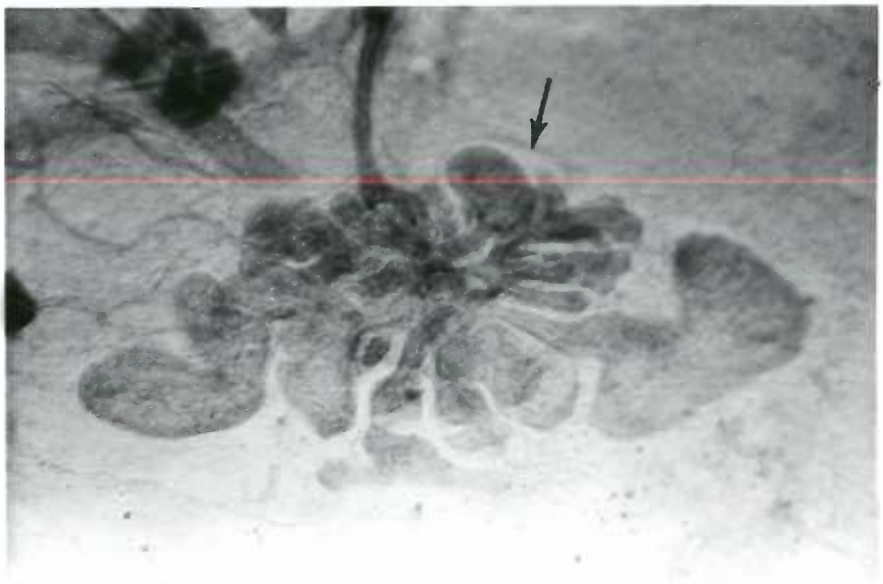
113

Figure 114:

Female, 53 years, normal breast (M-66-21). Subgross. The lobule is made up of broad, sharply defined ductules with smooth borders. Intralobular fibrous tissue is evident at the arrow. Hematoxylin. 10X.

Figure 115:

Corresponding histology of Figure 114. Communicating ductule lumina are lined by "apocrine-like" epithelium, characterized by basally placed nuclei and abundant eosinophilic cytoplasm. The surrounding stroma is loosely woven. Hematoxylin and eosin. 40X.



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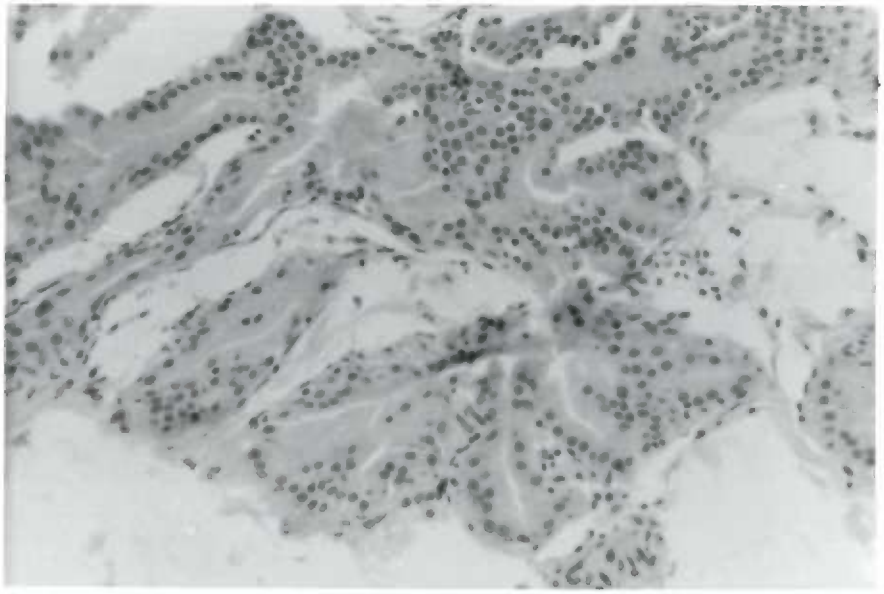


115

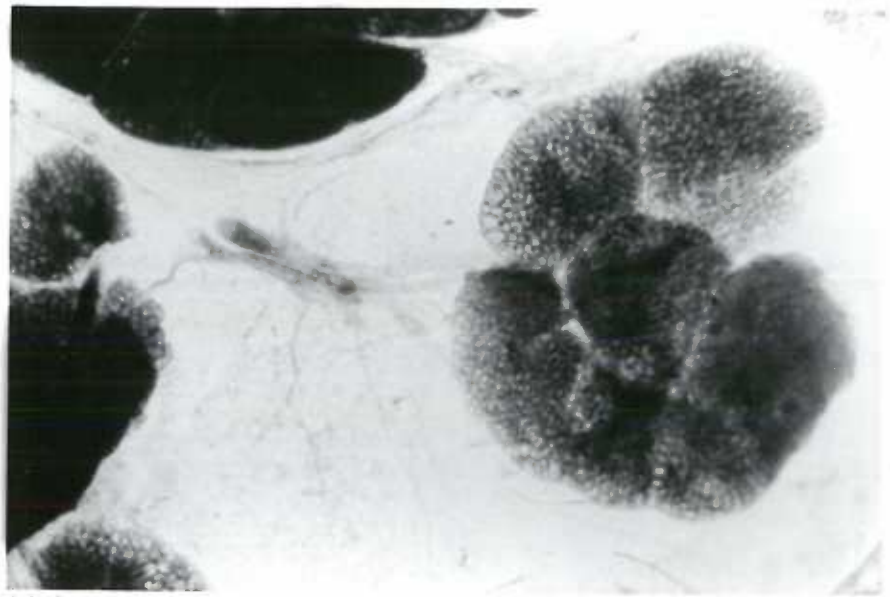
PRELACTATING AND POSTPARTUM BREASTS

Figure 116:

Female, 25 years, postpartum breast (M-66-7). Subgross. A well developed, segmented lobule has several small ducts leading into it. The acini are dilated and easily identified. Hematoxylin. 5X.

Figure 117:

Corresponding histology of Figure 116. Lobulo-alveolar development is illustrated. Hematoxylin and eosin. 10X.



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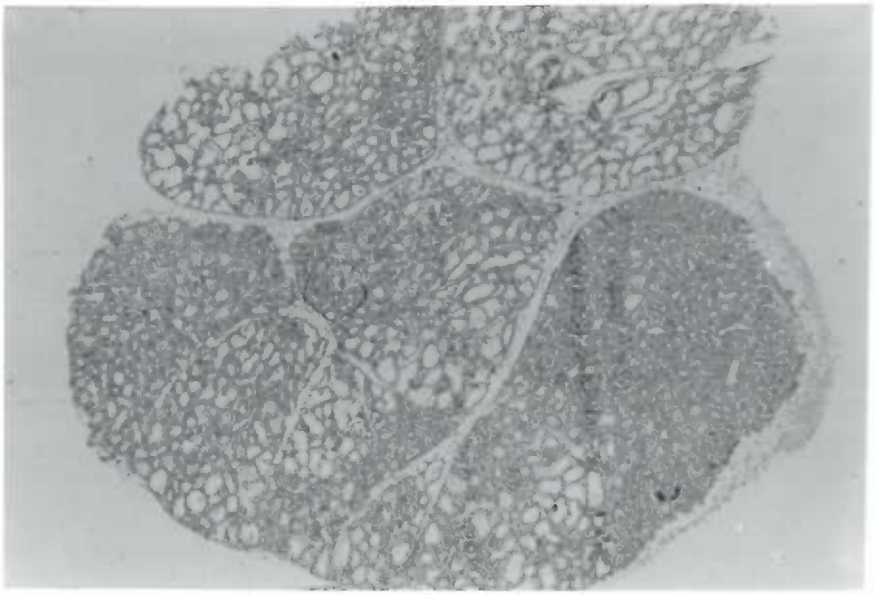
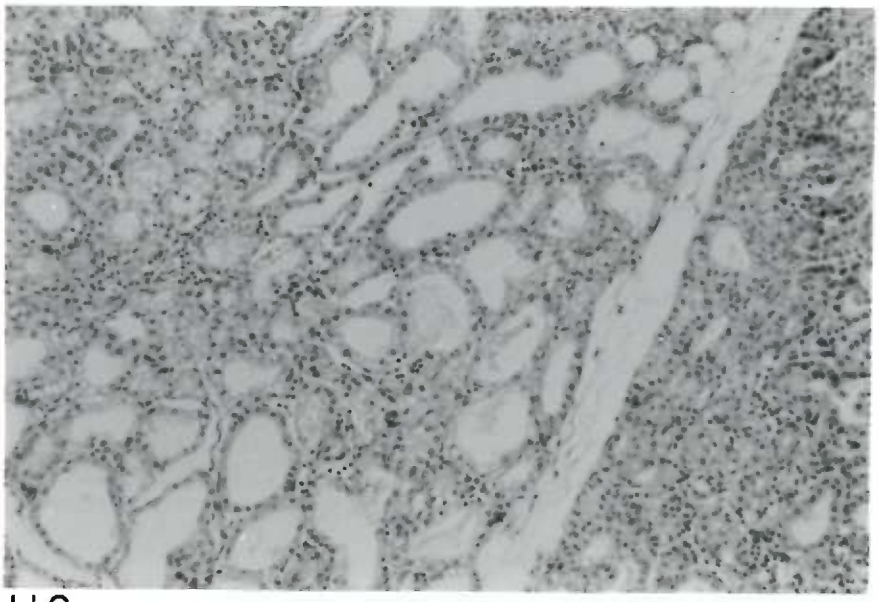


117

Figure 118:

Corresponding histology of Figure 116. Distended acini with intraluminal secretion. A few lymphocytes are observed in the stroma. Hematoxylin and eosin. 40X.



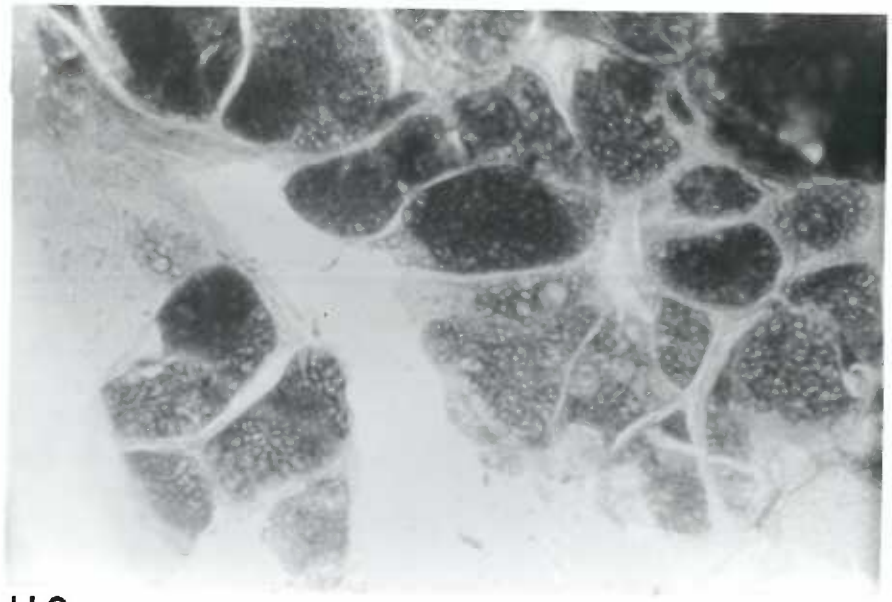
118

Figure 119:

Female, 25 years, postpartum breast (M-66-7). Subgross. Morphology similar to Figure 116. No recognizable stromal fat. Hematoxylin. 5X.

Figure 120:

Corresponding histology of Figure 119. The acini are lined by a single layer of epithelial cells and the lumina have scanty secretory product. Hematoxylin and eosin. 40X.



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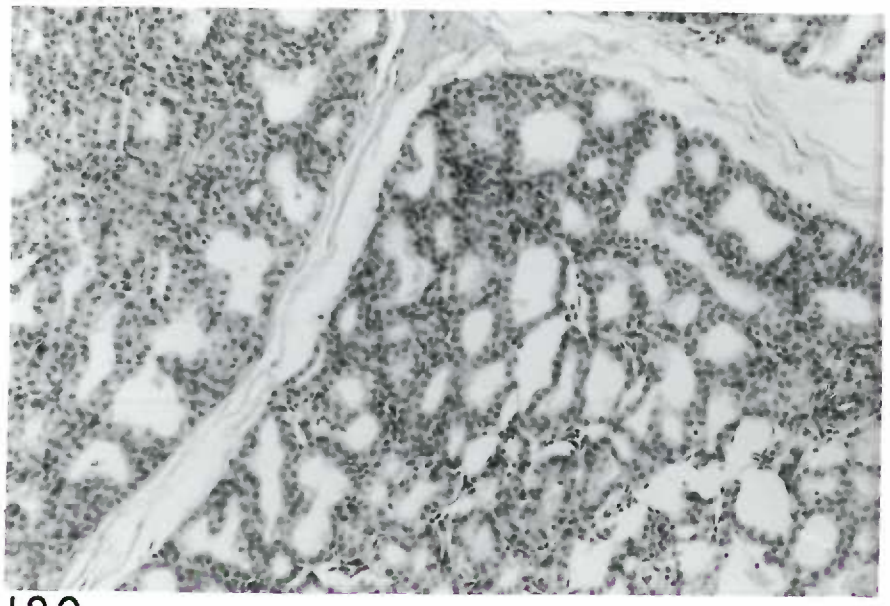


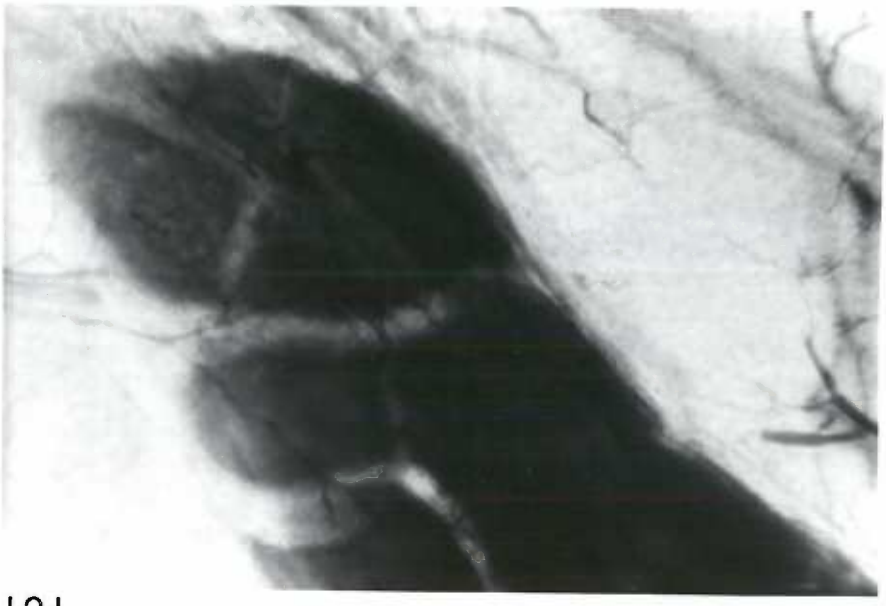
120

Figure 121:

Female, 19 years, prelactating breast (M-66-17). Subgross. A large, dense, segmented lobule is shown. The acini are not distinct and surrounding fat lobules are noted. Hematoxylin. 10X.

Figure 122:

Corresponding histology of Figure 121. Dilated acini are present, many containing secretory material. The epithelium is one to two cell layers thick and the moderately cellular stroma is abundant. Hematoxylin and eosin. 40X.



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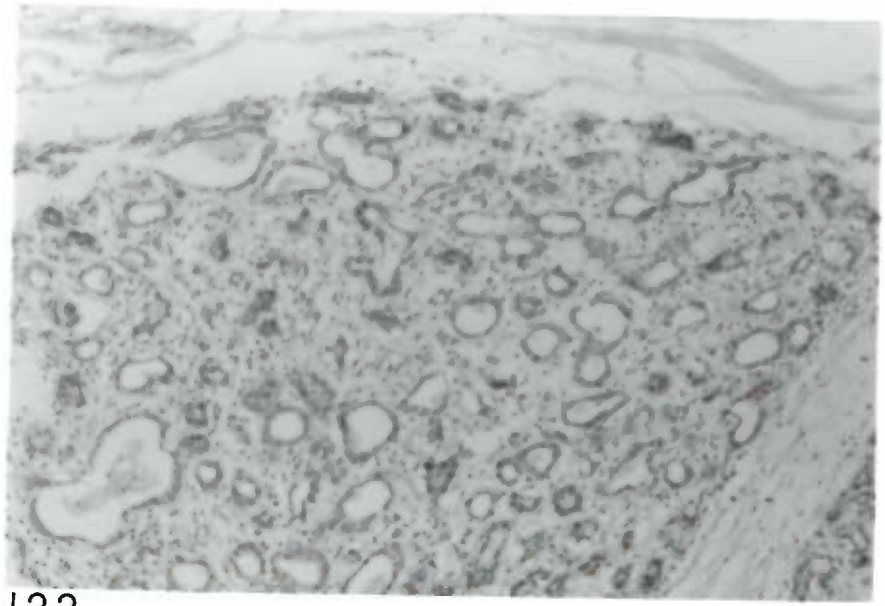


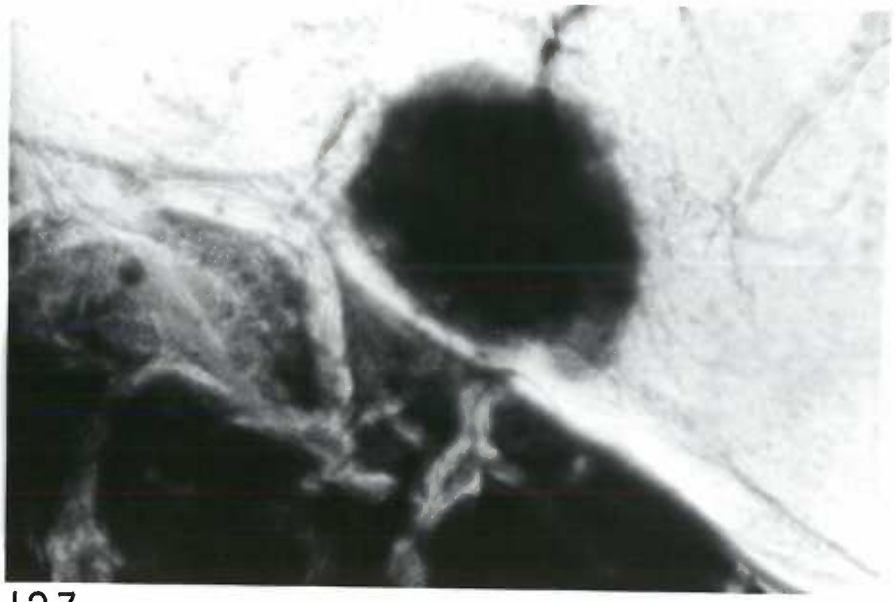
122

Figure 123:

Female, 19 years, prelactating breast (M-66-17). Subgross. An indistinct lobule extends into the adipose tissue beyond the contour of the other lobular formations. Hematoxylin. 10X.

Figure 124:

Corresponding histology of Figure 123. The histology is the same as that noted in Figure 121 except many of the lumina are not distended. Hematoxylin and eosin. 40X.



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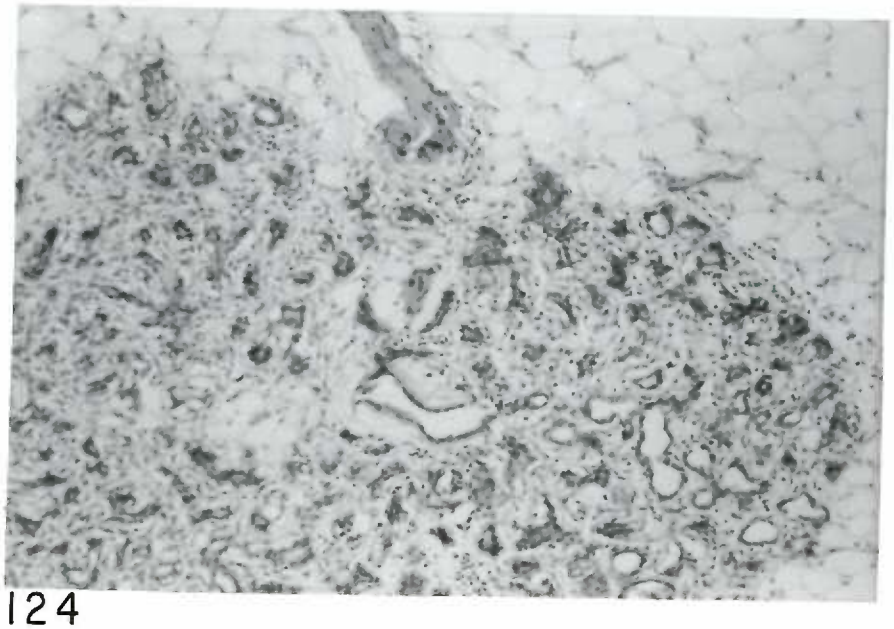


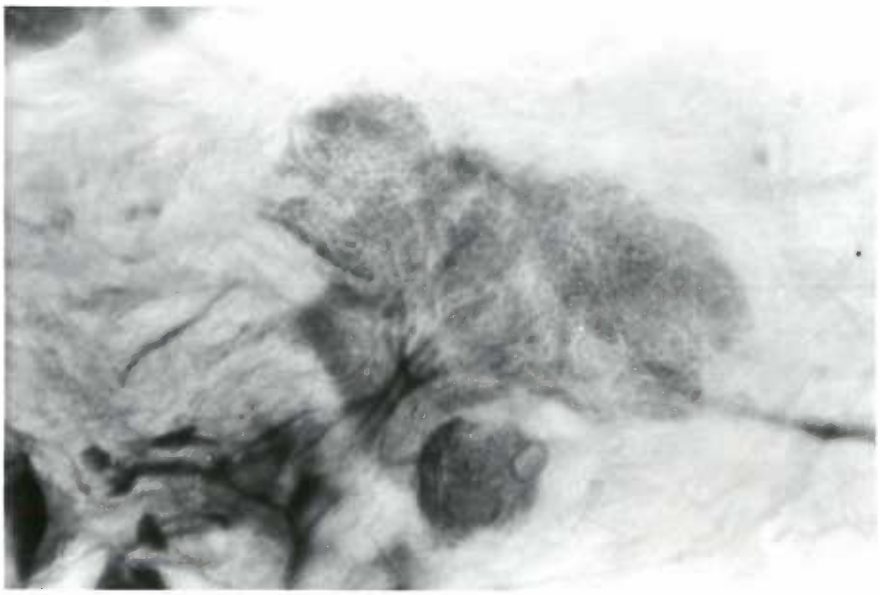
124

Figure 125:

Female, 19 years, prelactating breast (M-66-17). Subgross. This is a lobule from the same breast as Figures 121 and 123. Individual ductules are noted in a background of translucent intralobular stroma. Hematoxylin. 10X.

Figure 126:

Corresponding histology of Figure 125. The ductules are widely separated by loose connective tissue. The lumina are empty and the epithelium is two cell layers thick. Hematoxylin and eosin. 40X.



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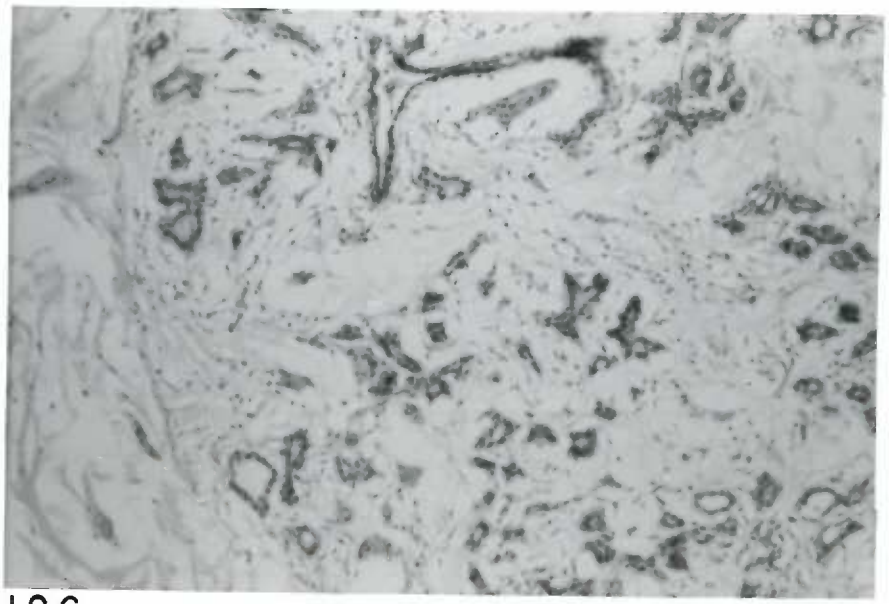


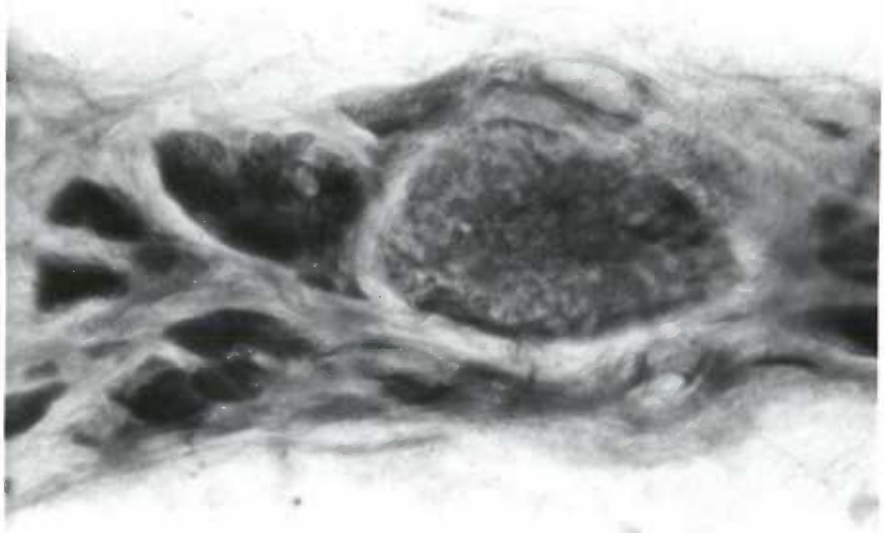
126

Figure 127:

Female, 41 years, normal breast (M-66-26). Subgross. This lobule occurs in the breast of a postmenopausal female. It is well defined, having visible acinar spaces within its borders. Note the different appearance of surrounding lobules. Hematoxylin. 10X.

Figure 128:

Corresponding histology of Figure 127. Large acinar spaces lined by plump cells are noted. The stroma is loose and relatively acellular. The lumina are empty. Hematoxylin and eosin. 40X.



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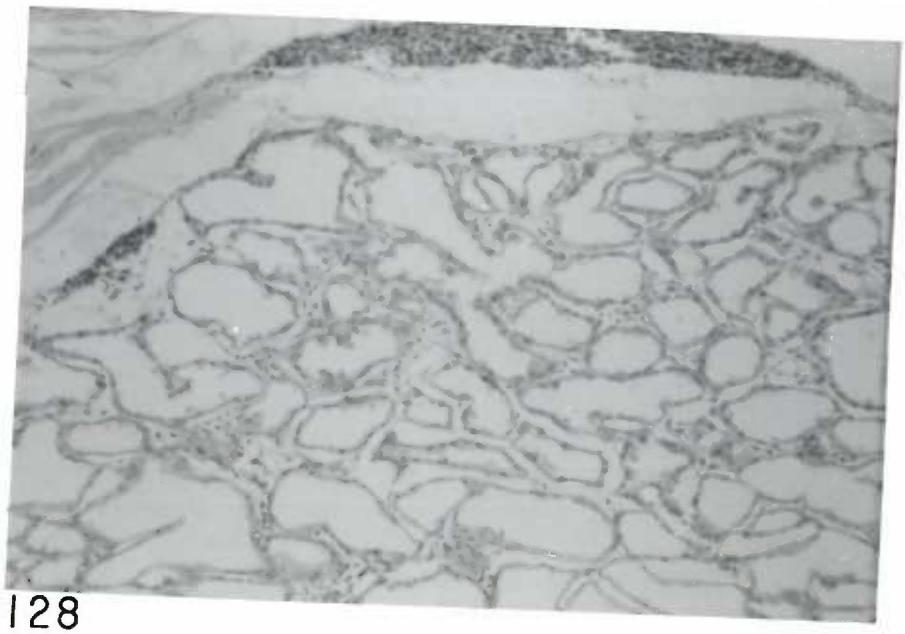
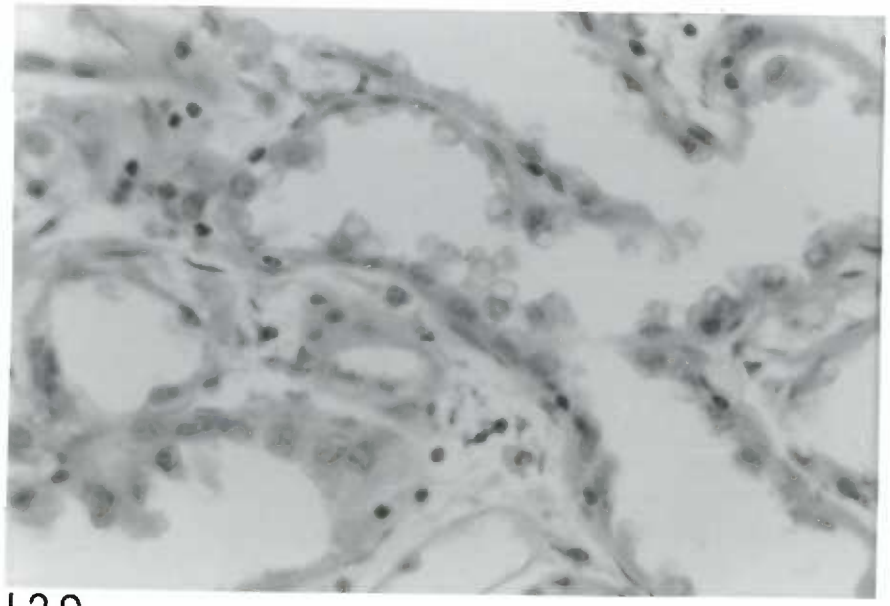


128

Figure 129:

Corresponding histology of Figure 127. A single layer of plump epithelial cells is noted. The epithelial cells have apical secretory vacuoles. No epithelial atypism is observed. Hematoxylin and eosin. 160X.



129

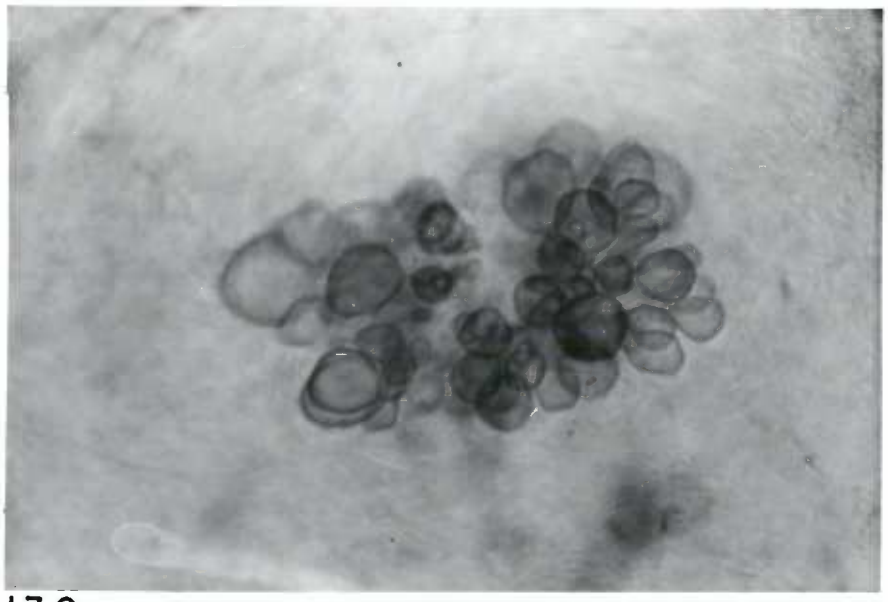
CYSTS

Figure 130:

Female, 19 years, normal breast (M-66-8). Subgross. Several dilated ductules in lobular formation. The cyst walls are smooth and the lumina do not contain apparent secretory product. No entering duct system is visible. Hematoxylin. 10X.

Figure 131:

Corresponding histopathology of Figure 130. The epithelium and stroma are not cytologically atypical or anaplastic. The lumina are dilated and contain a small amount of secretory product. Hematoxylin and eosin. 40X.



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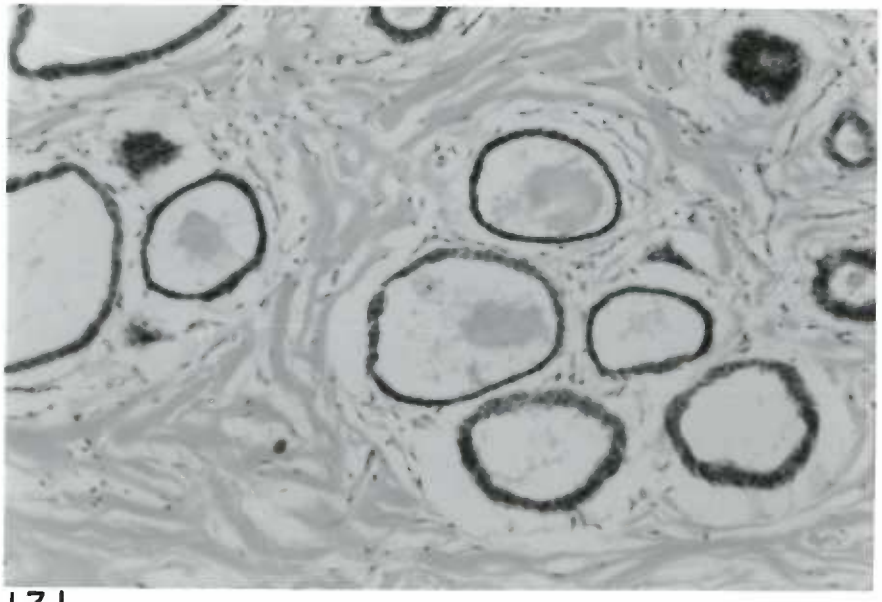


131

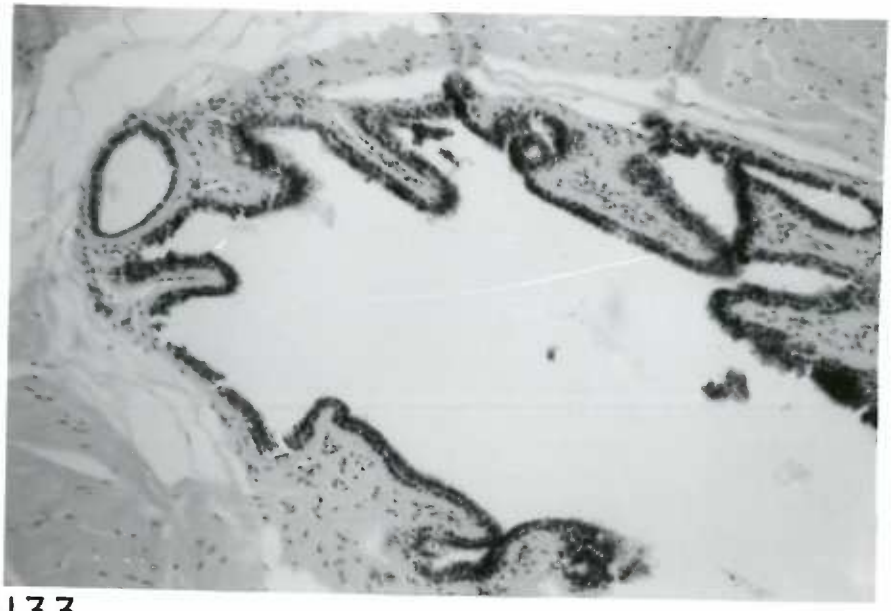
Figure 132:

Female, 19 years, normal breast (M-66-8). Subgross. A small lobular formation of dilated cystic structures lacks a visible communicating duct. Again, the walls are even-contoured and the lumina empty. Hematoxylin. 10X.

Figure 133:

Corresponding histology of Figure 132. The epithelium and stroma are not cytologically atypical. The epithelium is two cell layers thick. The lumen is dilated and is empty. Hematoxylin and eosin. 40X.

132



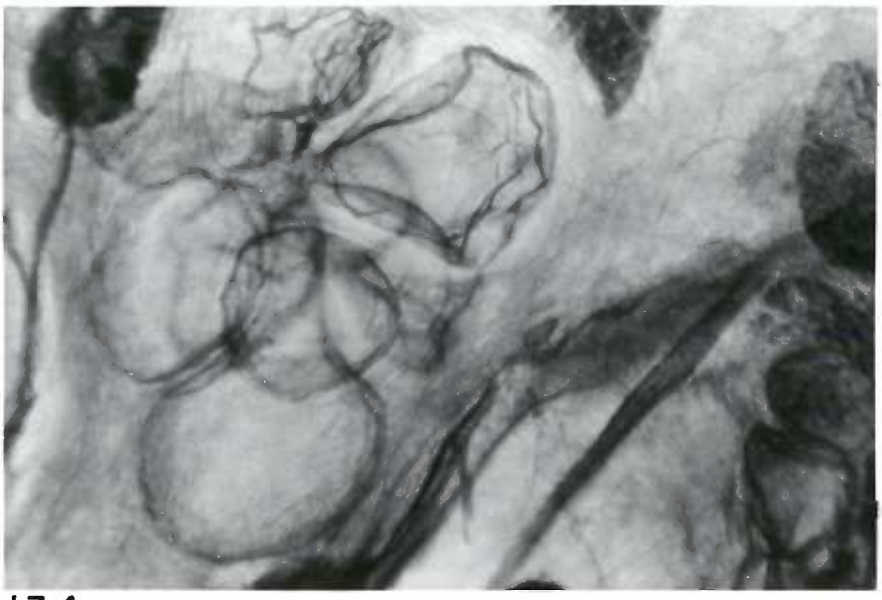
133

Figure 134:

Female, 28 years, normal breast (M-66-24). Subgross. The large dilated acini have thin, smooth, delicate walls and empty lumina. A communicating duct cannot be identified. Hematoxylin. 10X.

Figure 135:

Corresponding histology of Figure 134. The large acinar spaces are separated by dense strands of loosely woven connective tissue. The lining epithelium is cytologically not atypical, but is one cell layer in thickness. The lumina are empty. Hematoxylin and eosin. 40X.



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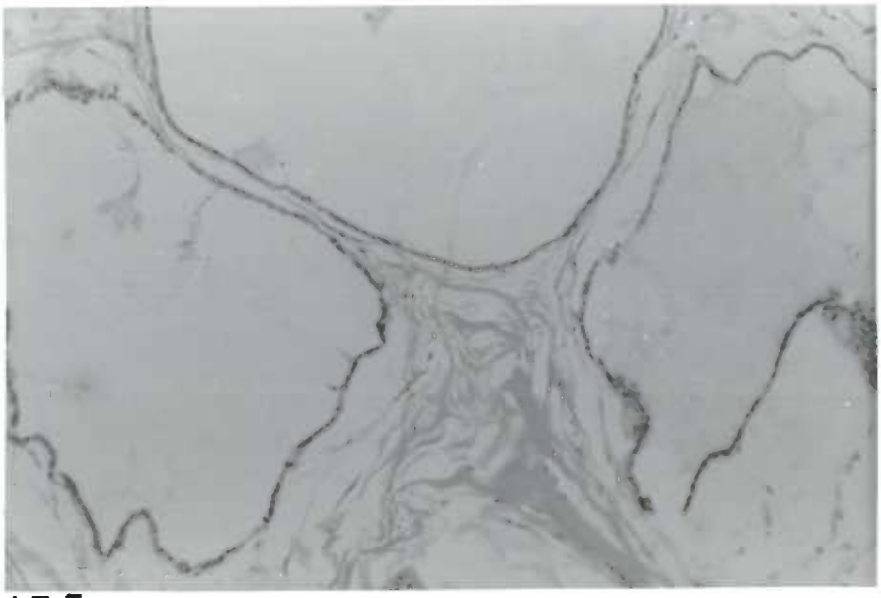


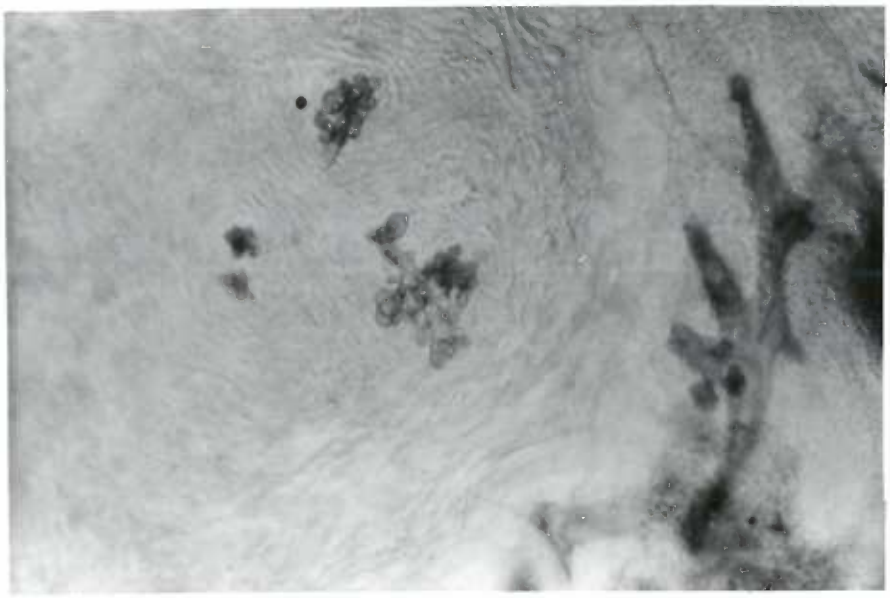
135

Figure 136:

Female, 19 years, normal breast (M-66-20). Subgross. Duct (center) has several dilated buds arising from it. Due to the plane of the section an entering duct cannot be identified. Hematoxylin. 10X.

Figure 137:

Corresponding histology of Figure 136. The microscopy is confirmatory, showing cytologically normal epithelium and stroma. The solid appearance of one ductule (lower right) is an artefact due to the plane of section. Hematoxylin and eosin. 40X.



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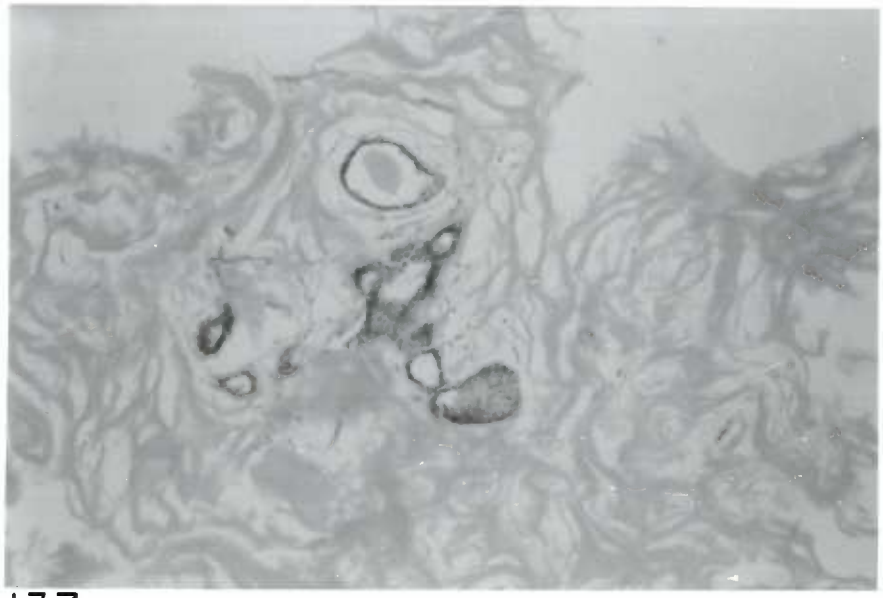


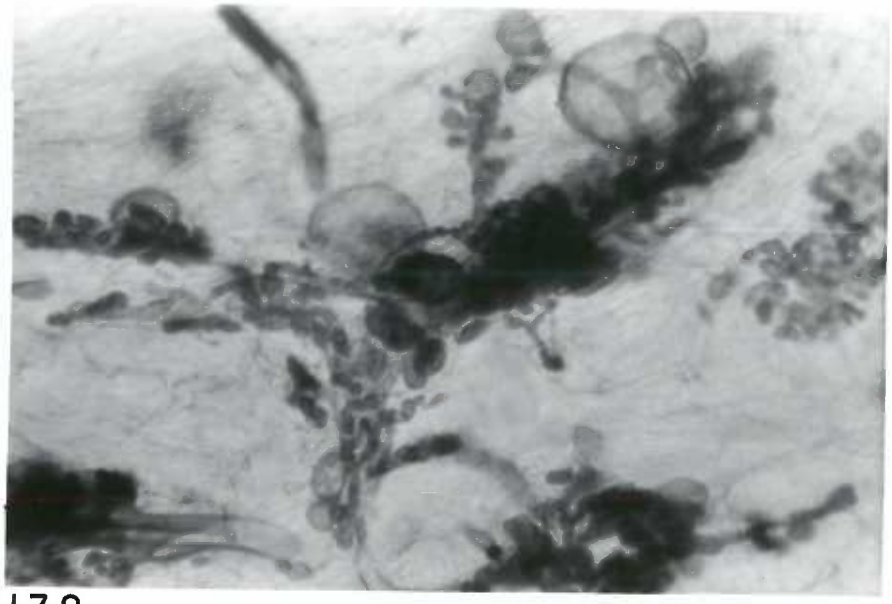
137

Figure 138:

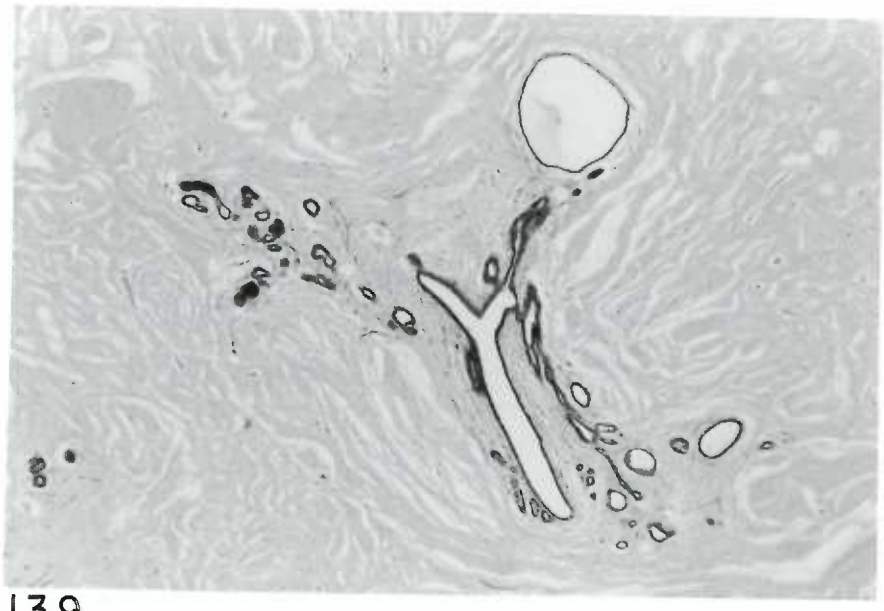
Female, 19 years, normal breast (M-66-8). Subgross. This is a complex formation of ducts and dilated ductules having thin, smooth walls and empty lumina. Hematoxylin. 10X.

Figure 139:

Corresponding histology of Figure 138. The microscopic correlation is evident. The lumina are empty. Hematoxylin and eosin. 10X.



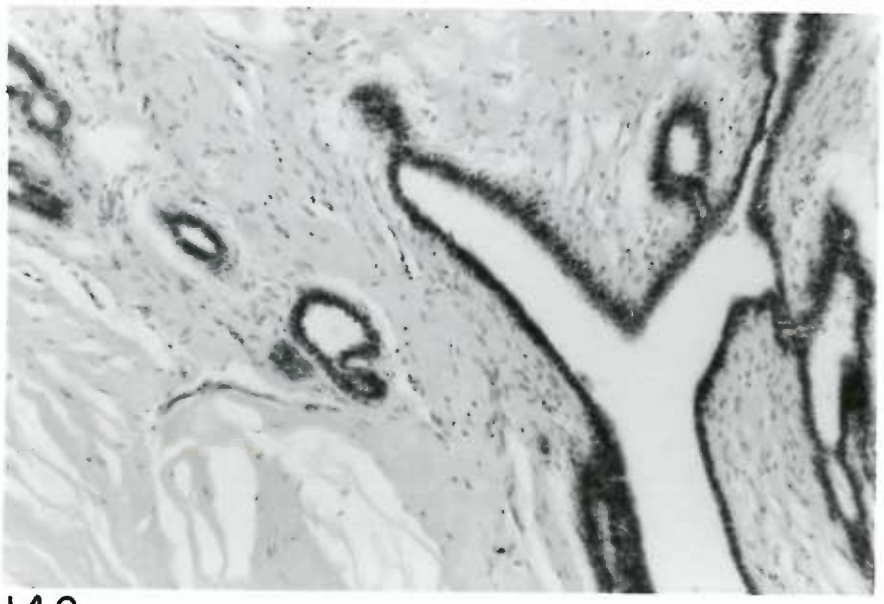
138



139

Figure 140:

Corresponding histology of Figure 138. The epithelium is two cell layers in thickness. Hematoxylin and eosin. 40X.



140

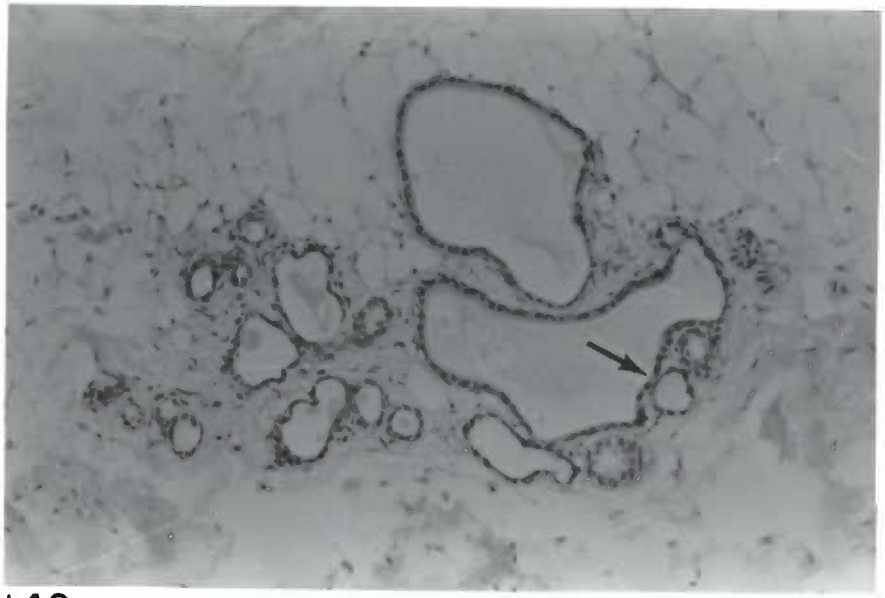
Figure 141:

Female, 45 years, normal breast (M-66-2). Subgross. A small lobule (upper right center) is composed of several dilated acini. The walls are smooth-contoured and the lumina appear empty. A large duct is entering the formation from below. Hematoxylin. 10X.

Figure 142:

Corresponding histology of Figure 141. Dilated ductule and acinar structures are apparent and contain a small amount of secretory material. The epithelium is generally one cell thick and is not cytologically atypical. Hematoxylin and eosin. 40X.

141



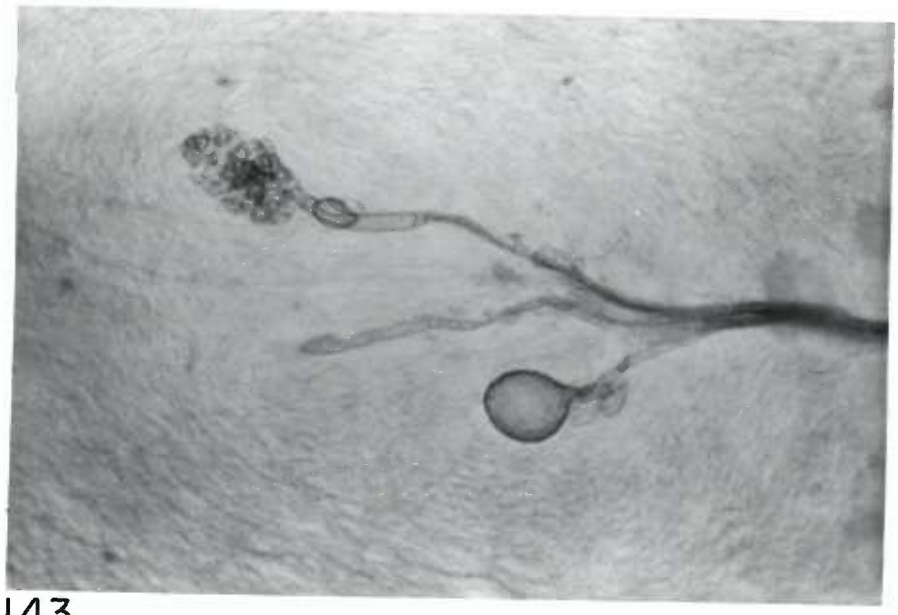
142

Figure 143:

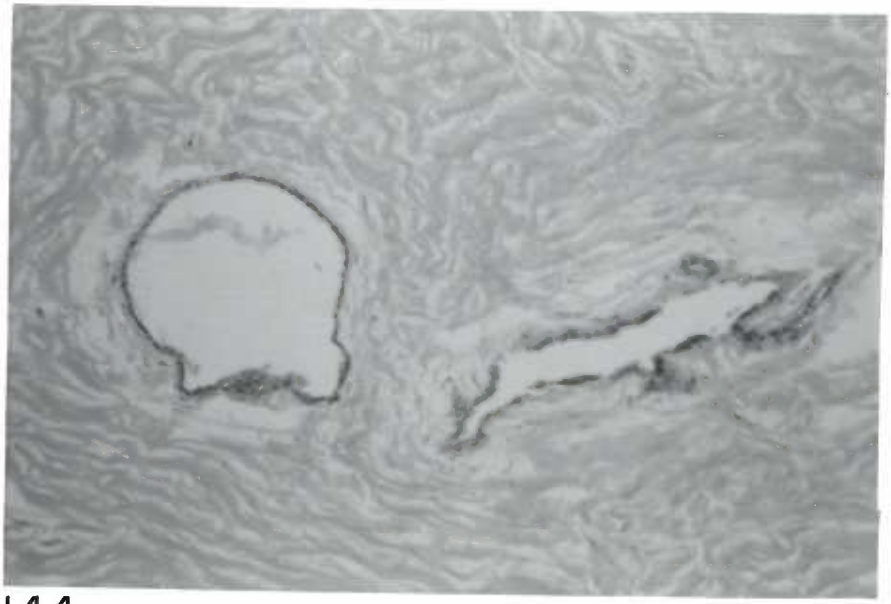
Female, 19 years, normal breast (M-66-20). Subgross. The terminal portion of a duct balloons into a cystic structure with smooth walls. A lobule is identified at the end of another duct. Hematoxylin. 10X.

Figure 144:

Corresponding histology of Figure 143. Hematoxylin and eosin. 40X.



143



144

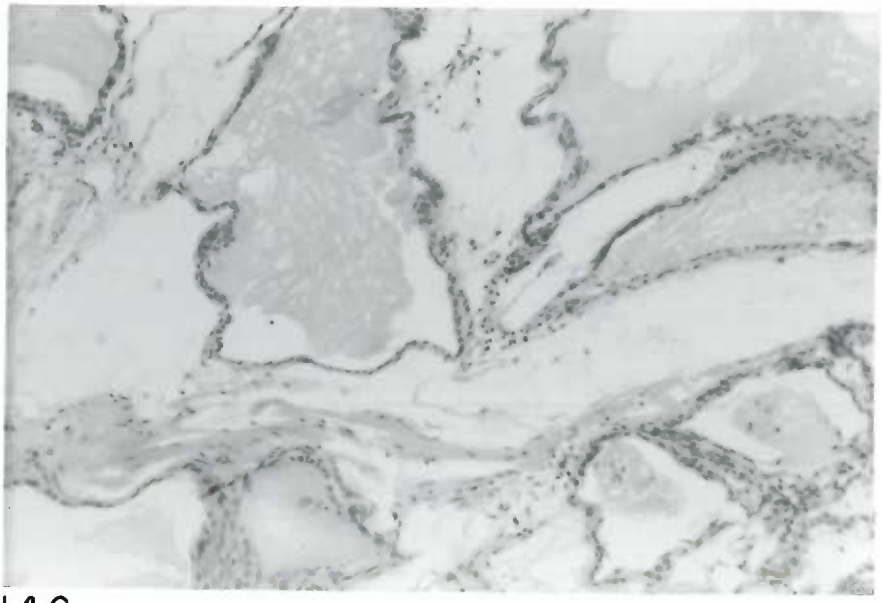
Figure 145:

Female, 40 years, normal breast (M-66-11). Subgross. Several large dilated ducts have thin, smooth walls. On close inspection, inspissated secretory material is observed (arrow). Hematoxylin. 10X.

Figure 146:

Corresponding histology of Figure 145. The large ducts are lined by normal epithelium and separated by loose stroma lacking an inflammatory reaction. Inspissated secretions are noted in the lumina. Hematoxylin and eosin. 40X.

145



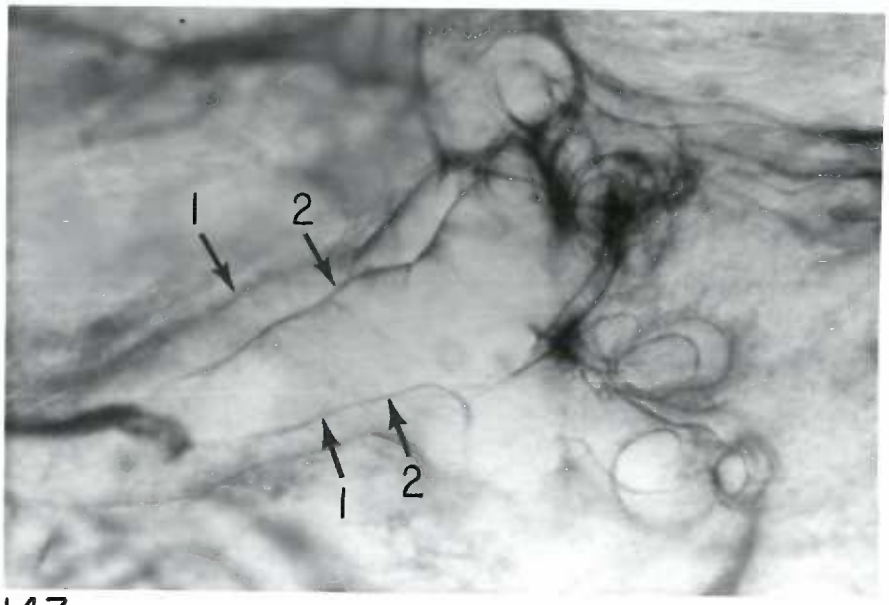
146

Figure 147:

Female, 88 years, normal breast (M-66-15). Subgross. A large branching duct with smooth walls (arrow 1) has easily identified material in the lumen (arrow 2). Hematoxylin. 10X.

Figure 148:

Corresponding histology of Figure 147. The microscopy is confirmatory. The epithelium and stroma are normal. No inflammation is seen. Hematoxylin and eosin. 10X.



147

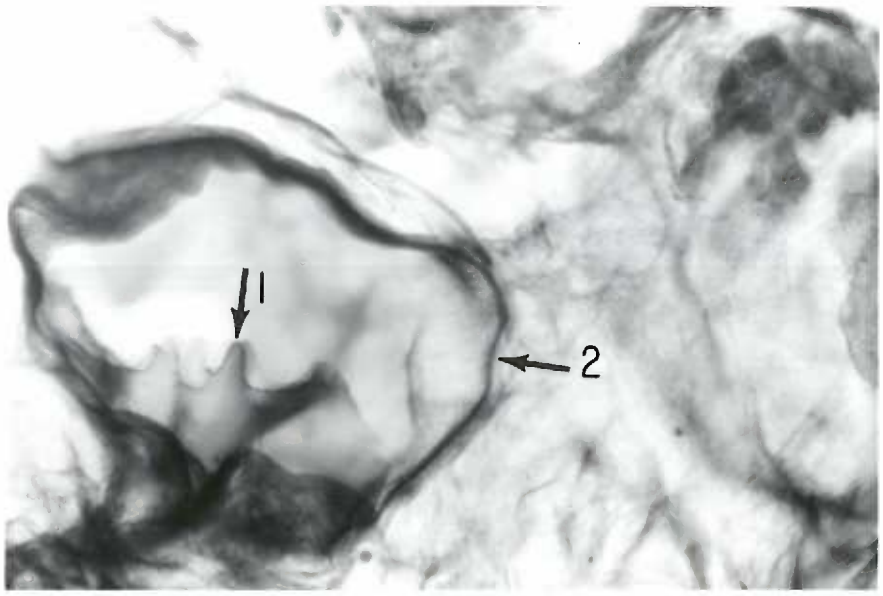
148

Figure 149:

Female, 57 years, normal breast (M-66-22). Subgross. The plane of section exposes the lumen of the duct and scalloped intraluminal material (arrow 1). The duct wall is smooth (arrow 2). Hematoxylin. 10X.

Figure 150:

Corresponding histology of Figure 149. The epithelium and stroma are normal. The inspissated material forms an acellular homogeneous mass. Hematoxylin and eosin, 40X.



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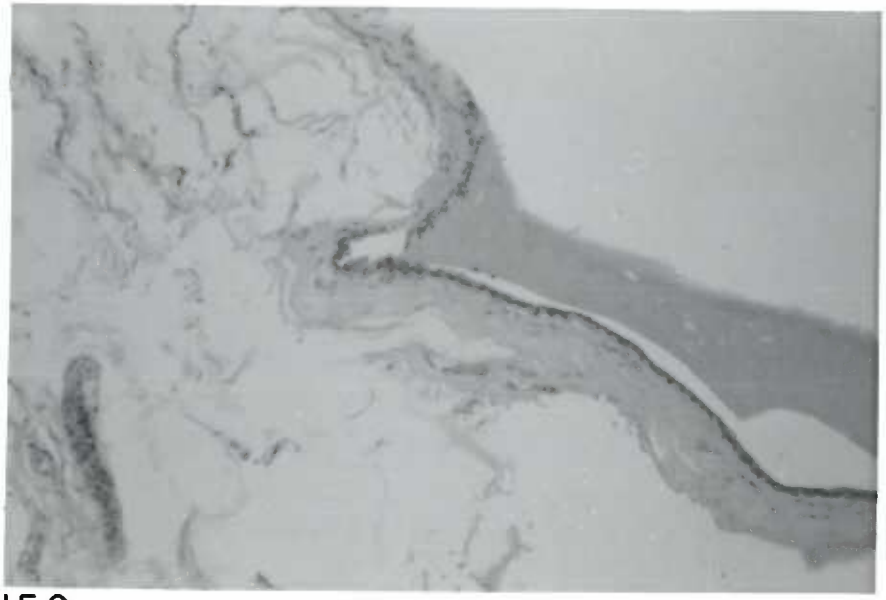


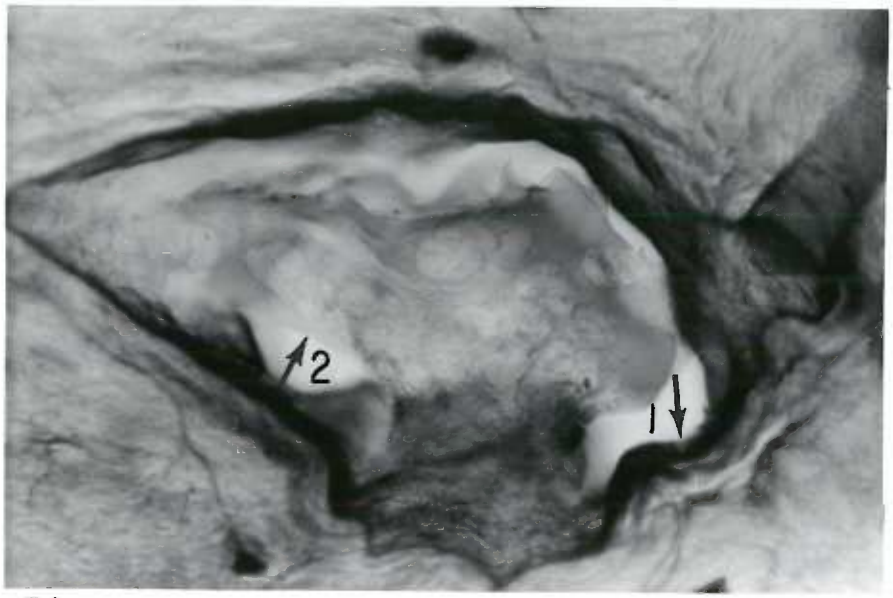
150

Figure 151:

Female, 56 years, normal breast (M-66-12). Subgross. A large duct has scalloped, smooth walls (arrow 1) and a large irregular mass of intraluminal material (arrow 2). Hematoxylin. 10X.

Figure 152:

Corresponding histology of Figure 151. The microscopy is confirmatory. No inflammation is noted. Hematoxylin and eosin. 10X.



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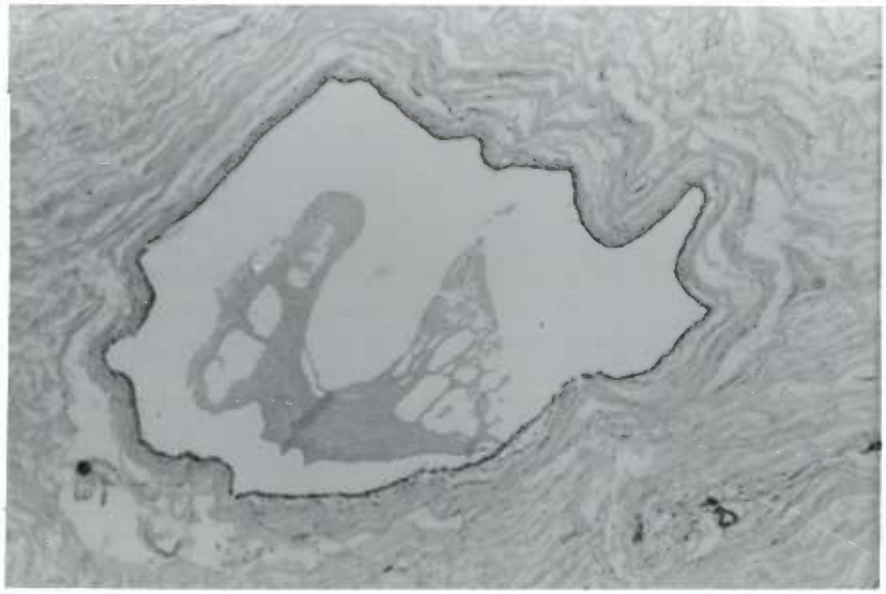


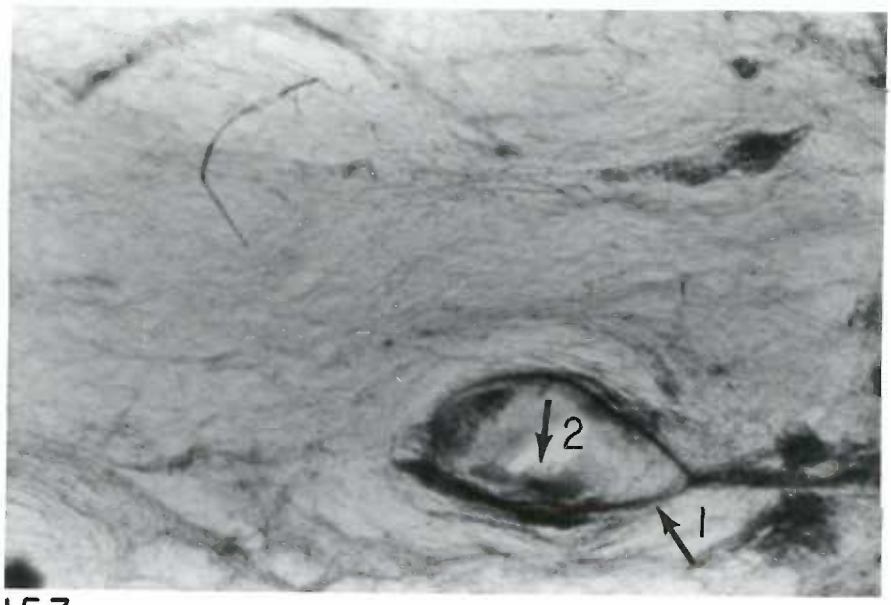
152

Figure 153:

Female, 56 years, breast with mammary dysplasia (M-66-4). Subgross. A dilated portion of a duct has smooth walls (arrow 1) and contains indistinctly outlined material (arrow) in its lumen. Hematoxylin. 14X.

Figure 154:

Corresponding histology of Figure 153. The dilated lumen is lined by normal epithelium and contains groups of intact cells which are not attached to the duct wall. A mild chronic inflammatory infiltrate is seen in the surrounding stroma. Hematoxylin and eosin. 40X.



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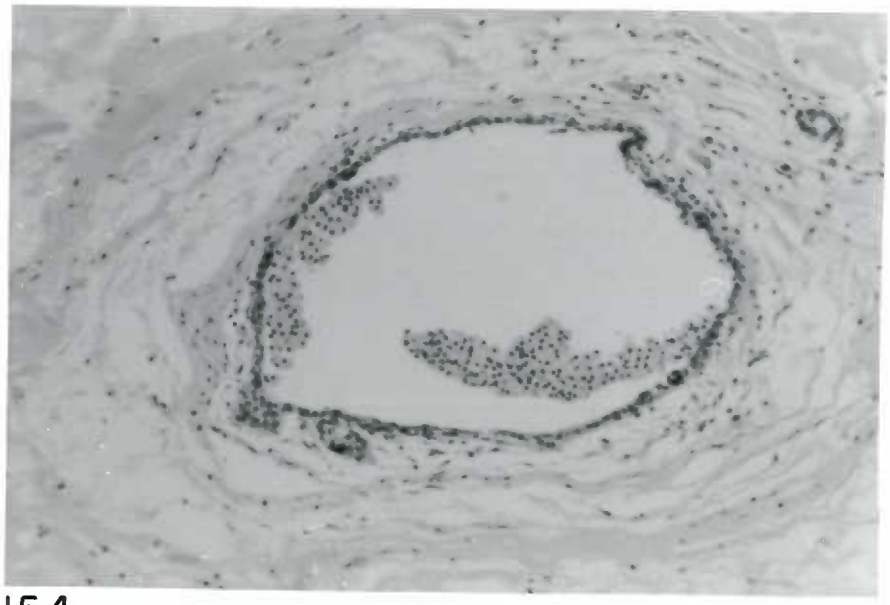
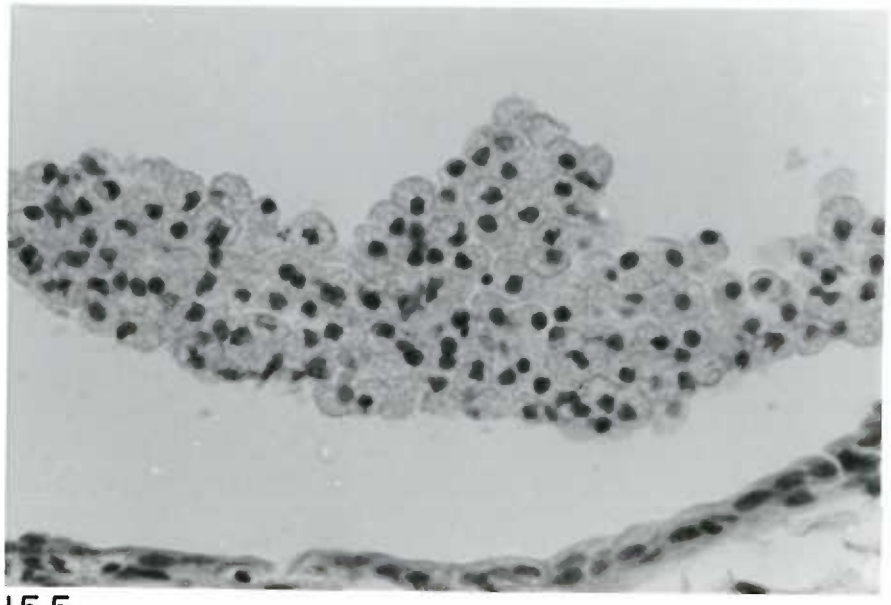


154

Figure 155:

Corresponding histology of Figure 153. The cellular material in the lumen is composed of cells with vacuolated cytoplasm, distinct cell membranes, and regular nuclei. These cells are interpreted as "fatty macrophages" or "colostrum" cells. Hematoxylin and eosin. 160X.



155

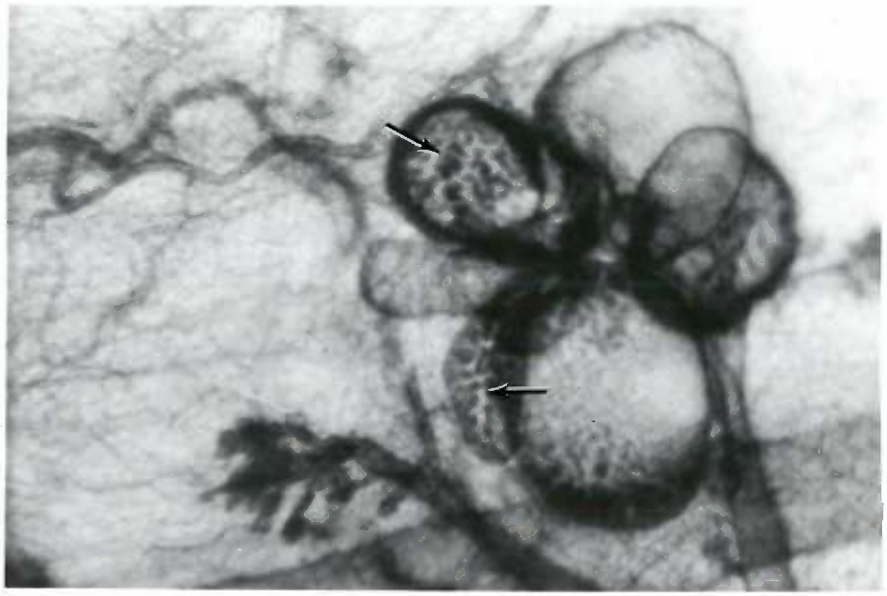
APOCRINE EPITHELIUM

Figure 156:

Female, 45 years, normal breast (M-66-2). Subgross. Several dilated ductules (acini) in a lobular arrangement have thickened walls with knobby densities projecting into empty lumina (arrows). Hematoxylin. 10X.

Figure 157:

Corresponding histology of Figure 156. The dilated lumina are empty and lined by epithelium with projecting epithelial tufts. Surrounding stroma is normal. Hematoxylin and eosin. 10X.

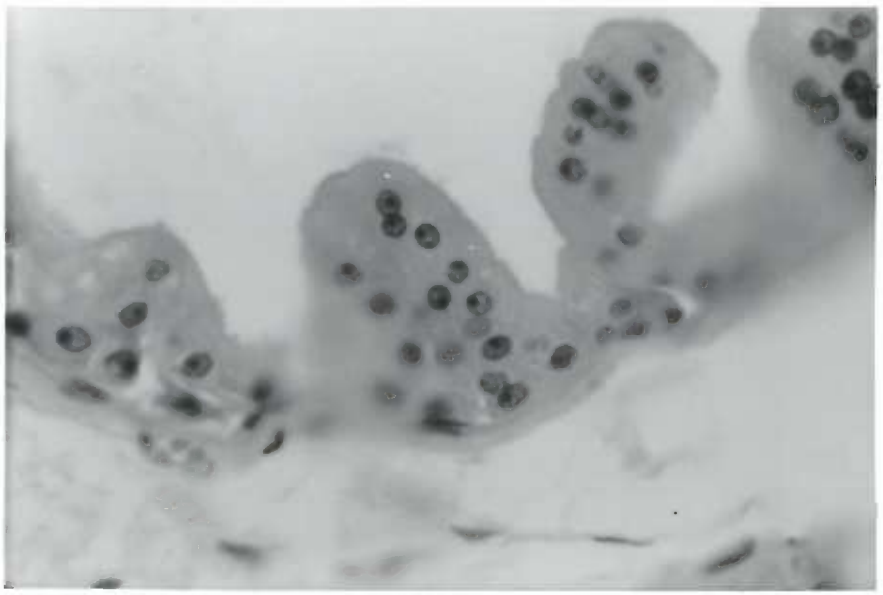


156

157

Figure 158:

Corresponding histology of Figure 156. Typical apocrine epithelium forms epithelial tufts lacking stromal cores. These are partly responsible for the subgross appearance. Hematoxylin and eosin. 160X.



158

AN ATLAS OF THE HUMAN BREAST:

SUBGROSS PATHOLOGY AND HISTOPATHOLOGY

VOLUME II

by

Ronald G. Marcum, B.S.

A THESIS
Presented to the Department of Pathology
and the Graduate Division of the University of Oregon Medical School
in partial fulfillment of
the requirements for the degree of
Master of Science

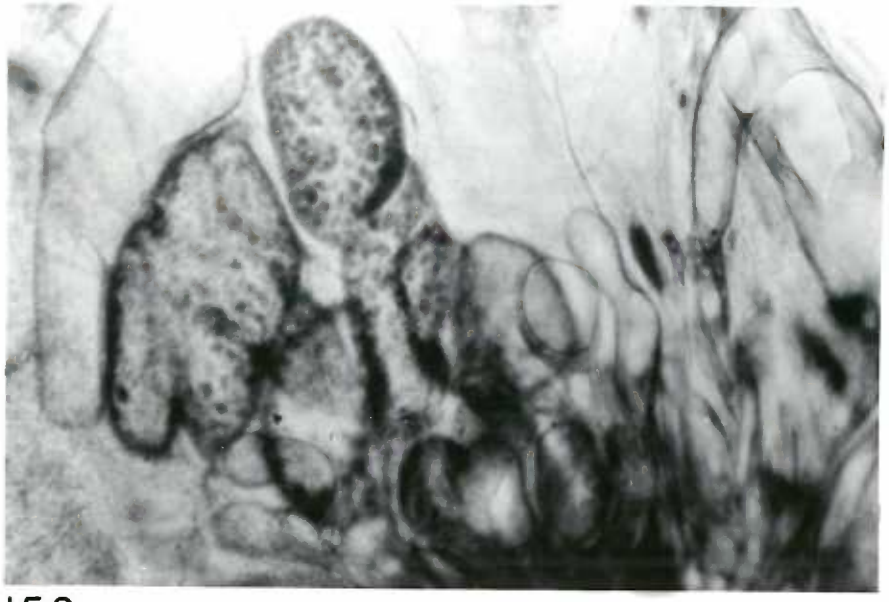
June 1969

Figure 159:

Female, 56 years, breast with mammary dysplasia (M-66-4). Subgross. Numerous dilated ducts have knobby densities projecting into lumina which appear empty. Compare those cysts with the adjacent smooth-walled, dilated ducts. Hematoxylin. 7X.

Figure 160:

Corresponding histology of Figure 159. Typical, tufted apocrine epithelium lines empty dilated lumina. Hematoxylin and eosin. 40X.



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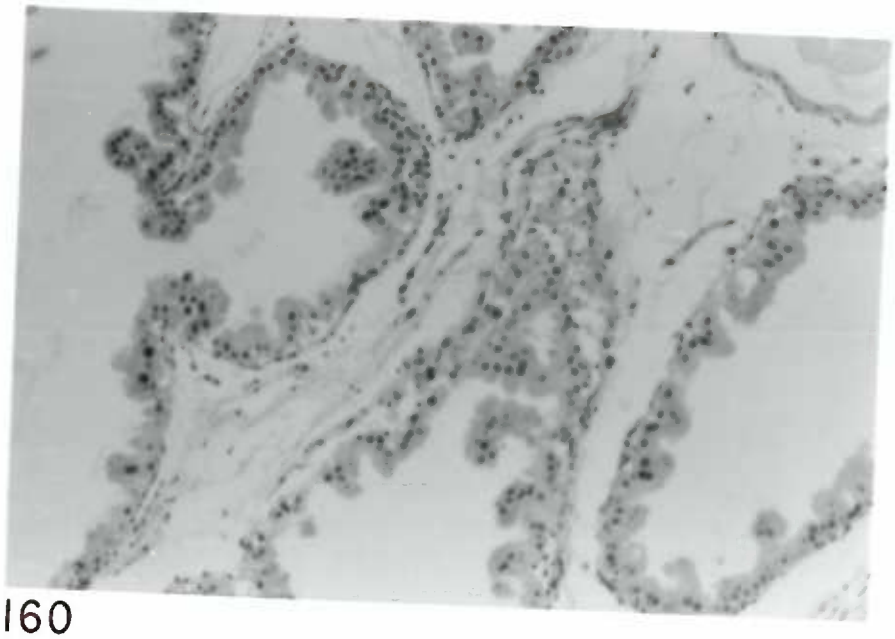


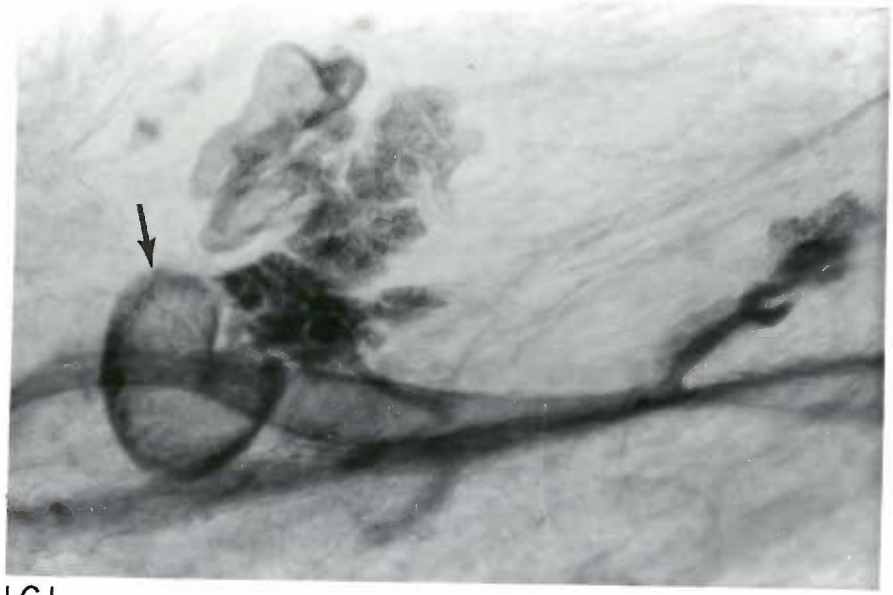
160

Figure 161:

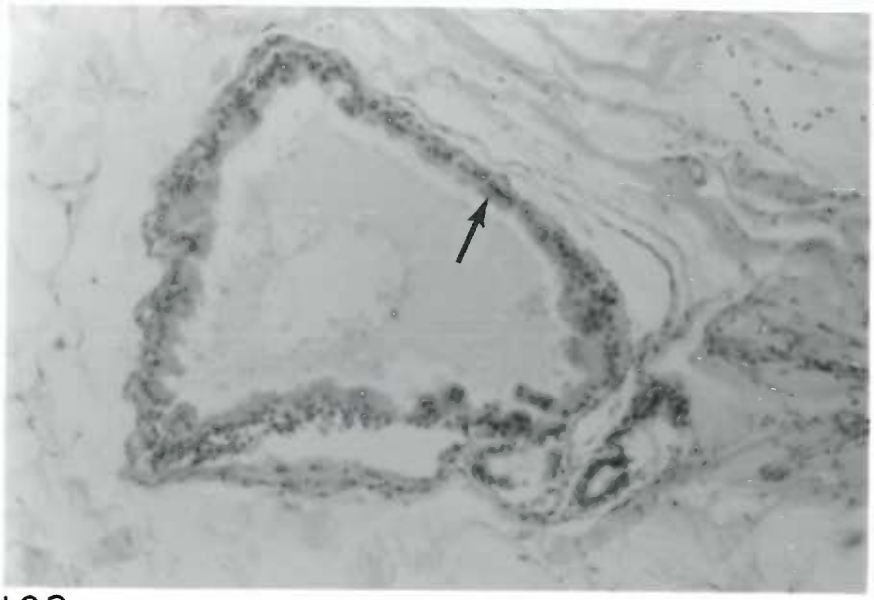
Female, 53 years, normal breast (M-66-21). Subgross. A large dilated ductule (arrow) has thickened walls, but lacks the discrete densities seen in Figures 156 and 159. The wall appears relatively smooth. Hematoxylin. 10X.

Figure 162:

Corresponding histology of Figure 161. The dilated lumen is lined by apocrine epithelium which has areas lacking the papillary projections (arrow), possibly accounting for the lack of knobby densities in the subgross preparation. Hematoxylin and eosin. 40X.



161



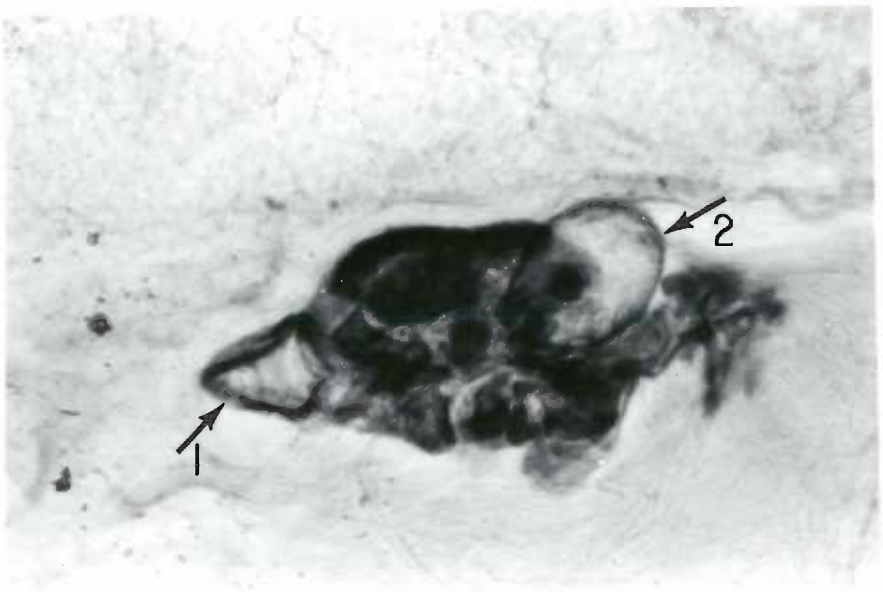
162

Figure 163:

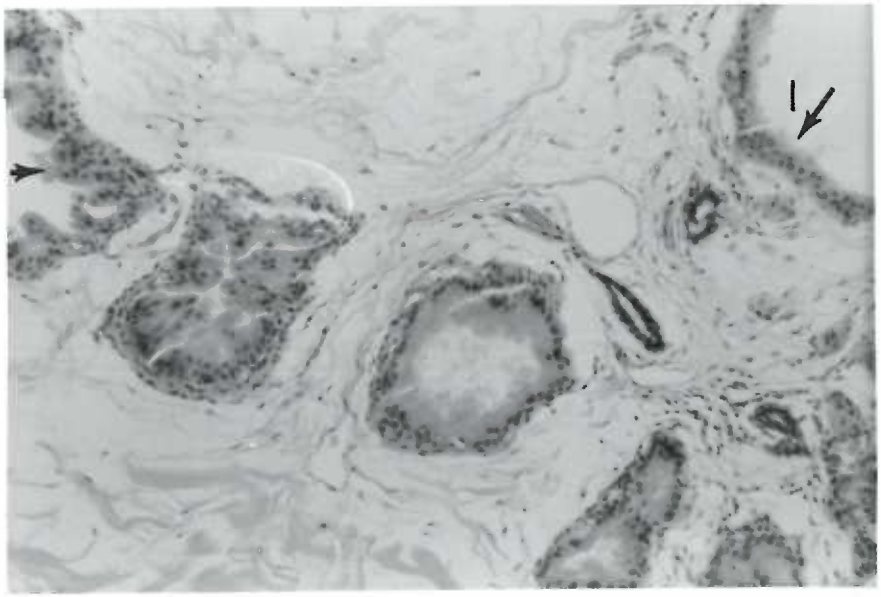
Female, 53 years, normal breast (M-66-21). Subgross. The lobular structure is composed of several dilated ductules (acini). Some have thickened walls as in Figure 161 (arrow 1), while others have smooth thin walls (arrow 2). Careful inspection of the center of the mass allows identification of knobby densities. Hematoxylin. 10X.

Figure 164:

Corresponding histology of Figure 163. Smooth apocrine epithelium (arrow 1) and papillary apocrine epithelium (arrow 2). Hematoxylin and eosin. 40X.



163



164

Figure 165:

Female, 56 years, normal breast (M-66-12). Subgross. The lobule has dilated ductules (acini) with smoothly thickened walls and empty lumina. Hematoxylin. 10X.

Figure 166:

Corresponding histology of Figure 165. Microscopy is confirmatory, showing relatively smooth apocrine epithelium. Hematoxylin and eosin. 10X.

165

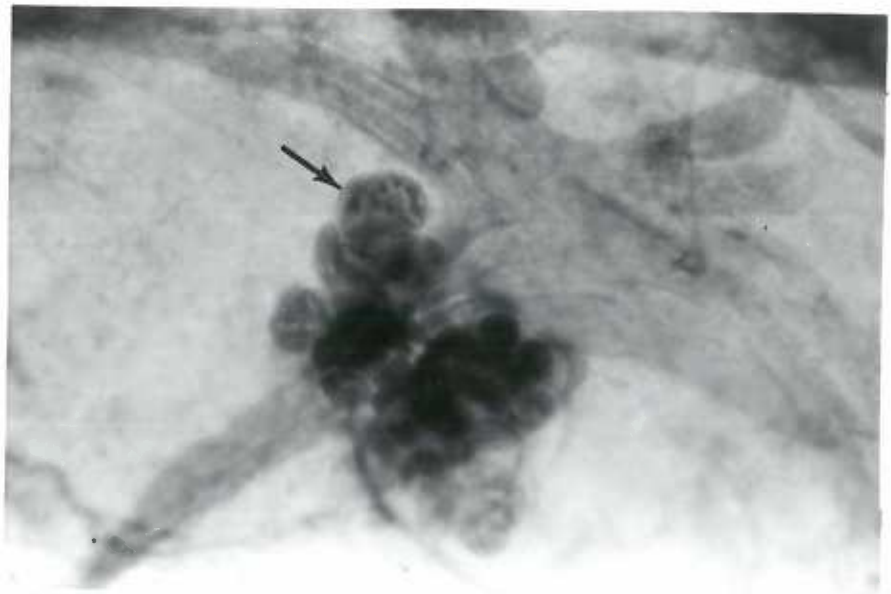
166

Figure 167:

Female, 70 years, breast with infiltrating ductal carcinoma (M-66-10). Subgross. Dilated ductules are located at a bifurcation of a duct and have walls with knobby densities (arrow). Hematoxylin. 10X.

Figure 168:

Corresponding histology of Figure 167. Apocrine epithelium lines the cystic space. The lumina are variously filled with amorphous material. Hematoxylin and eosin. 40X.



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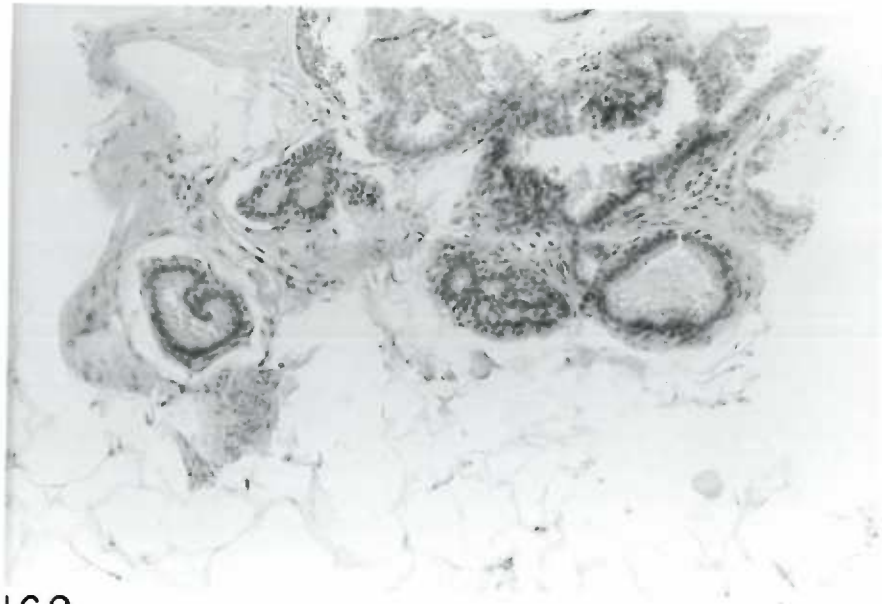


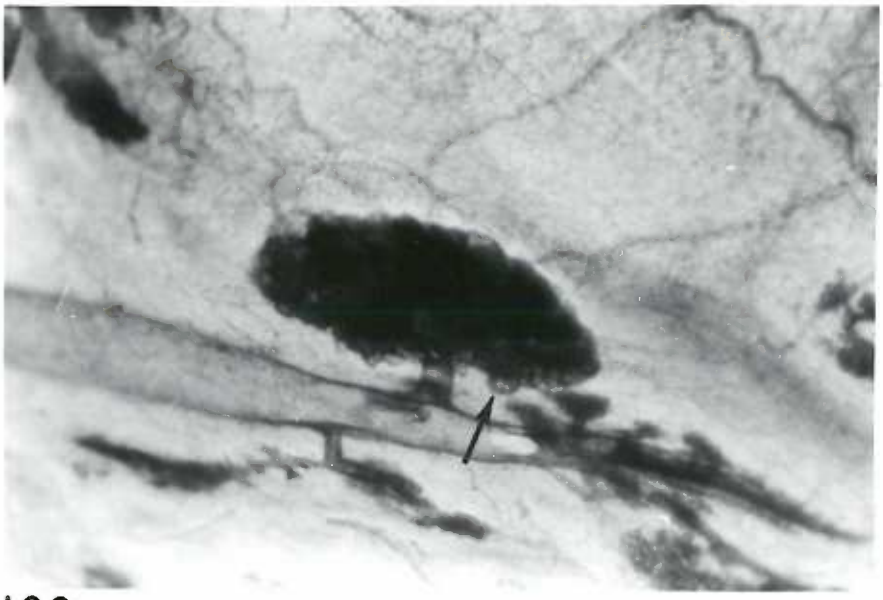
168

Figure 169:

Female, 45 years, normal breast (M-66-2). Subgross. This is a compact lobule with an entering duct. The lobule is composed of dilated ductules (acini). Thickening and papillary projections of the epithelium are noted (arrow). Hematoxylin. 10X.

Figure 170:

Corresponding histology of Figure 169. The epithelium is of the typical apocrine type. The lobular stroma is loose and normal. Hematoxylin and eosin. 40X.



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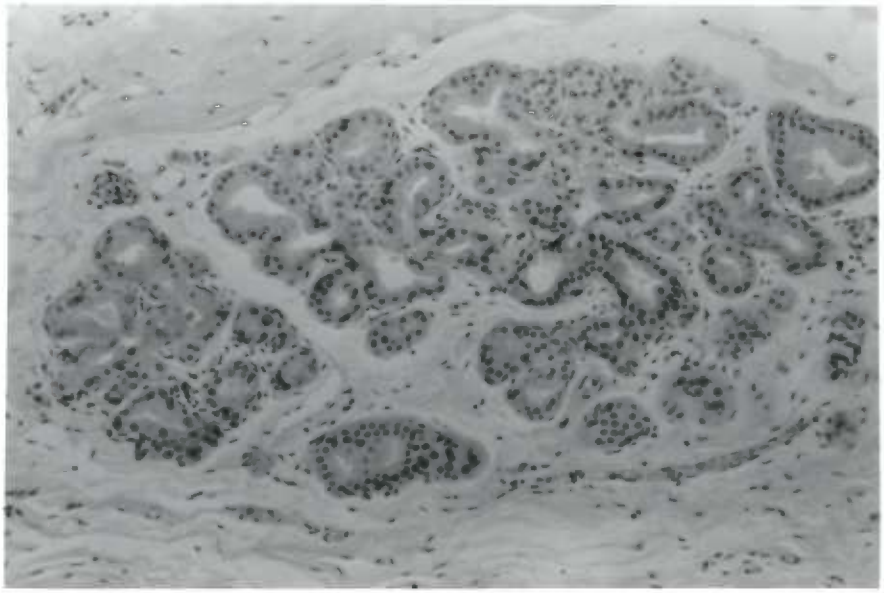


170

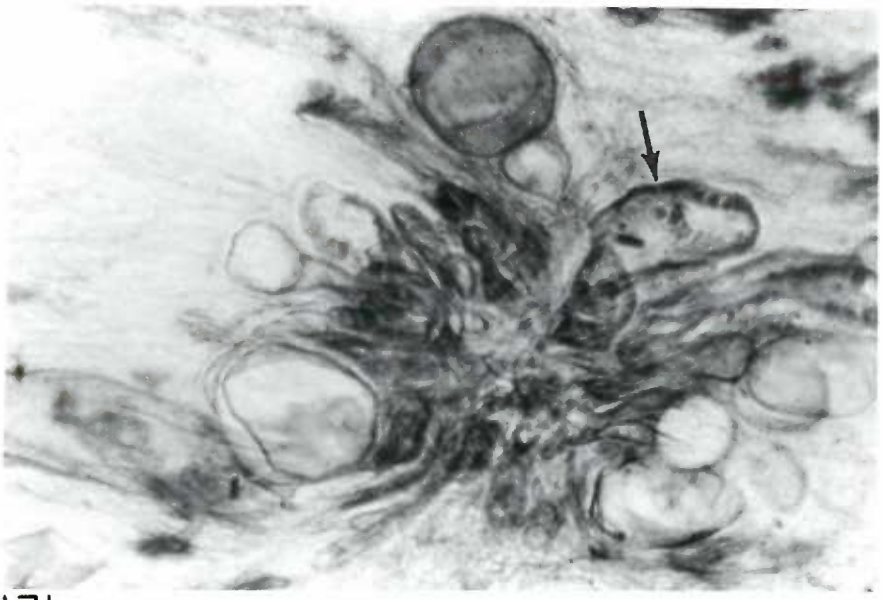
SCLEROSING ADENOSIS

Figure 171:

Female, 56 years, breast with mammary dysplasia (M-66-4). Subgross. Typical formation of sclerosing adenosis with the stellate or "cockleburr" pattern of ducts, some of which are distended, radiating from a translucent fibrous core. One area with papillary luminal projections (arrow) is noted. Hematoxylin. 8.5X.

Figure 172:

Corresponding histology of Figure 171. Microscopy confirms the typical pattern of sclerosing adenosis. A duct, matching the subgross structure at the arrow, has papillary apocrine epithelium. Hematoxylin and eosin. 10X.



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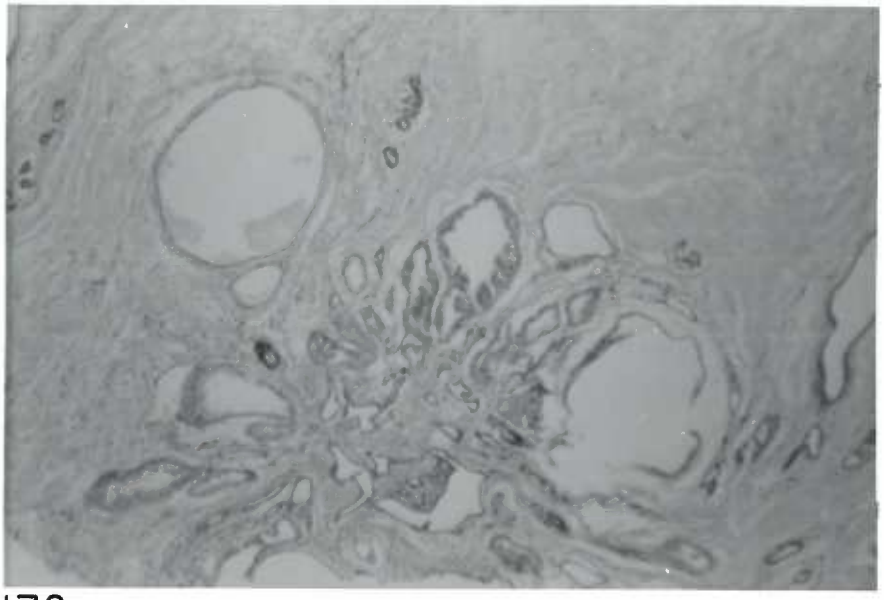


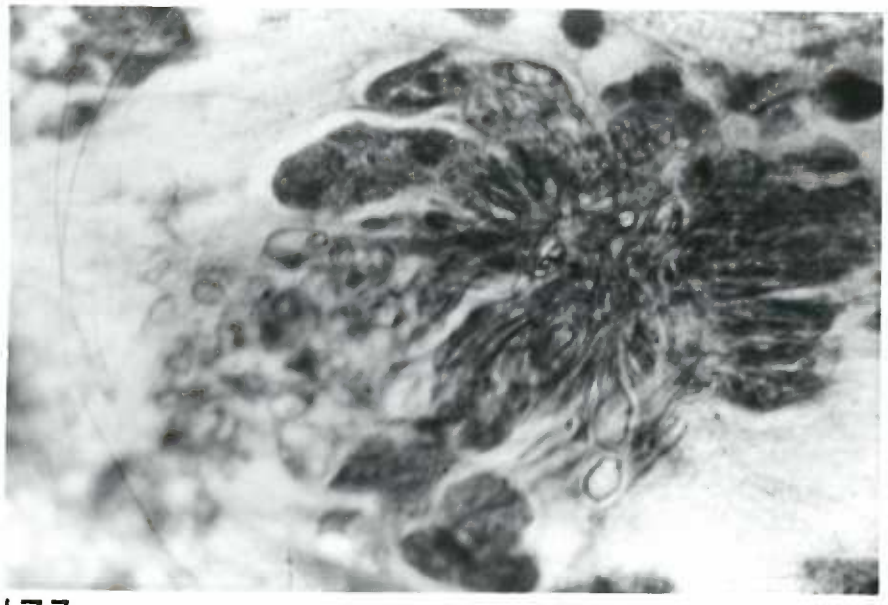
172

Figure 173:

Female, 56 years, breast with mammary dysplasia (M-66-4). Subgross. The stellate appearance due to radiating ducts is evident. Hematoxylin. 14X.

Figure 174:

Corresponding histology of Figure 173. Typical of sclerosing adenosis. No cytological atypism is apparent. Hematoxylin and eosin. 40X.



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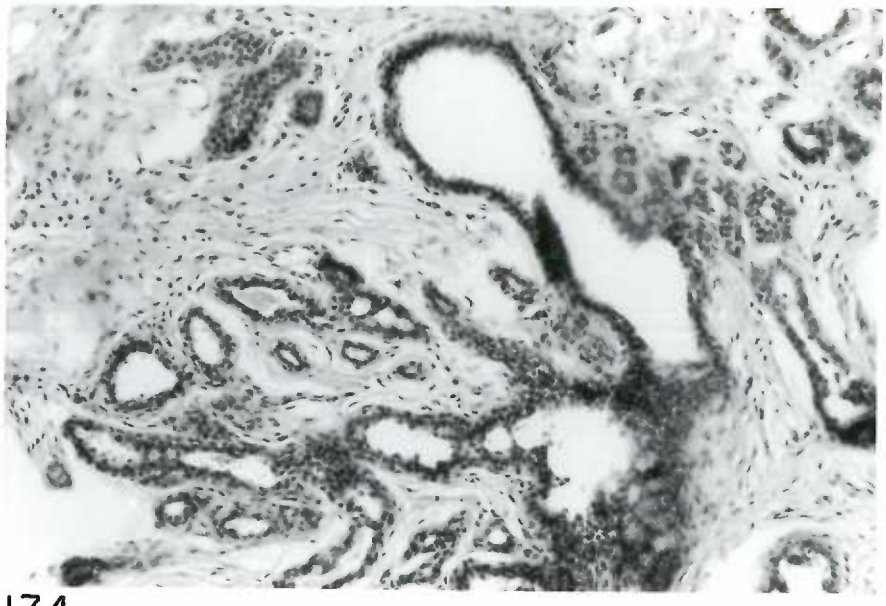


174

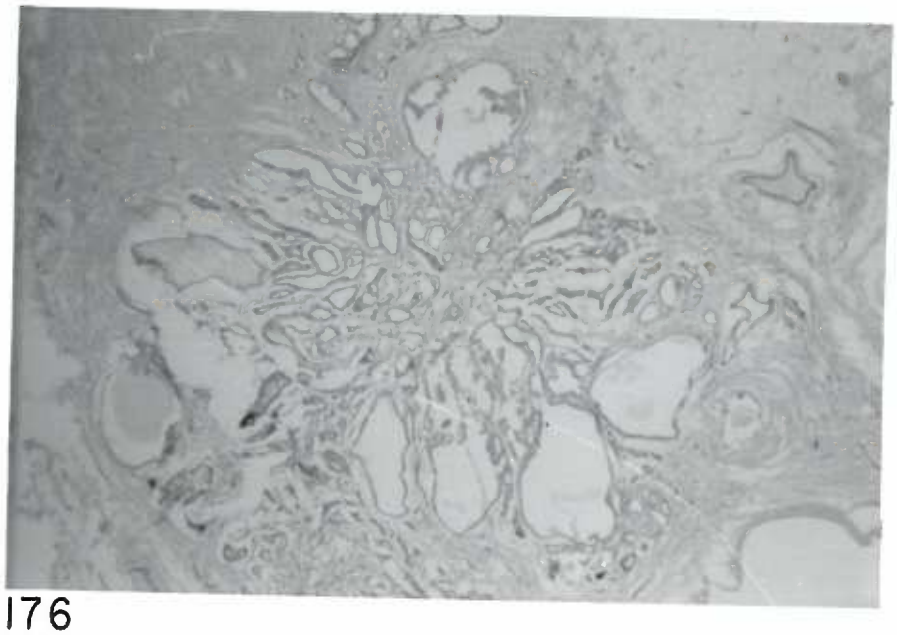
Figure 175:

Female, 47 years, normal breast (M-66-28). Subgross. The stellate pattern is present, but less apparent. Several cystic spaces are noted. Hematoxylin. 10X.

Figure 176:

Corresponding histology of Figure 175. Typical pattern of sclerosing adenosis is observed. Note the central prominence of fibrous tissue and the radiating, peripherally dilated ducts. Hematoxylin and eosin. 10X.

175



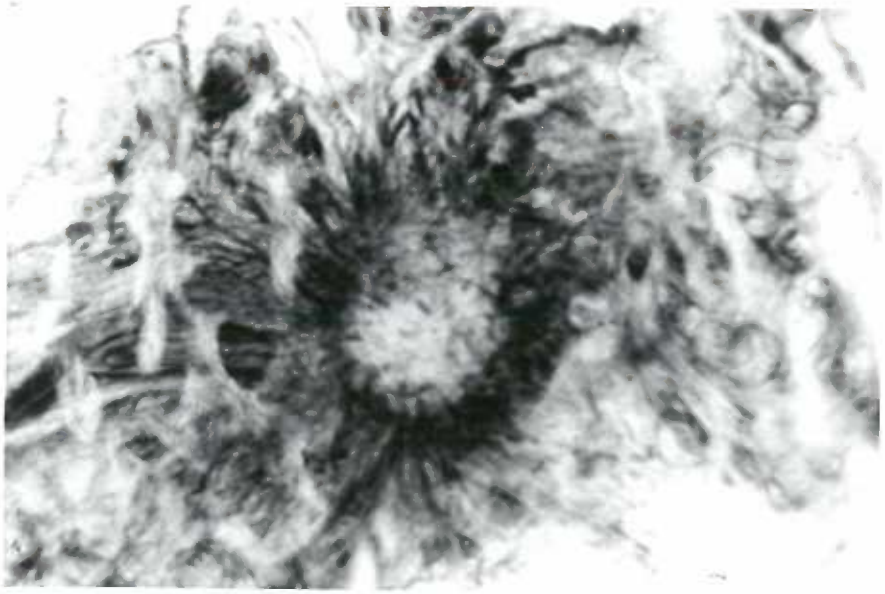
176

Figure 177:

Female, 56 years, breast with mammary dysplasia (M-66-4). Subgross. The characteristic stellate appearance has a prominent translucent fibrous core. Hematoxylin. 8X.

Figure 178:

Corresponding histology of Figure 177. Large area of central fibrosis with peripheral ducts. Hematoxylin and eosin. 10X.



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178

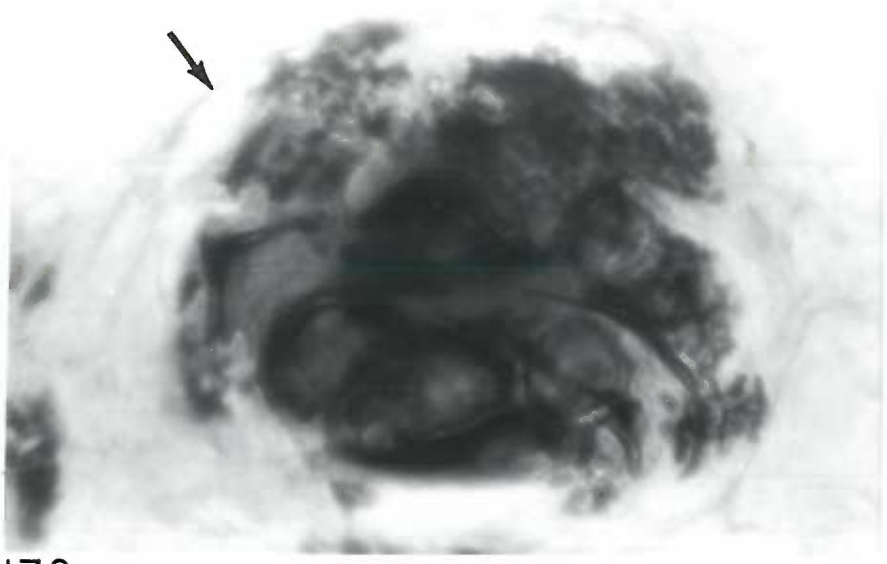
FIBROADENOMA

Figure 179:

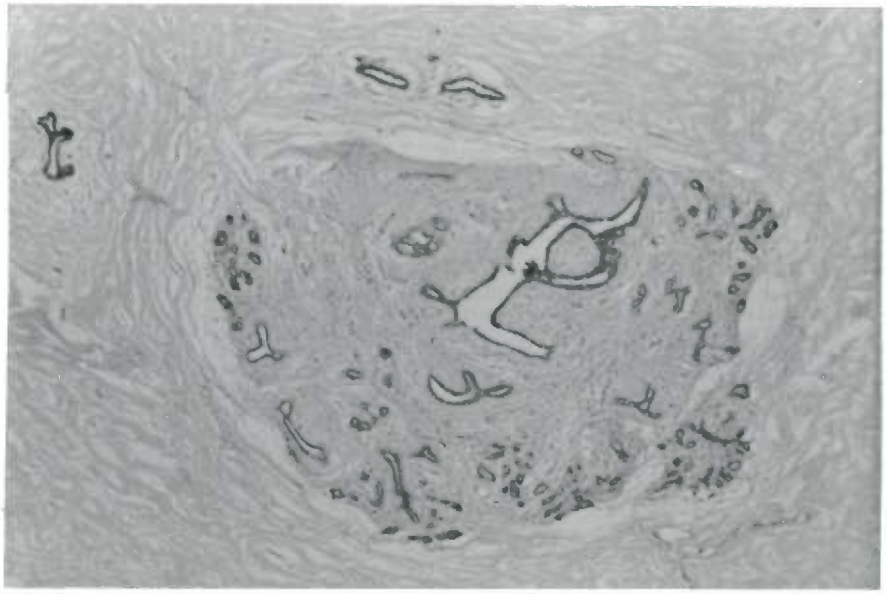
Female, 19 years, normal breast (M-66-8). Subgross. Epithelial elements are confined by investing fibrous tissue (arrows). No entering ducts are identified and the identifiable ducts and lobules are relatively undistorted. Hematoxylin. 10X.

Figure 180:

Corresponding histology of Figure 177. An increased amount of fibrous tissue in conjunction with mild distortion of ducts is consistent with the histopathology of fibroadenoma. The epithelium is normal. Hematoxylin and eosin. 10X.



179



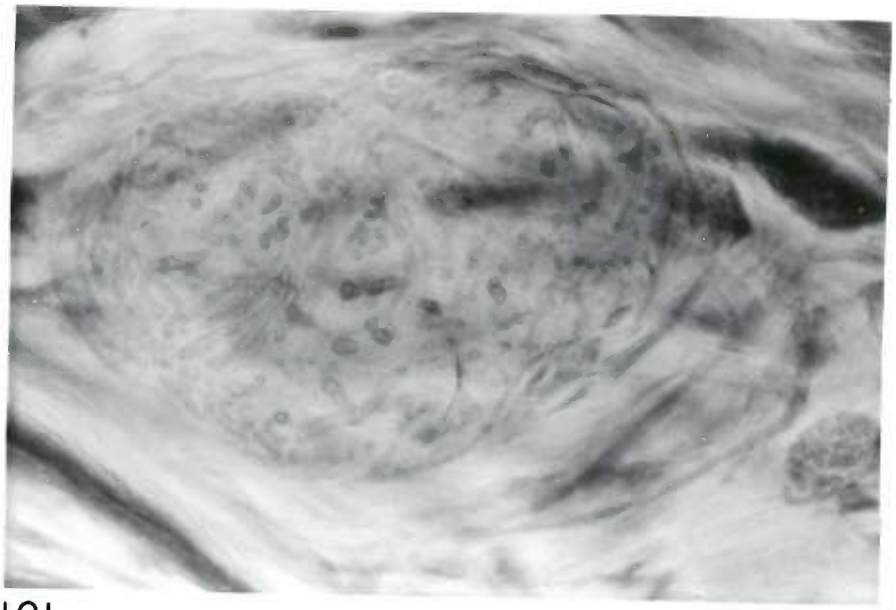
180

Figure 181:

Female, 56 years, normal breast (M-66-12). Subgross. Pale, confined ductules are easily noted. This is another appearance of fibroadenoma. Hematoxylin. 10X.

Figure 182:

Corresponding histology of Figure 181. The histopathology confirms the above. Hematoxylin and eosin. 10X.



181

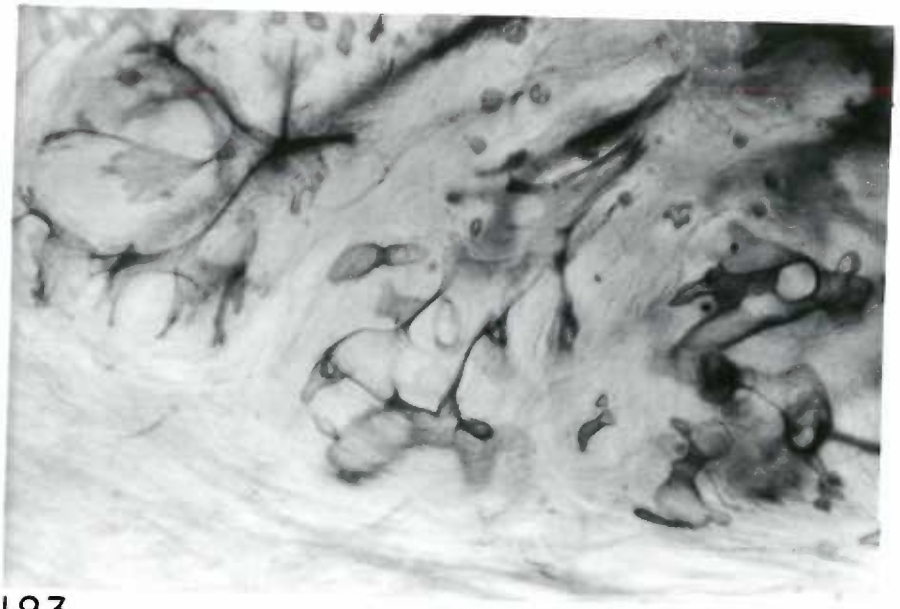
182

Figure 183:

Female, 19 years, normal breast (M-66-20). Subgross. Several ducts are flattened, distorted, and embedded in fibrous tissue. Hematoxylin. 10X.

Figure 184:

Corresponding histology of Figure 183. Confirmatory microscopy reveals a fibroadenoma of the intracanalicular type. Hematoxylin and eosin. 10X.



183

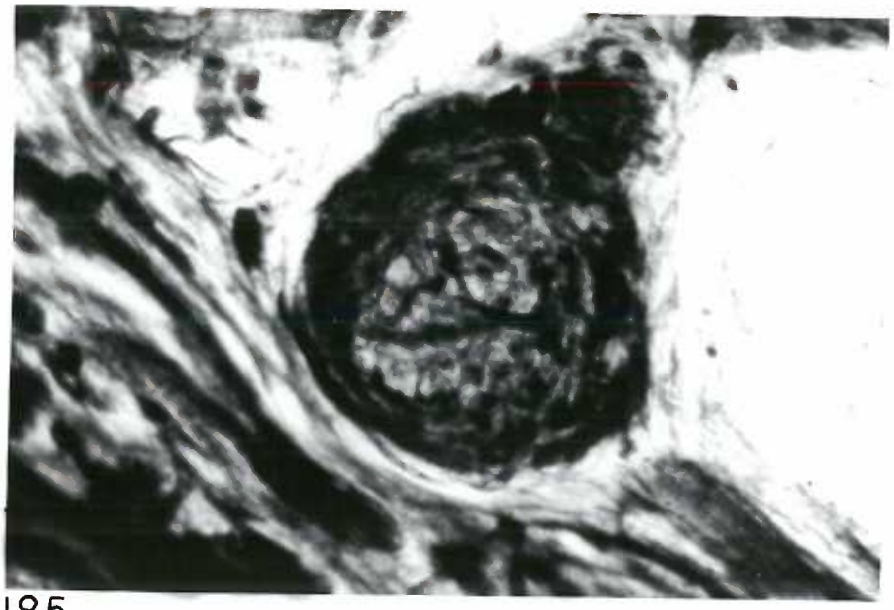
184

Figure 185:

Female, 56 years, breast with mammary dysplasia (M-66-4). Subgross. A sharply defined fibroepithelial mass with ducts coursing through more translucent fibrous tissue. Hematoxylin. 8X.

Figure 186:

Corresponding histology of Figure 185. This is typical of pericanalicular fibroadenoma. Hematoxylin and eosin. 10X.



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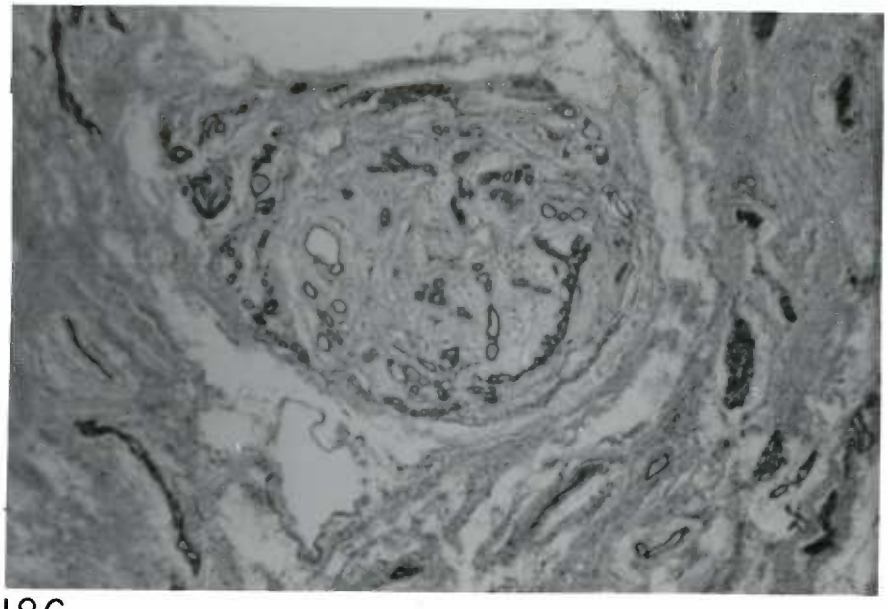


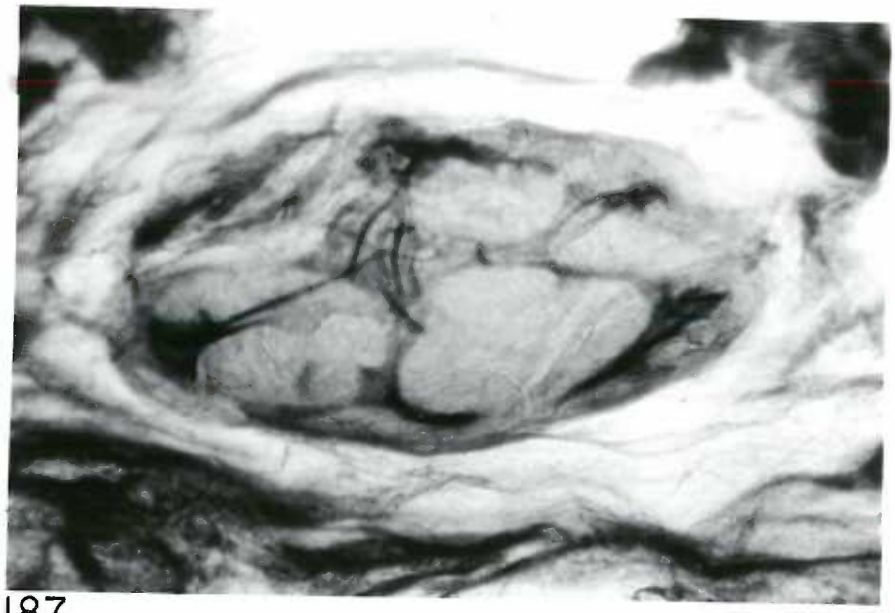
186

Figure 187:

Female, 56 years, breast with mammary dysplasia (M-66-4). Subgross. Sharply defined fibroepithelial mass with distorted ductules. Hematoxylin. 10X.

Figure 188:

Corresponding histology of Figure 187. A typical intracanalicular fibroadenoma. Hematoxylin and eosin. 10X.



187

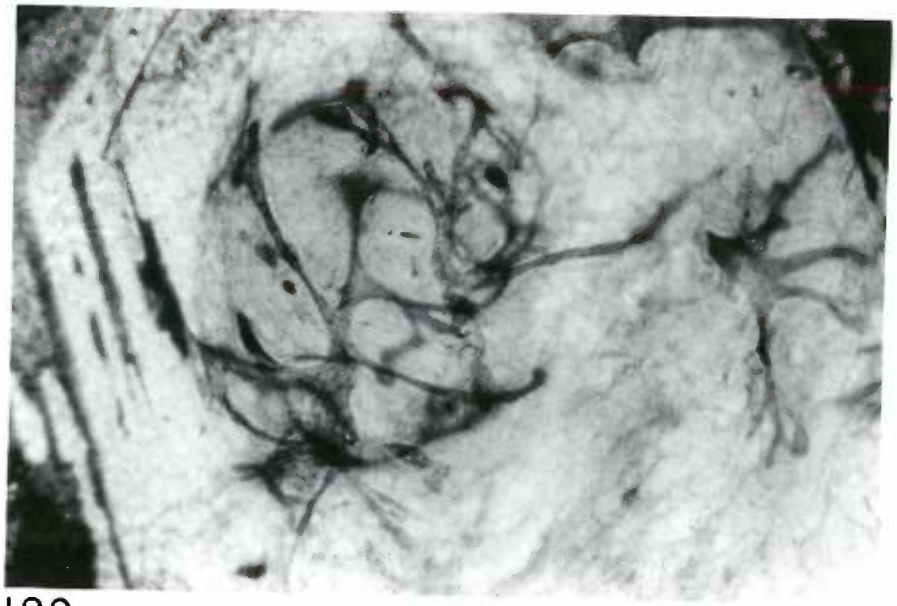
188

Figure 189:

Female, 56 years, breast with mammary dysplasia (M-66-4). Subgross. Another typical subgross appearance of a fibroadenoma. Hematoxylin. 10X.

Figure 190:

Corresponding histology of Figure 189. Microscopy is confirmatory. Hematoxylin and eosin. 40X.



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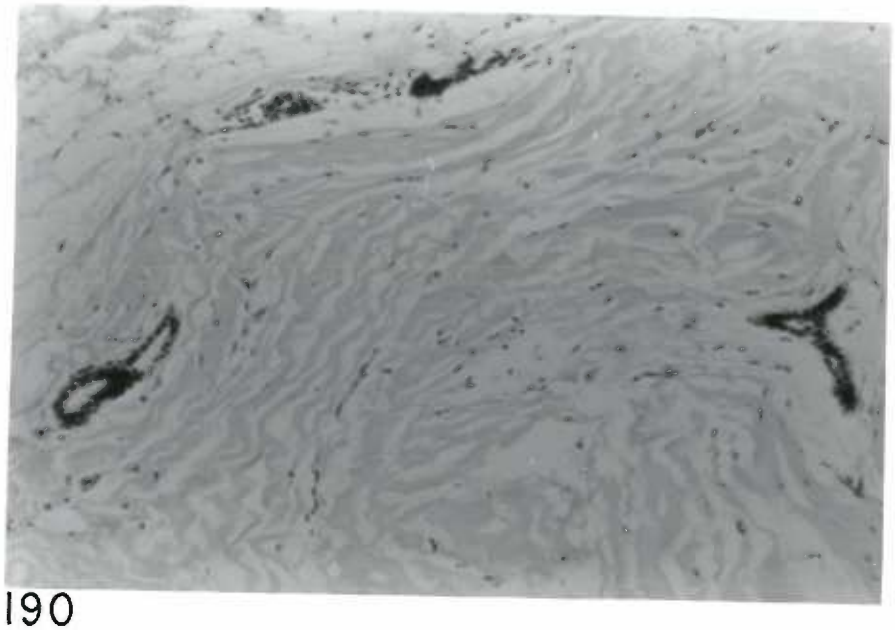


190

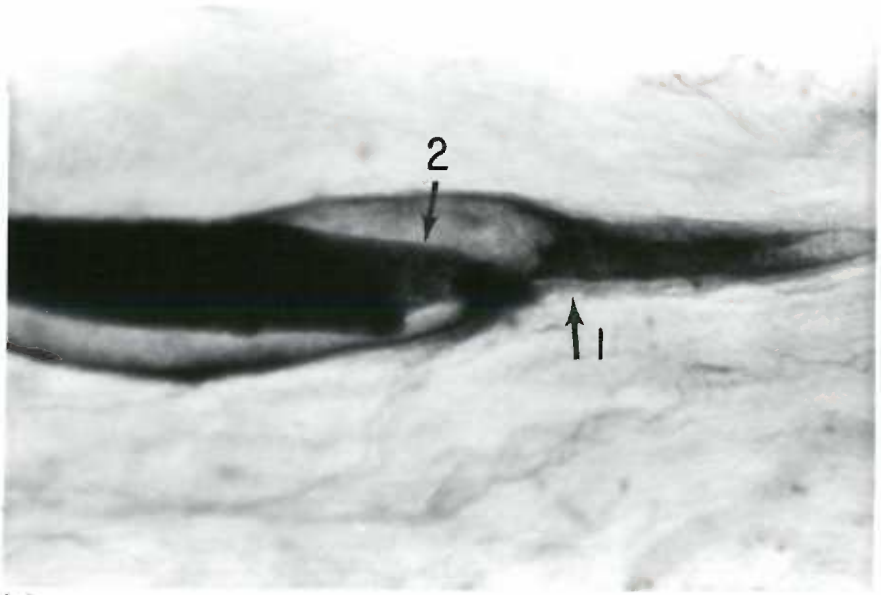
MAMMARY DUCT ECTASIA

Figure 191:

Female, 53 years, normal breast (M-66-21). Subgross. A segmentally dilated duct with haziness in the periductal stroma (arrow 1) has a large mass of inspissated material in the lumen (arrow 2). The smaller segment of duct has a poorly visible lumen. Hematoxylin. 10X.

Figure 192:

Corresponding histology of Figure 191. A section from the area of duct widening shows an increase in periductal fibrous tissue with a moderate inflammatory infiltrate. The lumen is partially filled with cells. The duct wall appears to have a defect (arrow). The picture is consistent with mammary duct ectasia. Hematoxylin and eosin. 40X.



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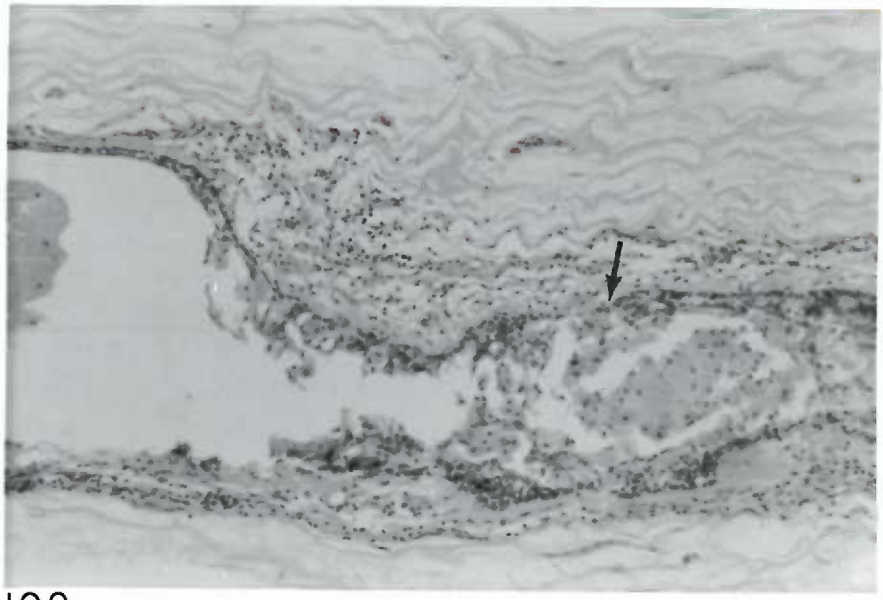


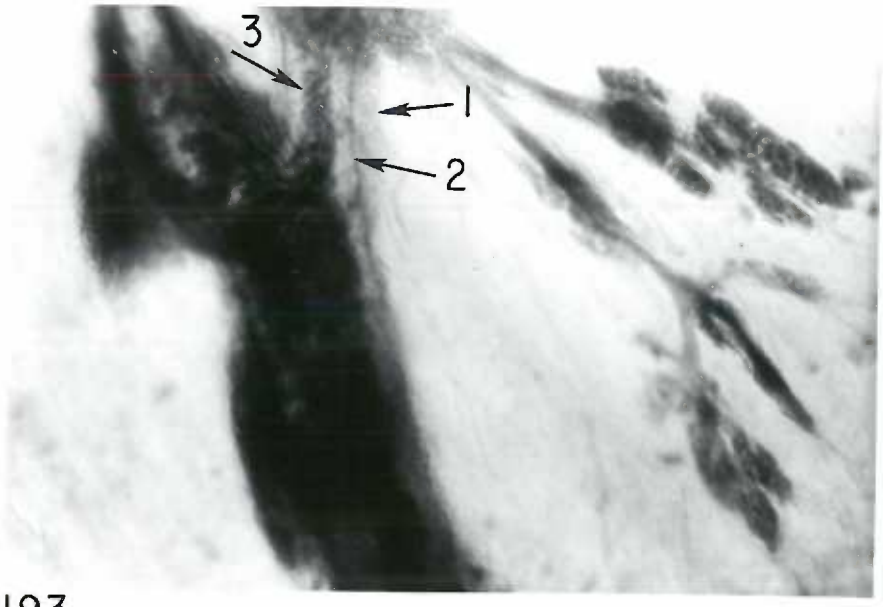
192

Figure 193:

Female, 53 years, normal breast (M-66-21). Subgross. A dilated duct is seen. The following are identifiable: 1) periductal haziness (arrow 1), 2) thickened duct wall (arrow 2), 3) intraluminal material (arrow 3). Hematoxylin. 10X.

Figure 194:

Corresponding histology of Figure 193. The microscopy shows a marked periductal inflammatory reaction, somewhat thickened duct wall, and exfoliated cells in the duct lumen. Hematoxylin and eosin. 10X.



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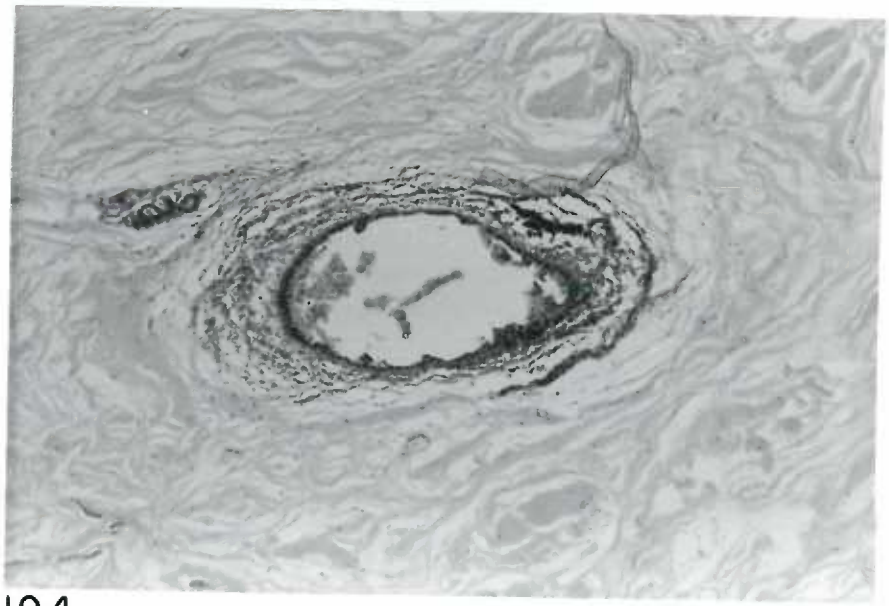
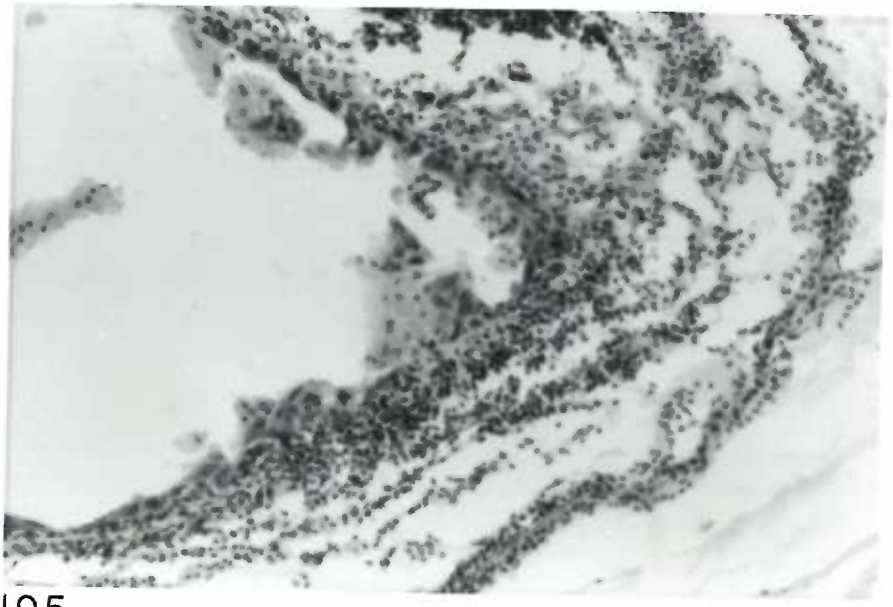


194

Figure 195:

Corresponding histology of Figure 193. A higher power shows the intense inflammation and exfoliation which occurs in mammary duct ectasia. Hematoxylin and eosin. 40X.



195

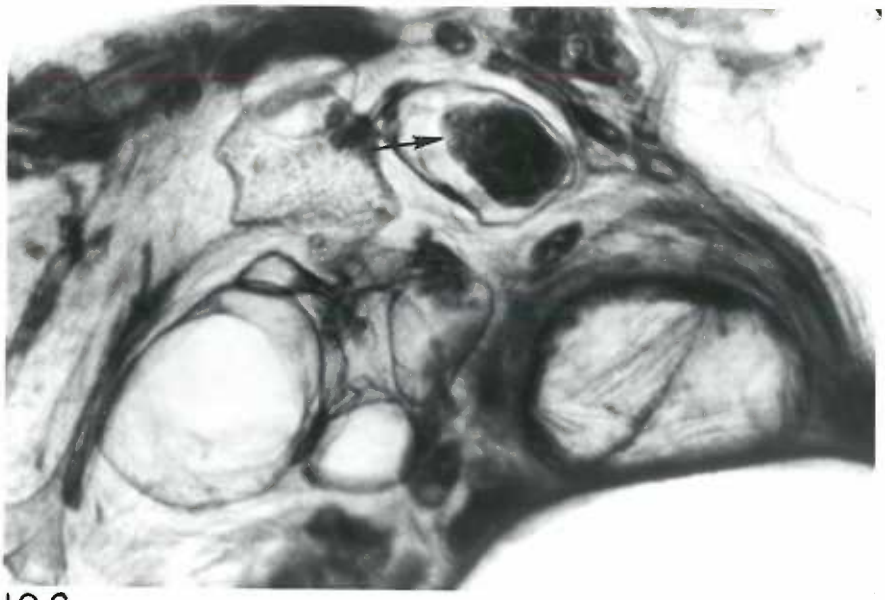
PAPILLOMAS AND PAPILLOMATOSIS

Figure 196:

Female, 56 years, breast with mammary dysplasia (M-66-4). Subgross. A rounded intraluminal mass is present in a dilated duct (arrow). Hematoxylin. 8X.

Figure 197:

Corresponding histology of Figure 196. A large intraductal papilloma is attached to the duct wall by a small delicate stalk (arrow). The stromal core is covered by normal epithelium. Hematoxylin and eosin. 40X.



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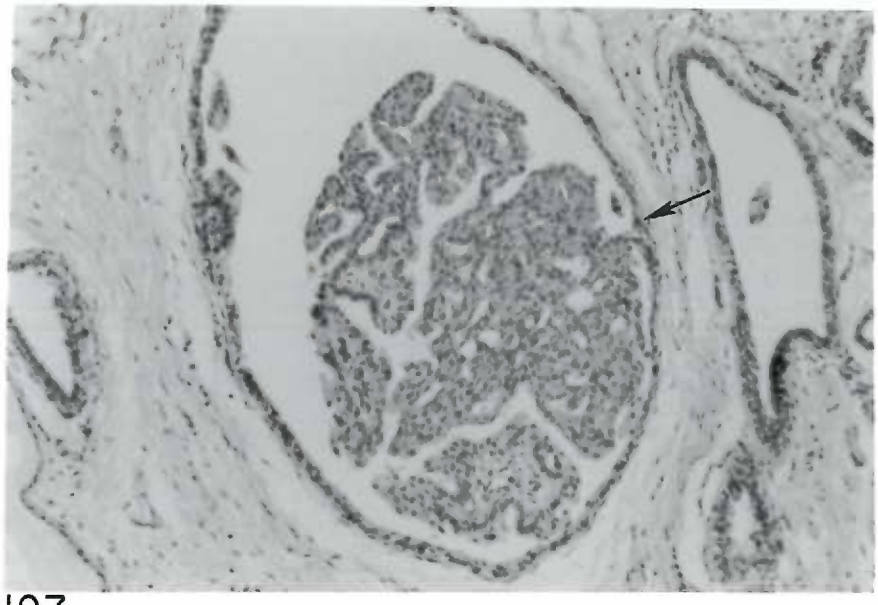


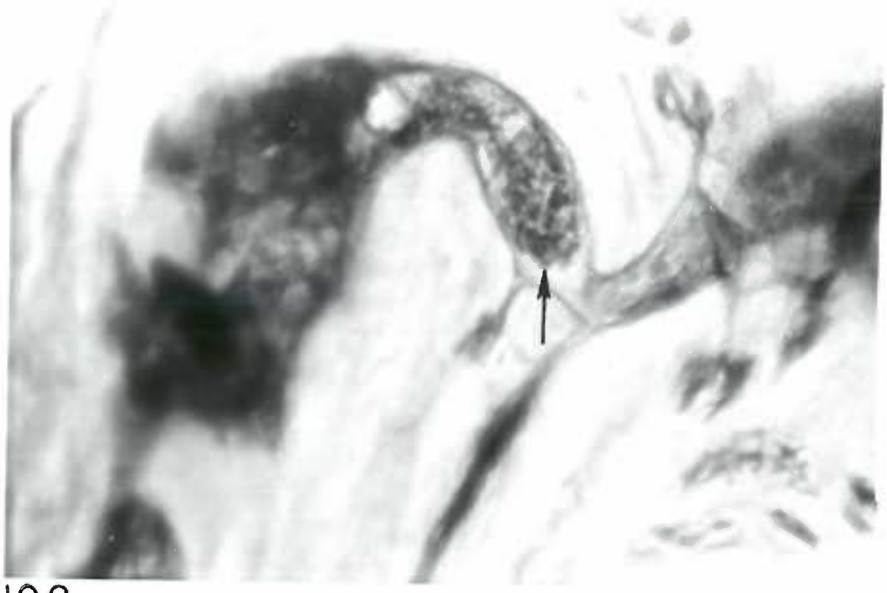
197

Figure 198:

Female, 57 years, normal breast (M-66-22). Subgross. A dilated duct has several irregular intraluminal densities (arrow). Hematoxylin. 10X.

Figure 199:

Corresponding histology of Figure 198. Several papillary projections with stromal cores covered by normal epithelium are noted. Consistent with papillomatosis. Hematoxylin and eosin. 40X.



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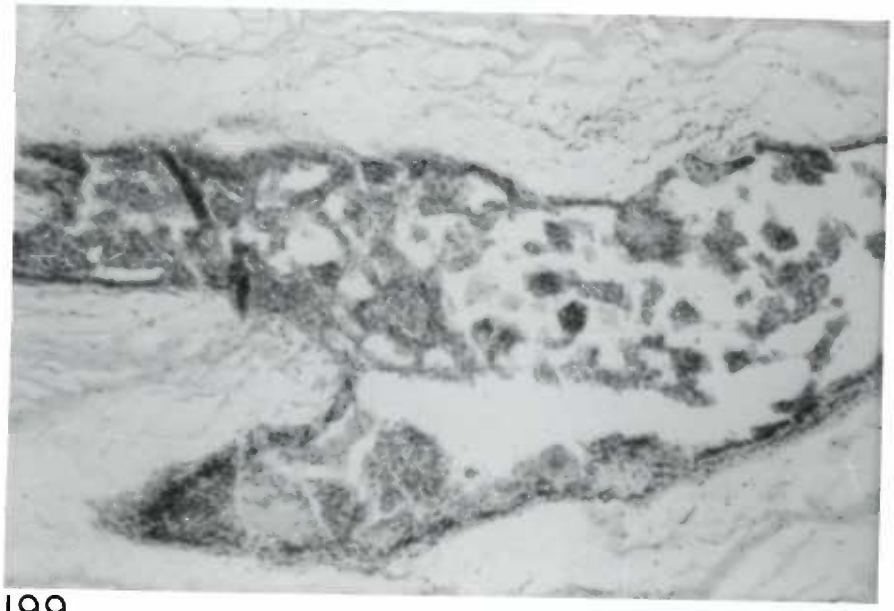


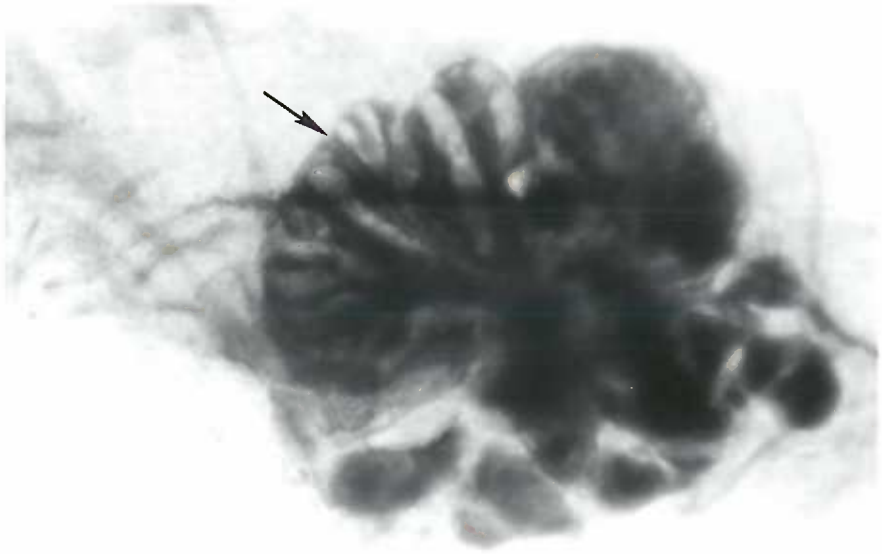
199

Figure 200:

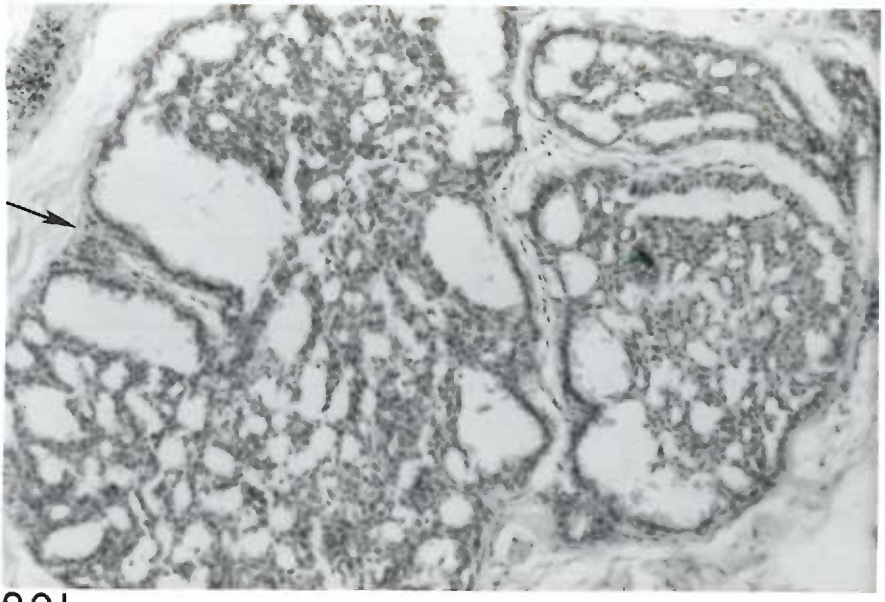
Female, 70 years, breast with infiltrating duct carcinoma (M-66-10). Subgross. This lobule has a smooth contour and variable densities throughout. Several folds (arrow) are seen. Hematoxylin. 10X.

Figure 201:

Corresponding histology of Figure 200. Epithelial invested stroma forms a cribriform pattern in the lumina. The folds correspond to bands of intralobular stroma (arrow). Hematoxylin and eosin. 40X.



200



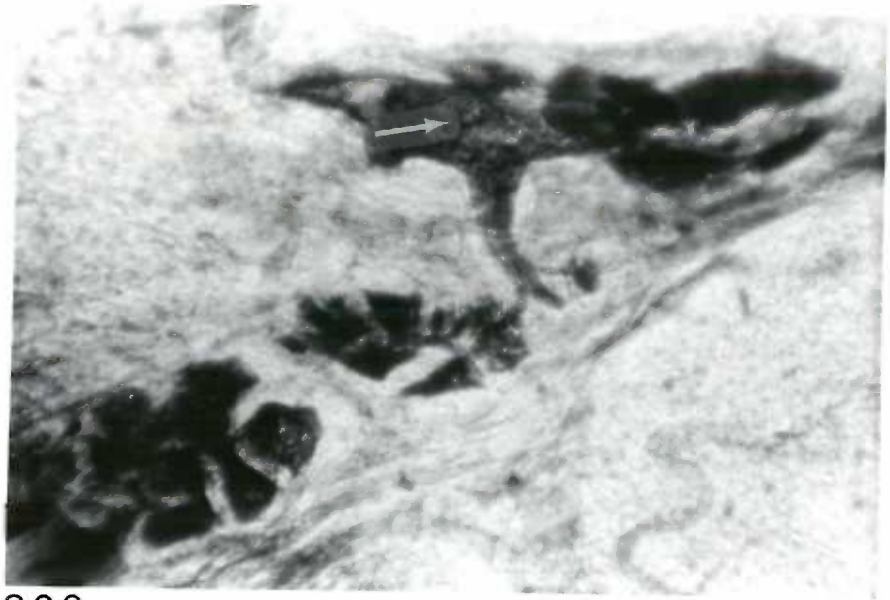
201

Figure 202:

Female, 57 years, normal breast (M-66-22). Subgross. Dense ducts with visible irregular nodular densities (arrow) in the lumina. Hematoxylin. 10X.

Figure 203:

Corresponding histology of Figure 202. Typical papillomatosis is seen. No atypism is noted. Hematoxylin and eosin. 10X.



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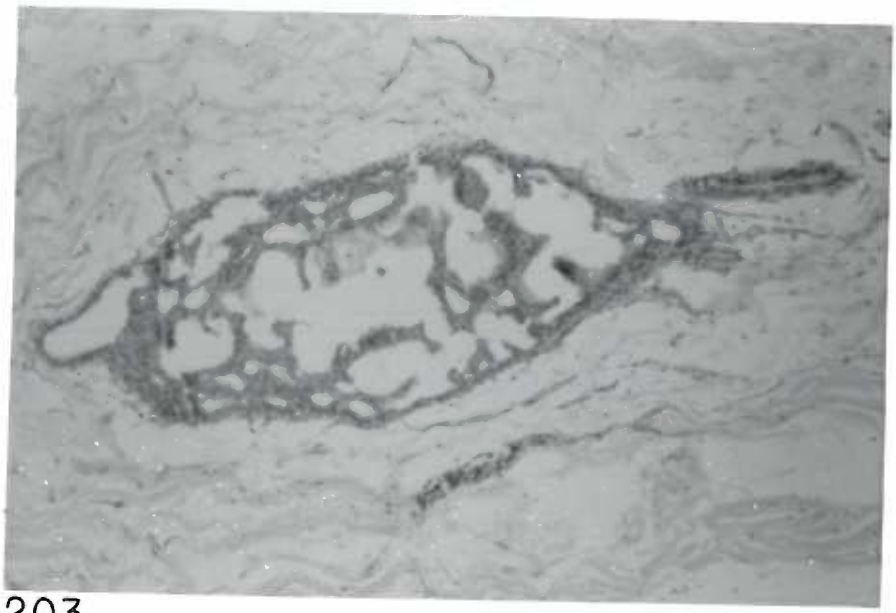


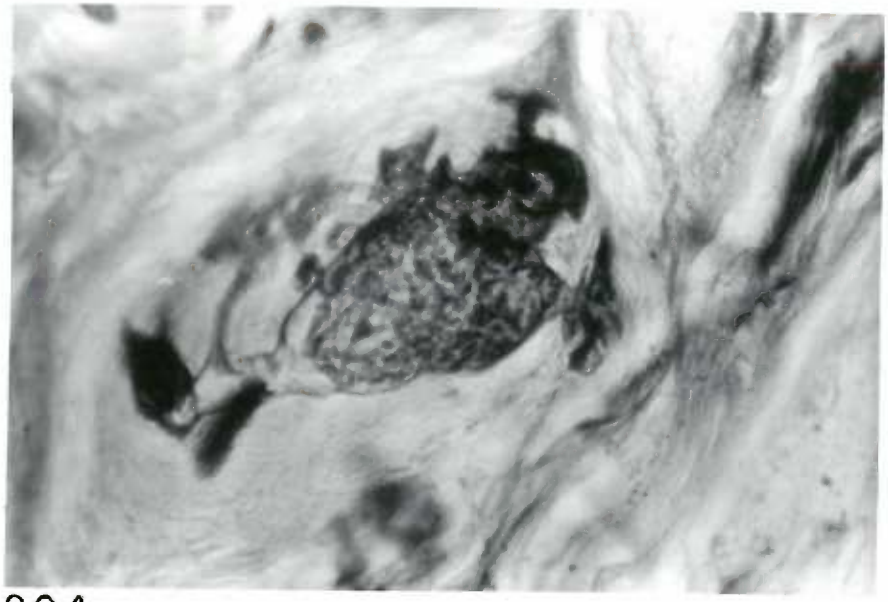
203

Figure 204:

Female, 57 years, normal breast (M-66-22). Subgross. A dilated duct has several irregular densities in the lumen. Hematoxylin. 10X.

Figure 205:

Corresponding histology of Figure 204. Papillomatosis. There are stromal elements in the intraluminal projections. Some secretory material and exfoliated cells are seen in the duct spaces. Hematoxylin and eosin. 40X.



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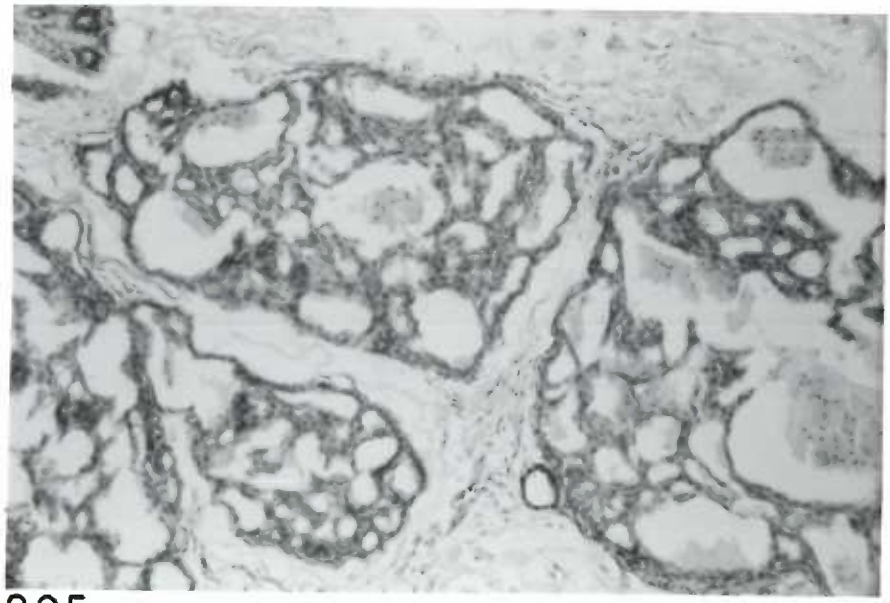


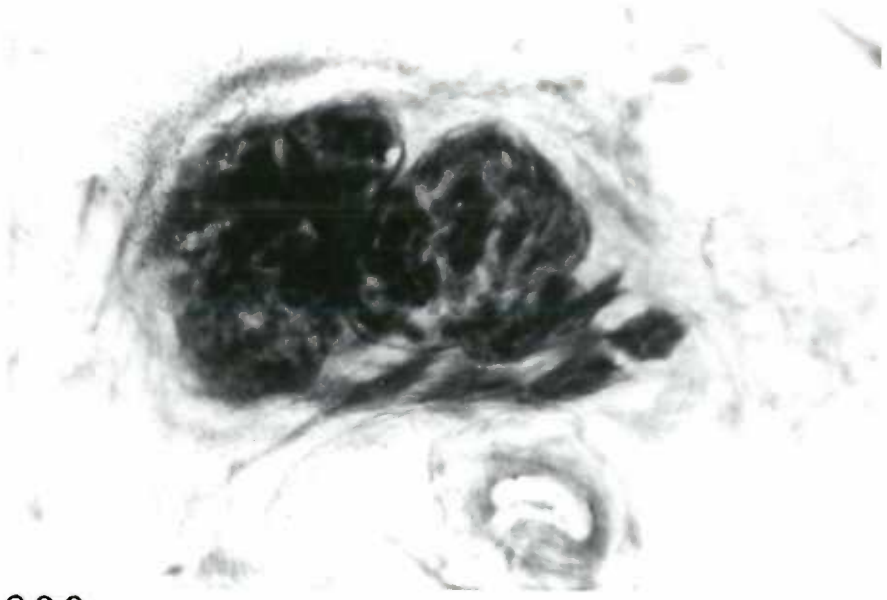
205

Figure 206:

Female, 57 years, normal breast (M-66-22). Subgross. A lobule composed of dilated acini has larger intraluminal densities than were seen in earlier subgross figures (Figs. 198 and 204). Hematoxylin. 10X.

Figure 207:

Corresponding histology of Figure 206. Typical intraductal papillomatosis is illustrated. Hematoxylin and eosin. 40X.



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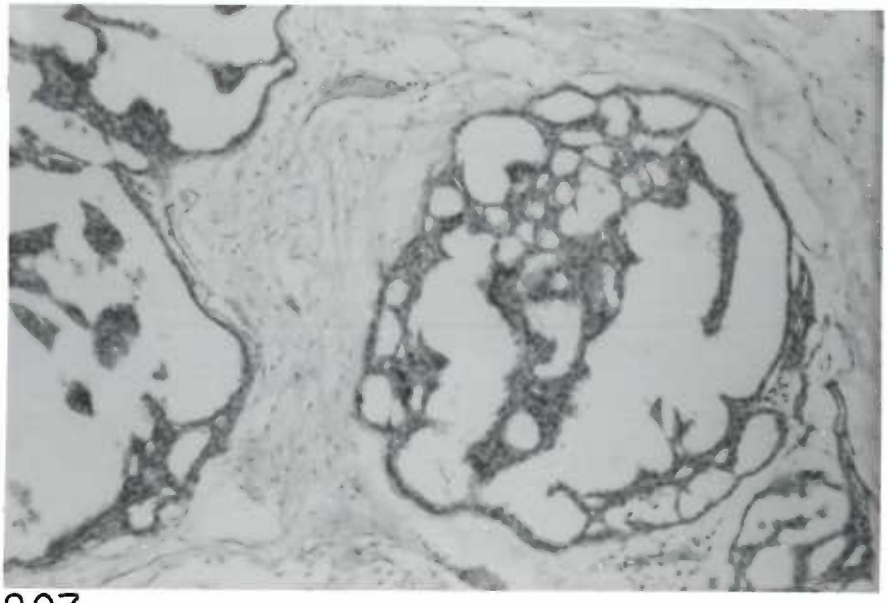


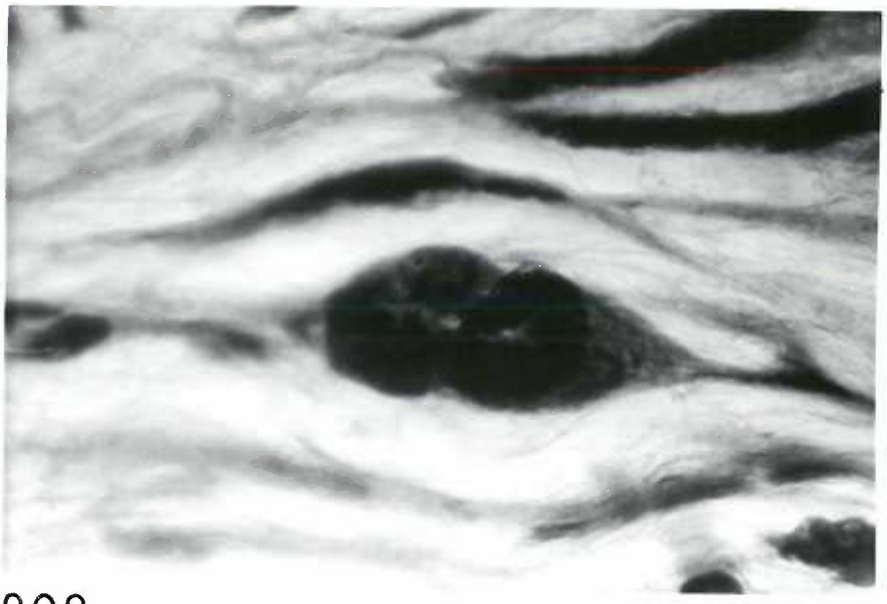
207

Figure 208:

Female, 57 years, normal breast (M-66-22). Subgross. A fusiform dilatation of a duct shows intraluminal densities. There is subtotal occlusion of the duct. Hematoxylin. 10X.

Figure 209:

Corresponding histology of Figure 208. Intraductal papillomatosis is seen without epithelial atypism. Hematoxylin and eosin. 40X.



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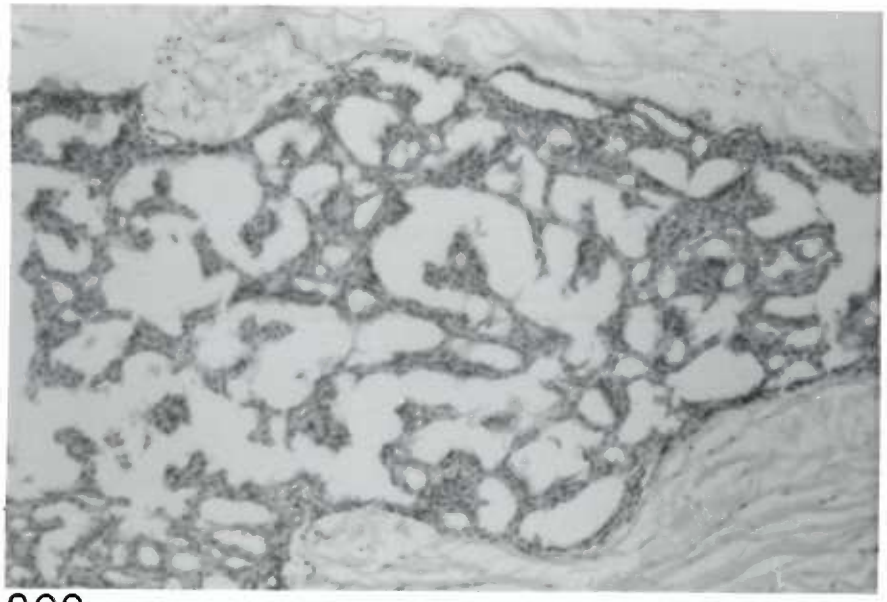


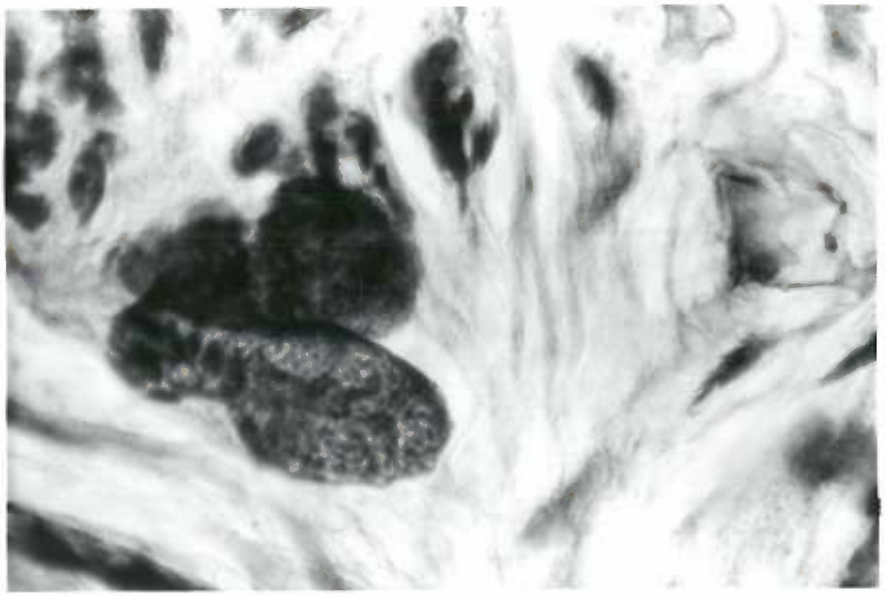
209

Figure 210:

Female, 57 years, normal breast (M-66-22). Subgross. A smoothly contoured structure with internal stippling is similar to those seen in Figures 198 and 204. Hematoxylin. 10X.

Figure 211:

Corresponding histology of Figure 210. On microscopy, a relatively normal lobule is observed. Hematoxylin and eosin. 40X.



210

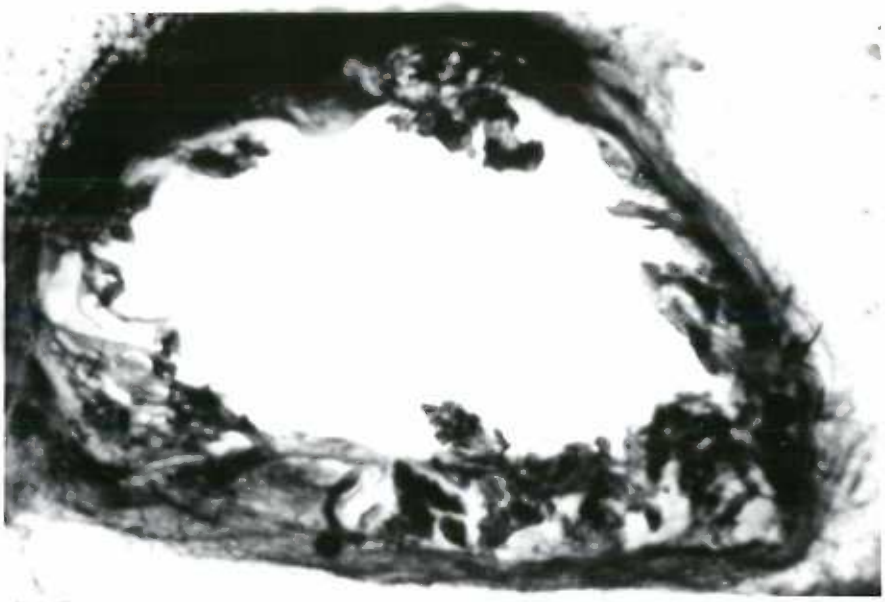
211

Figure 212:

Female, 65 years, breast with mammary dysplasia (M-66-5). Subgross. The cross-section of a large duct shows multiple luminal projections. Hematoxylin. 5X.

Figure 213:

Corresponding histology of Figure 212. Stromal stalks are covered by normal epithelium. These account for the luminal projections in the subgross preparation. Characteristic of papillomatosis. Hematoxylin and eosin. 40X.



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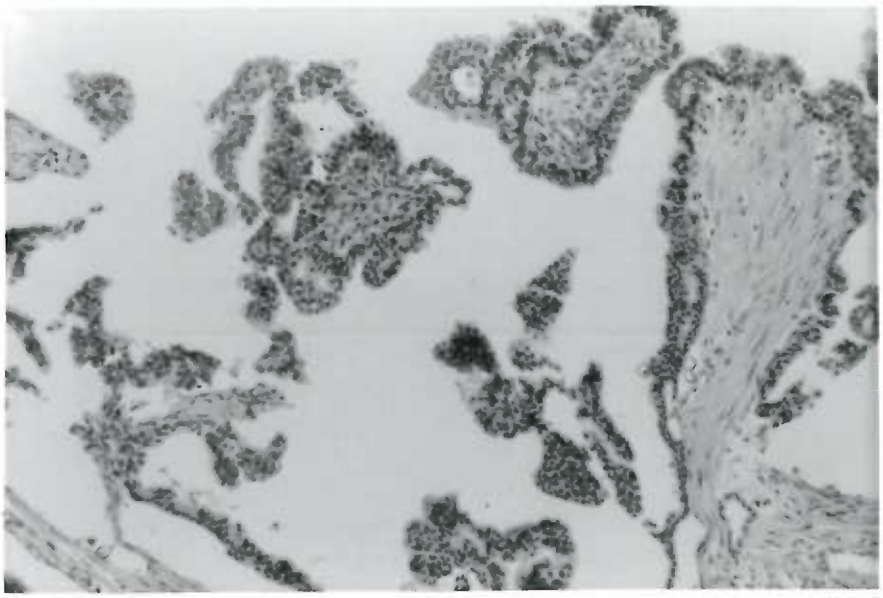


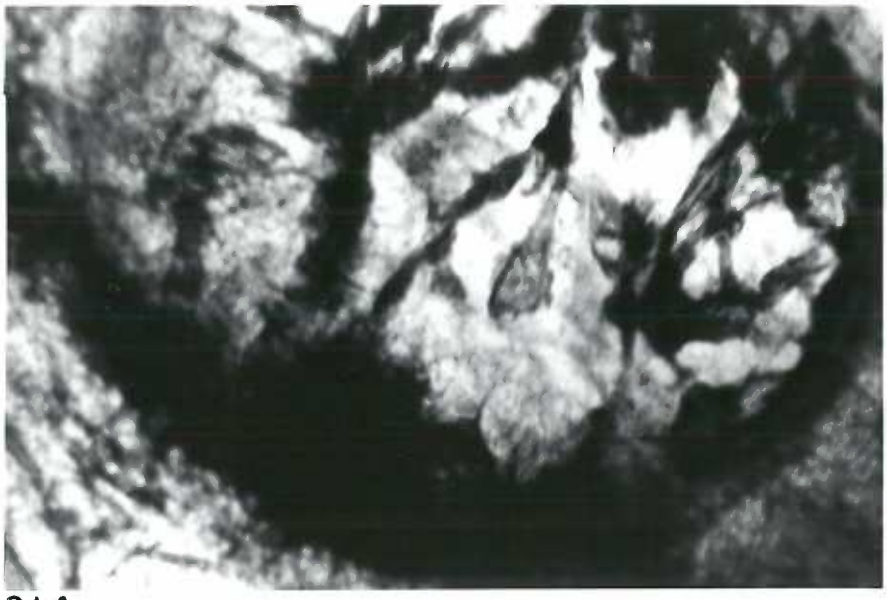
213

Figure 214:

Female, 65 years, breast with mammary dysplasia (M-66-5). Subgross. A cross-section of a large duct shows extensive intraluminal projections, some of which extend nearly across the lumen. Hematoxylin. 9X.

Figure 215:

Corresponding histology of Figure 214. Papillomatosis and epithelial hyperplasia. No cytological atypism. Hematoxylin and eosin. 40X.



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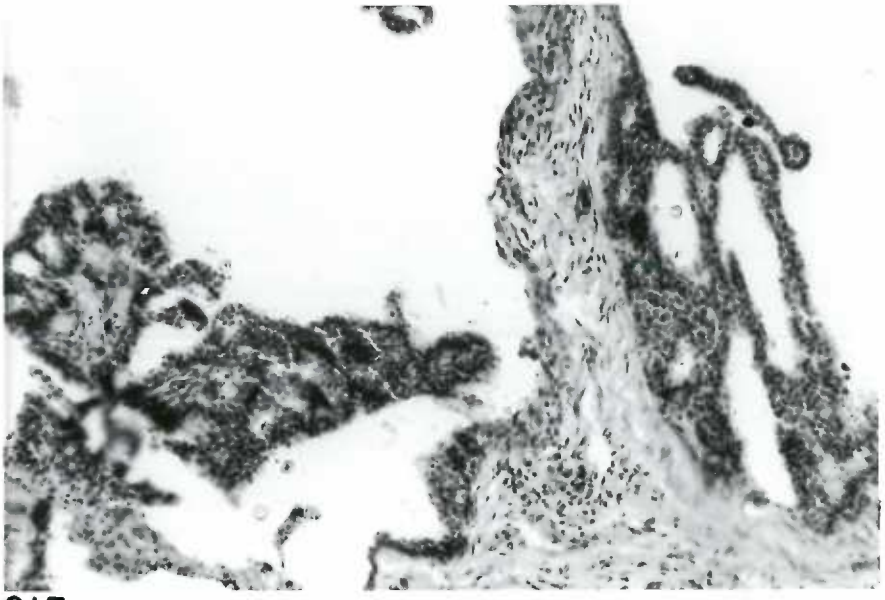


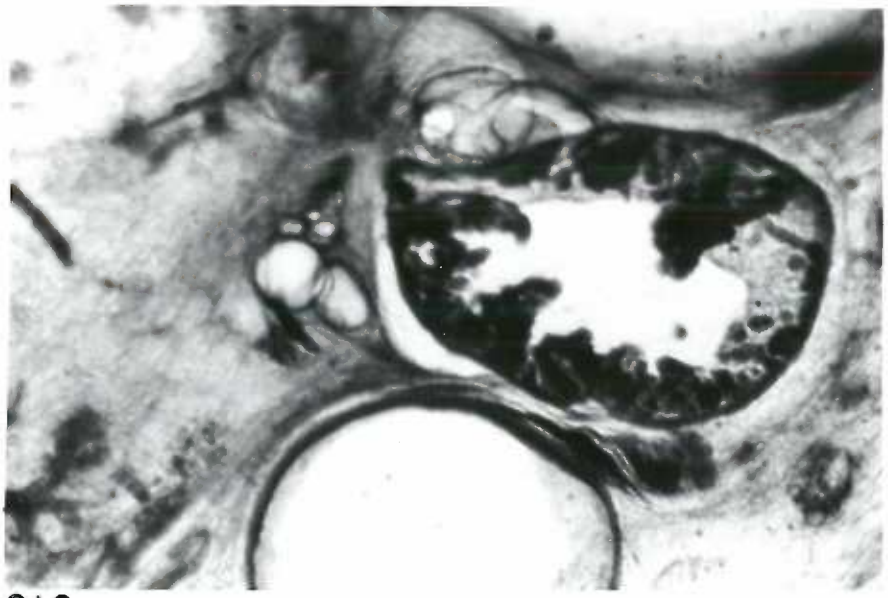
215

Figure 216:

Female, 56 years, breast with mammary dysplasia (M-66-4). Subgross. This cross-section of a dilated duct illustrates multiple discrete papillomata. Hematoxylin. 8.5X.

Figure 217:

Corresponding histology of Figure 216. The correlation between histology and subgross morphology is readily recognizable. Hematoxylin and eosin. 10X.



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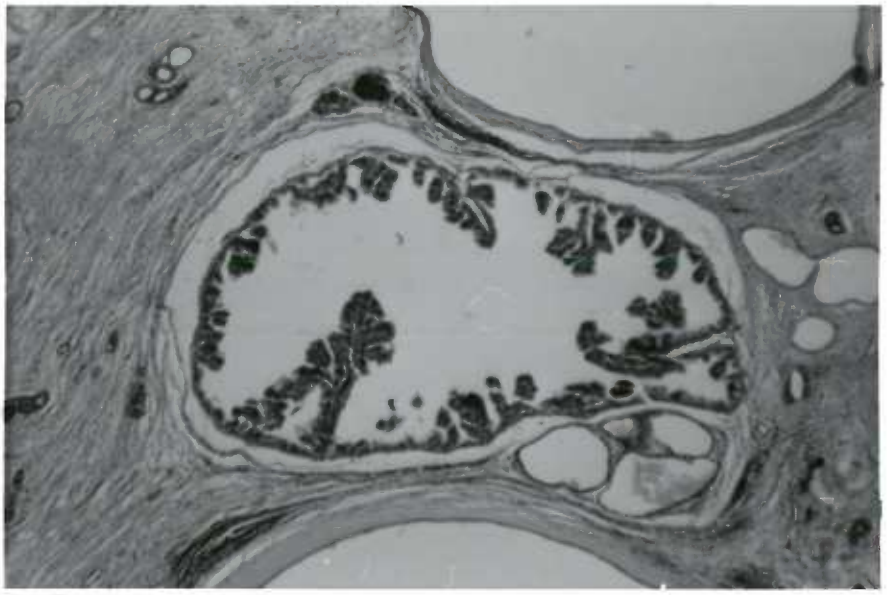
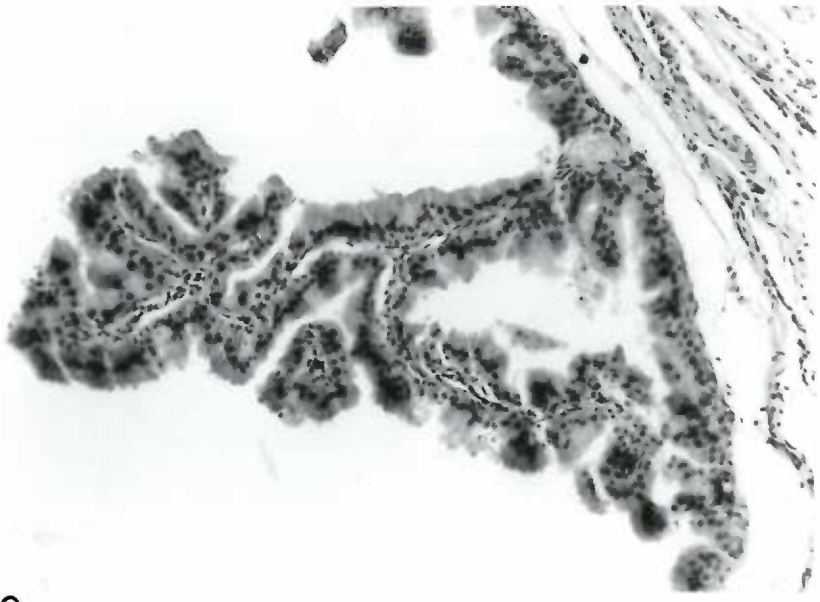


217

Figure 218:

Corresponding histology of Figure 216. Papillary intraluminal projections composed of stroma surfaced by apocrine epithelium are responsible for the subgross papillomata. Hematoxylin and eosin. 40X.



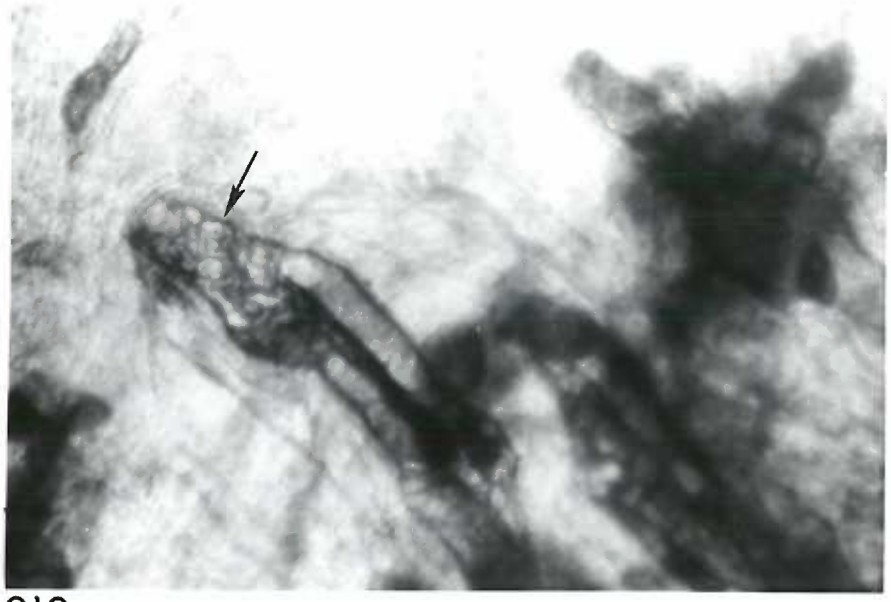
218

Figure 219:

Female, 70 years, breast with infiltrating ductal carcinoma (M-66-10). Subgross. Note the duct with several translucent areas (arrow) in the lumen. Hematoxylin. 10X.

Figure 220:

Corresponding histology of Figure 219. Epithelium mixed with stroma forms a cribriform pattern which is partially responsible for the subgross formation. Hematoxylin and eosin. 40X.



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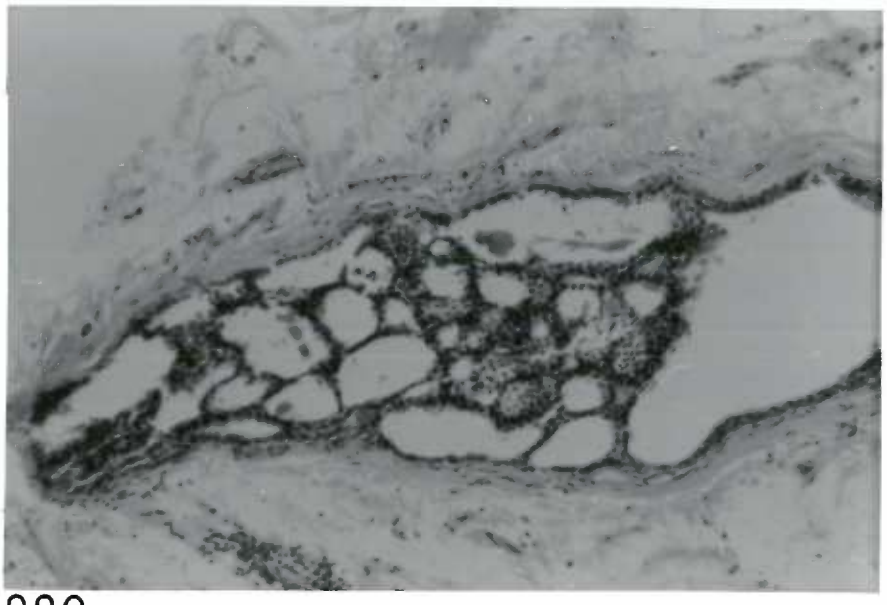


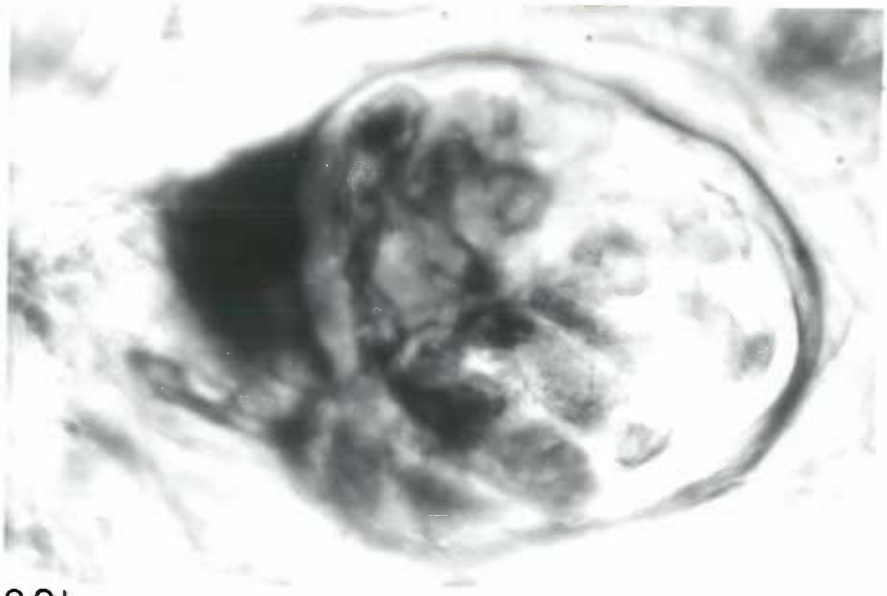
220

Figure 221:

Female, 57 years, normal breast (M-66-22). Subgross. Duct viewed end-on. Lobulated intraluminal mass which largely fills the lumen. Hematoxylin. 10X.

Figure 222:

Corresponding histology of Figure 221. The intraluminal mass is formed by a branching fibrous stalk covered by a thin layer of normal epithelium. A marked inflammatory infiltrate is observed at the base of the papilloma (arrow). Hematoxylin and eosin. 10X.



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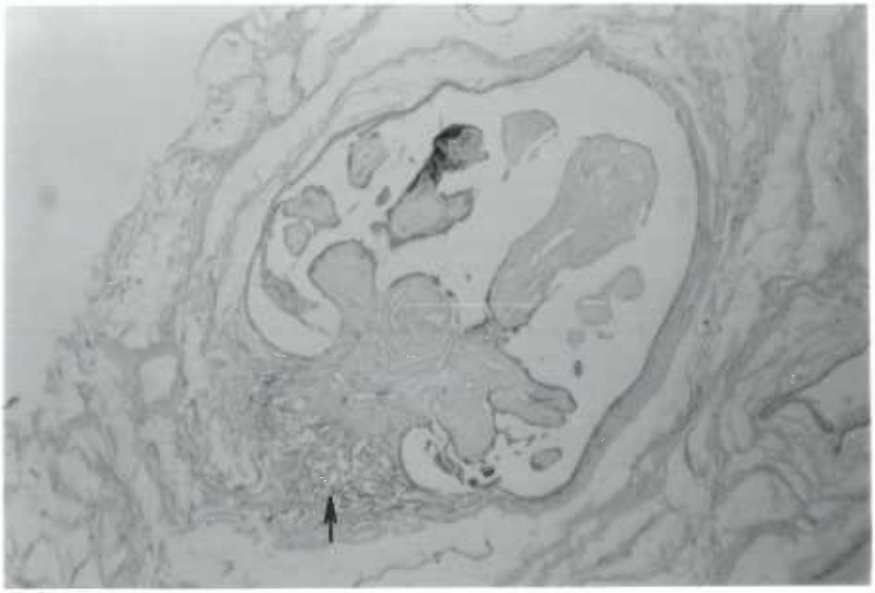


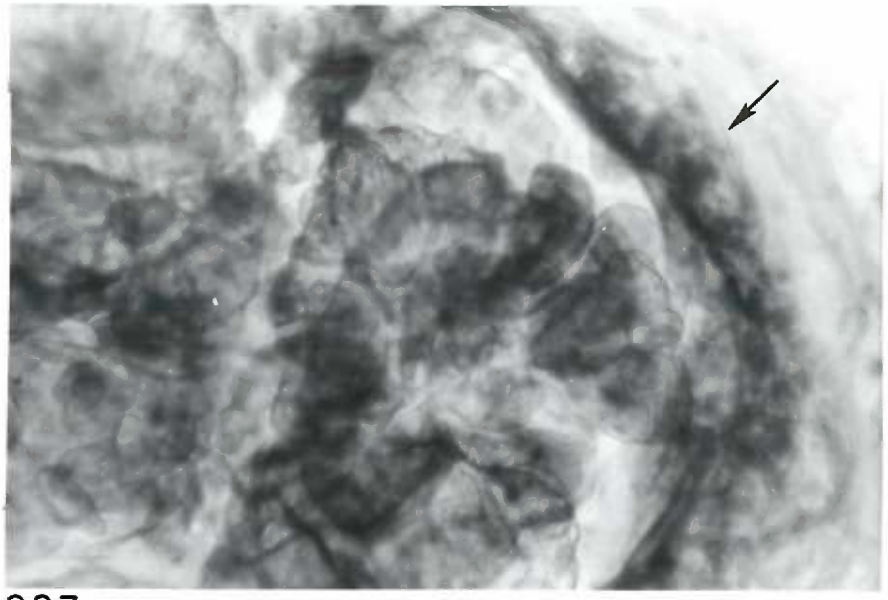
222

Figure 223:

Female, 19 years, normal breast (M-66-8). Subgross. A smooth, lobulated mass subtotally fills the lumen of a large duct. Note several small densities bordering the external surface of the duct (arrow). Hematoxylin. 10X.

Figure 224:

Corresponding histology of Figure 223. The intraluminal mass has a broad fibrous core surfaced by a thin layer of normal ductal epithelium. Note the several epithelial evaginations, or possible ductules, branching out from the duct wall. These correspond to the densities at the arrow in Figure 223. Hematoxylin and eosin. 10X.



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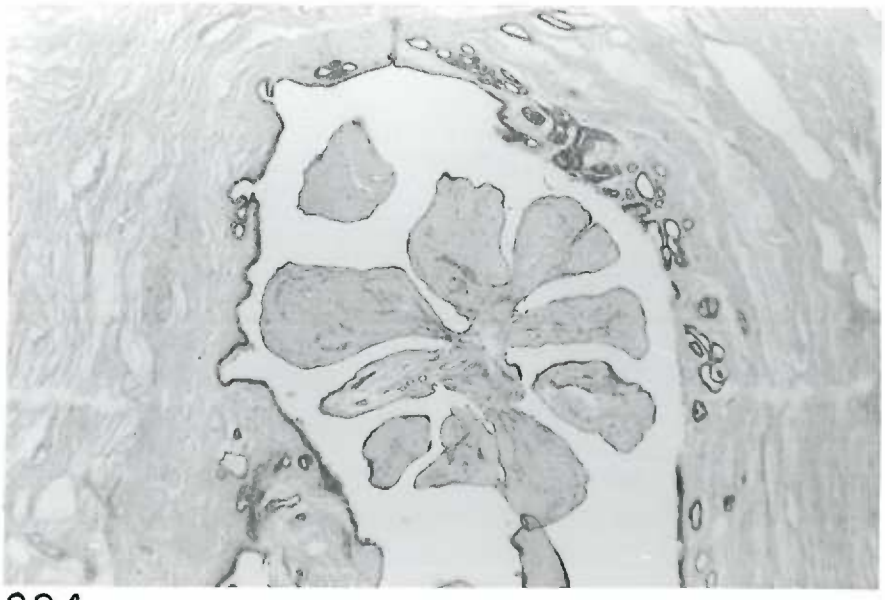


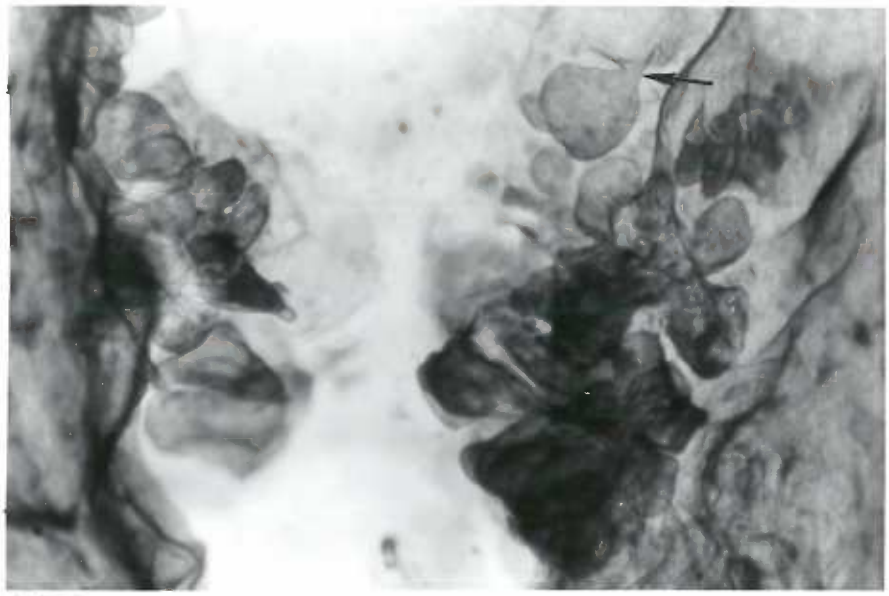
224

Figure 225:

Female, 19 years, normal breast (M-66-8). Subgross. Note the smooth intraluminal masses which can be identified as being attached to the duct wall (arrow). Hematoxylin. 10X.

Figure 226:

Corresponding histology of Figure 225. Fibrous, luminal projections are attached to the duct wall and are covered by normal ductal epithelium. Hematoxylin and eosin. 10X.



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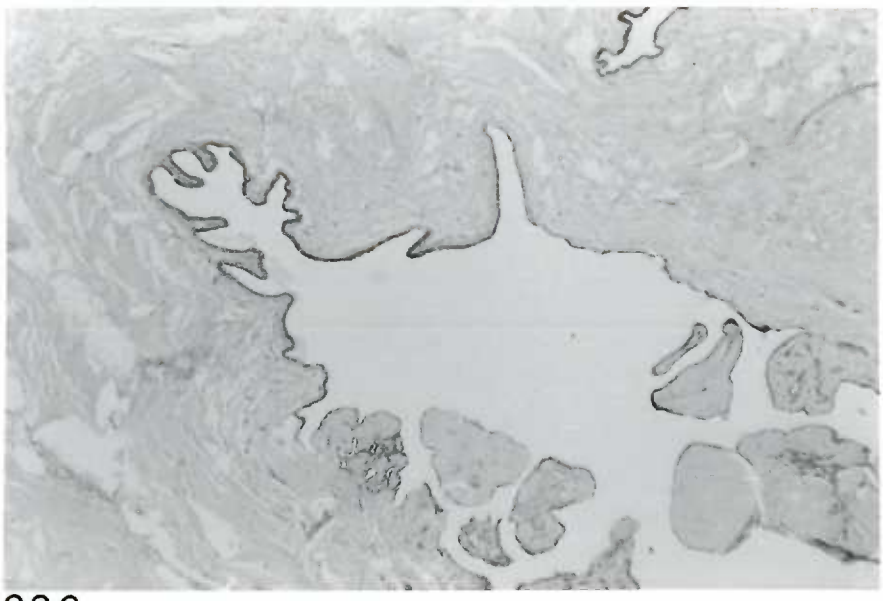


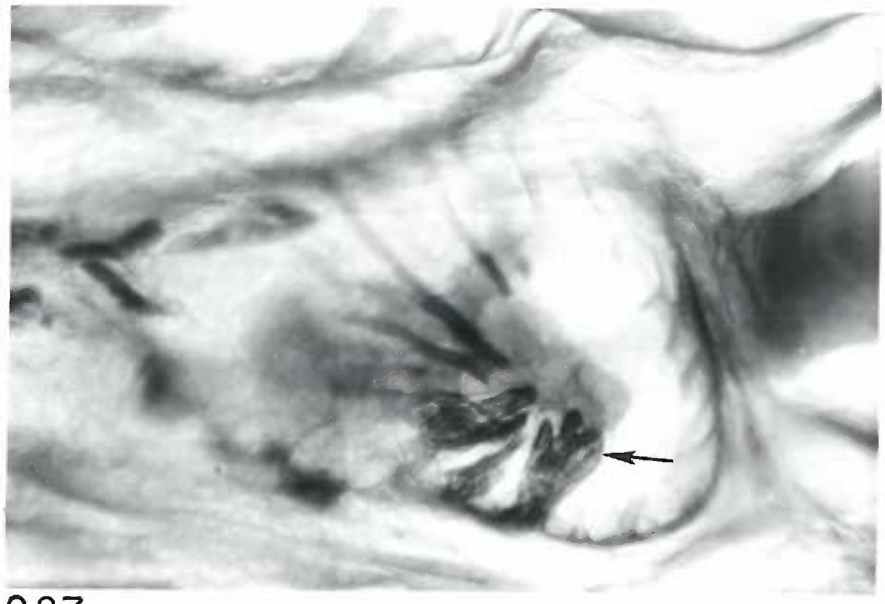
226

Figure 227:

Female, 57 years, normal breast (M-66-22). Subgross. A scalloped duct is cut in cross-section, illustrating the extreme prominence of some of the ridges (arrow). Hematoxylin. 10X.

Figure 228:

Corresponding histology of Figure 227. Duct ridge composed of a broad stromal core covered by normal epithelium. Hematoxylin and eosin. 40X.



227

228

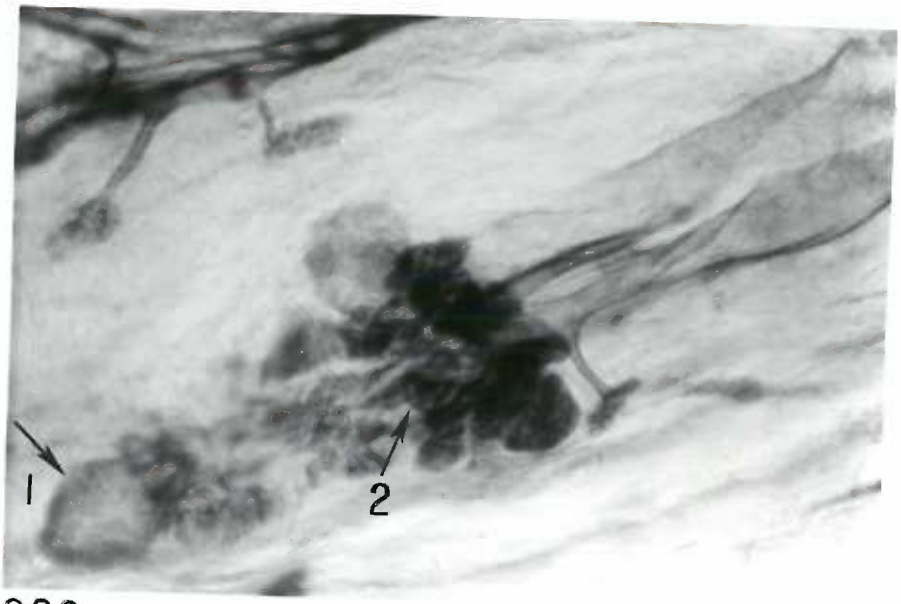
EPITHELIOSIS

Figure 229:

Female, 56 years, normal breast (M-66-12). Subgross. A lobule with cystic ductules is noted. The walls are diffusely thickened (arrow 1) or involved with knobby, irregular densities (arrow 2). Hematoxylin. 10X.

Figure 230:

Corresponding histology of Figure 229. Mild epitheliosis without atypism is seen. The periductal stroma is normal. Hematoxylin and eosin. 40X.



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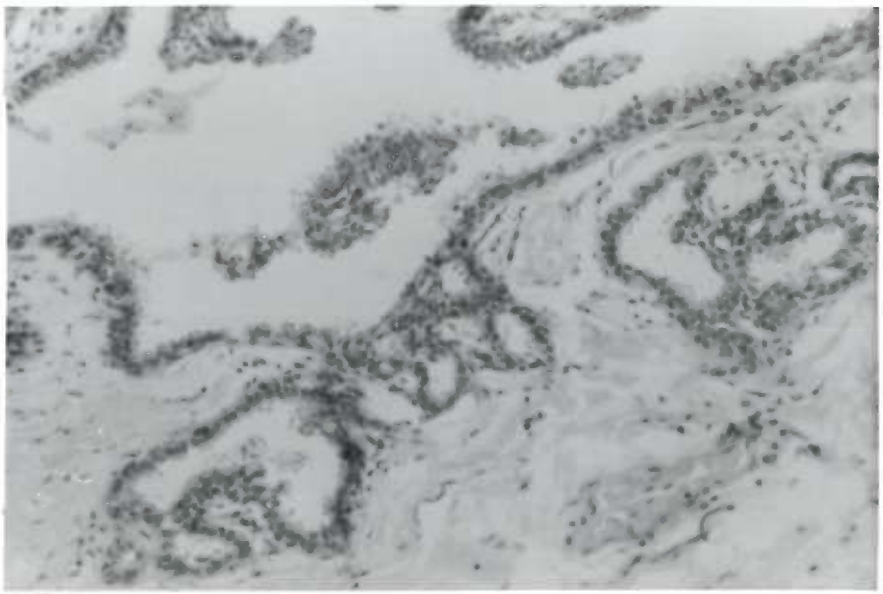


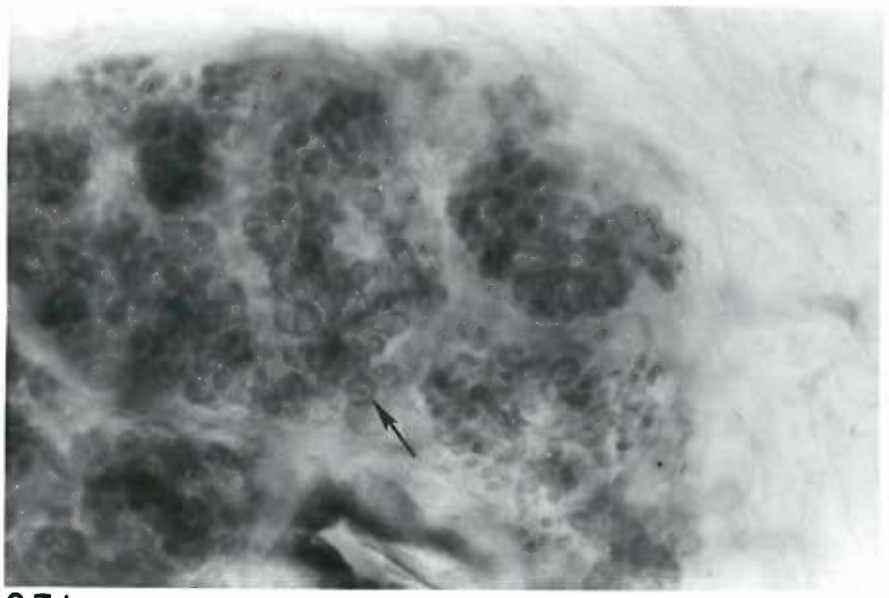
230

Figure 231:

Female, 19 years, normal breast (M-66-8). Subgross. A markedly enlarged lobule (adenosis) is composed of ductules. Many of the ductule walls appear thickened (arrow). Hematoxylin. 10X.

Figure 232:

Corresponding histology of Figure 231. Microscopy shows the lobular formation and corresponding ductules. The intralobular stroma is not distinctly different from interlobular stroma. Hematoxylin and eosin. 10X.



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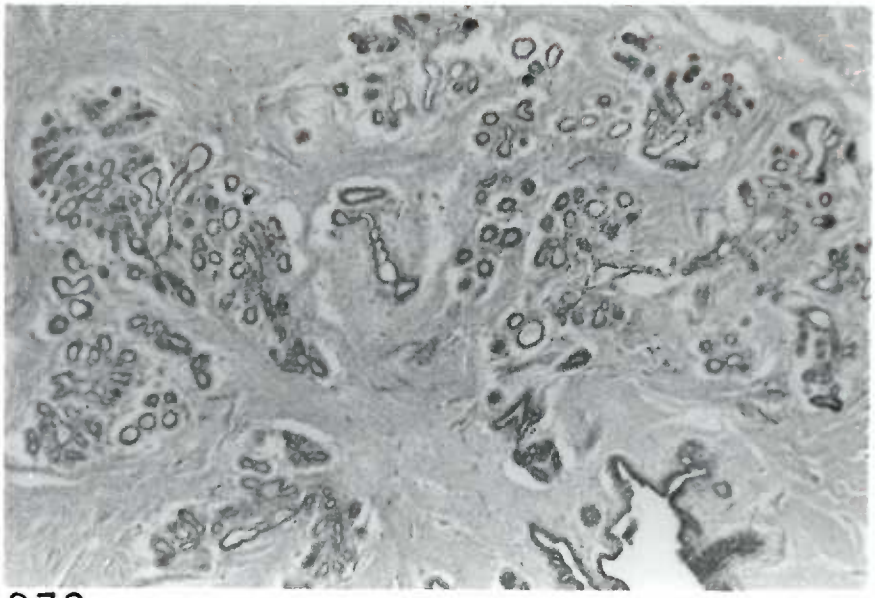
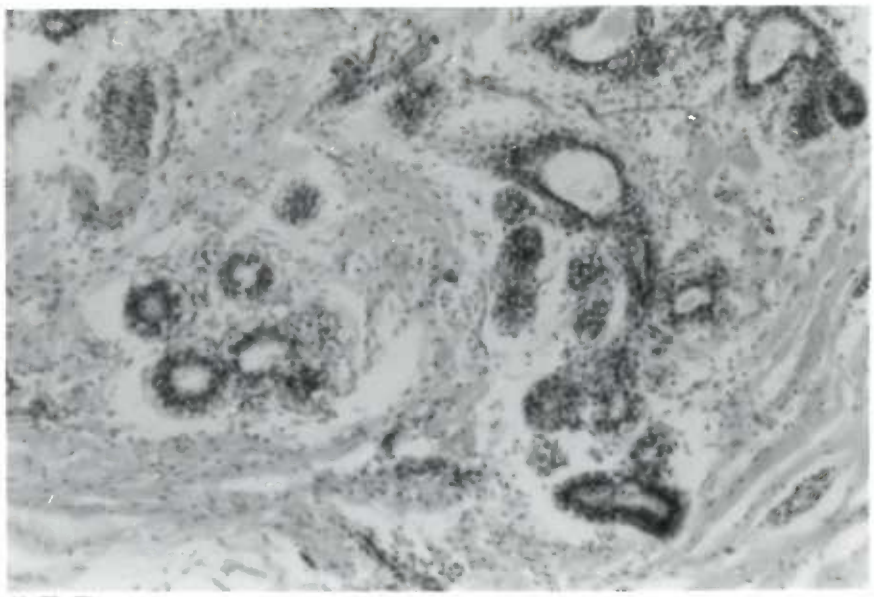


232

Figure 233:

Corresponding histology of Figure 231. Microscopy shows mild epitheliosis without atypism. The stroma is normal and has a light diffuse infiltrate of lymphocytes. Hematoxylin and eosin. 40X.



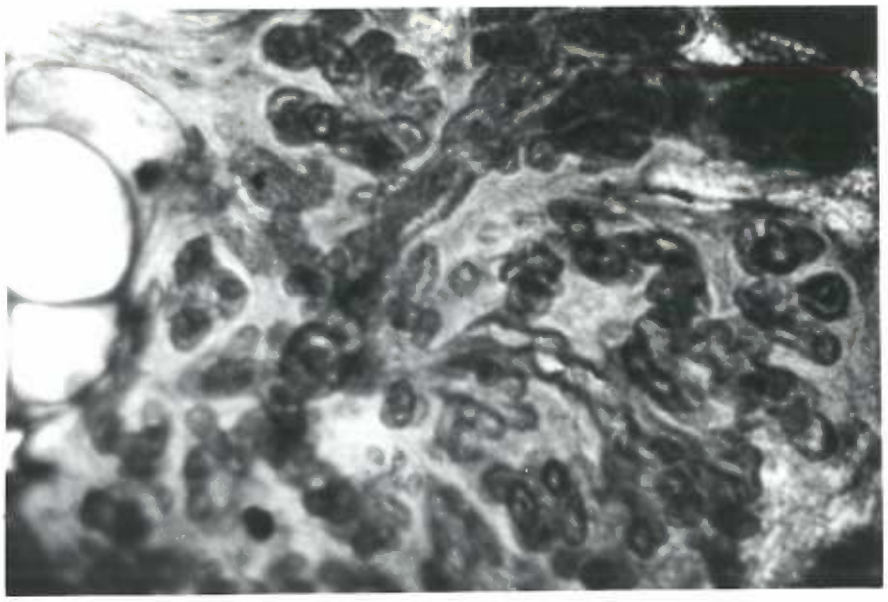
233

Figure 234:

Female, 56 years, breast with mammary dysplasia (M-66-4). Subgross. An enlarged lobule (adenosis) is composed of dilated ductules with irregularly thickened walls. Hematoxylin. 8.5X.

Figure 235:

Corresponding histology of Figure 234. Moderate to severe epitheliosis is evident. The stroma is normal. Hematoxylin and eosin. 40X.



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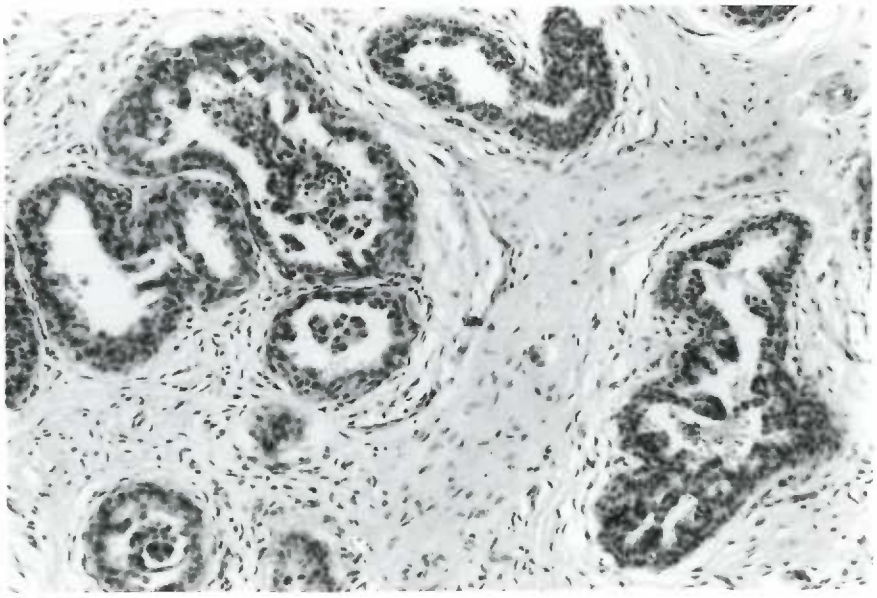
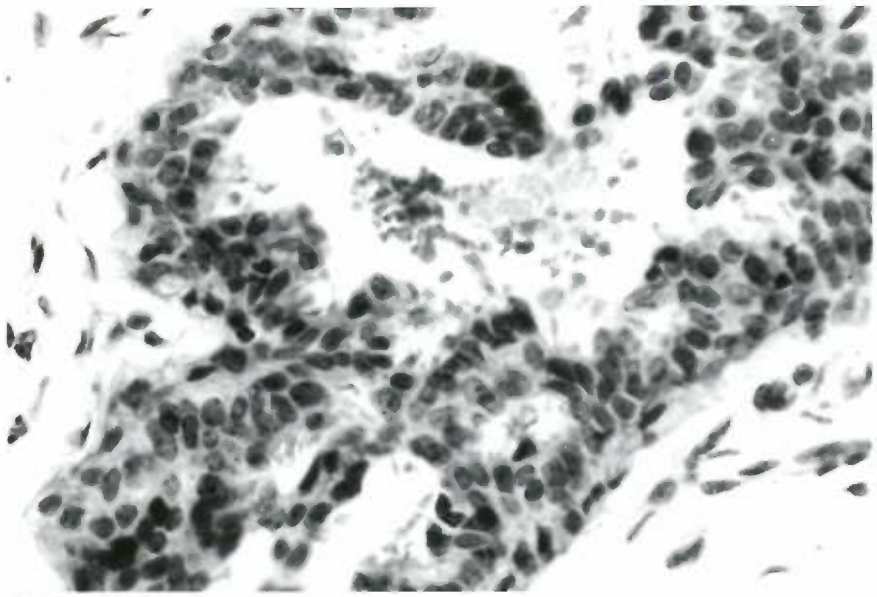


235

Figure 236:

Corresponding histology of Figure 234. Note hyperchromatic nuclei, some nuclear pleomorphism, and partial loss of cell polarity. No stromal invasion is noted. Hematoxylin and eosin. 160X.



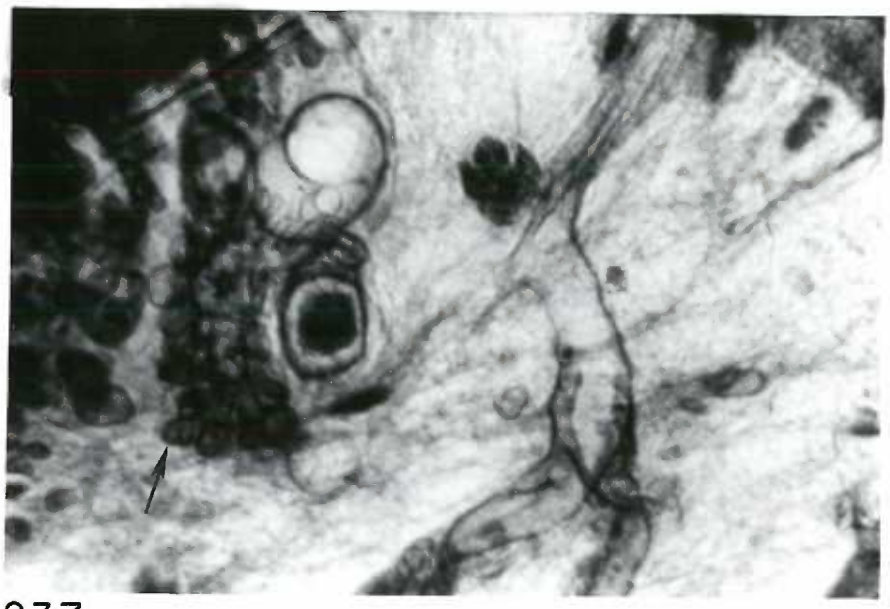
236

Figure 237:

Female, 56 years, breast with mammary dysplasia (M-66-4). Note the lobule which is composed of ductules with thickened walls (arrow). Hematoxylin. 11X.

Figure 238:

Corresponding histology of Figure 237. There is moderate epitheliosis with papillary projections and cribriform pattern. Note the peculiar thickening of the duct wall at the arrow. Hematoxylin and eosin. 40X.



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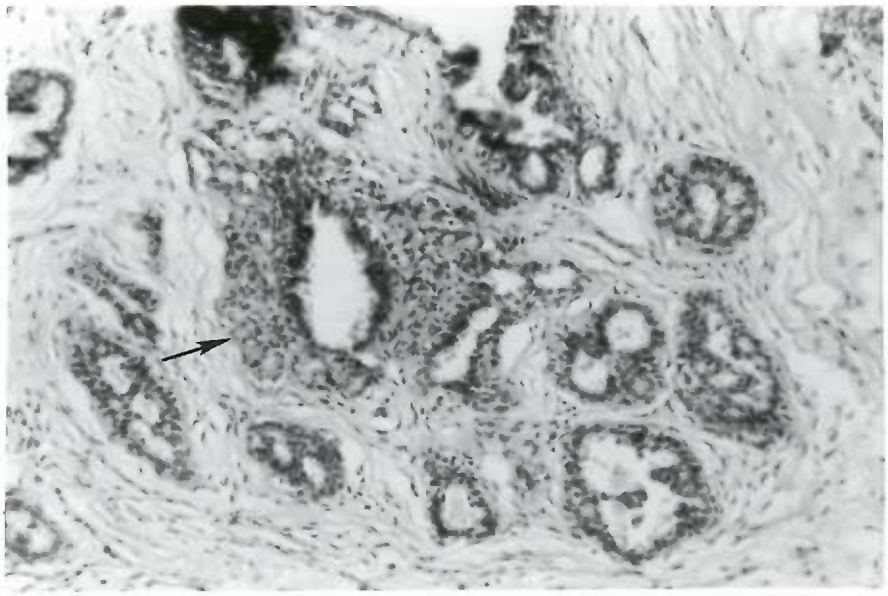

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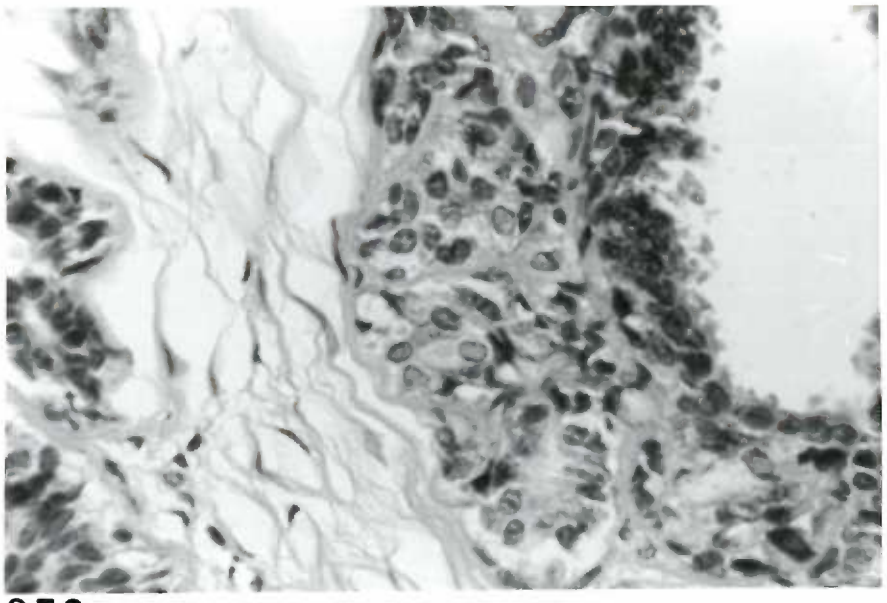
Figure 239:

Corresponding histology of Figure 237. The thickened duct wall has nests of normal epithelial cells with investing myoepithelial cells. Hematoxylin and eosin. 160X.



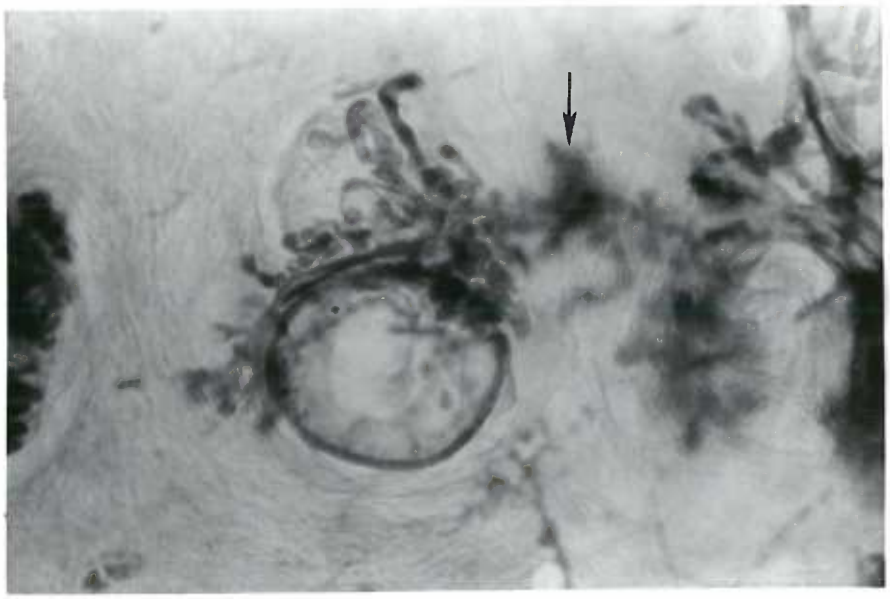
239

Figure 240:

Female, 19 years, normal breast (M-66-8). Subgross. Several cystic ducts in a lobular configuration are seen. No definite densities are seen; however, some are suggested (arrow). Hematoxylin. 10X.

Figure 241:

Corresponding histology to Figure 240. Microscopic correlation is illustrated. Note the two ducts with marked epitheliosis. Hematoxylin and eosin. 10X.



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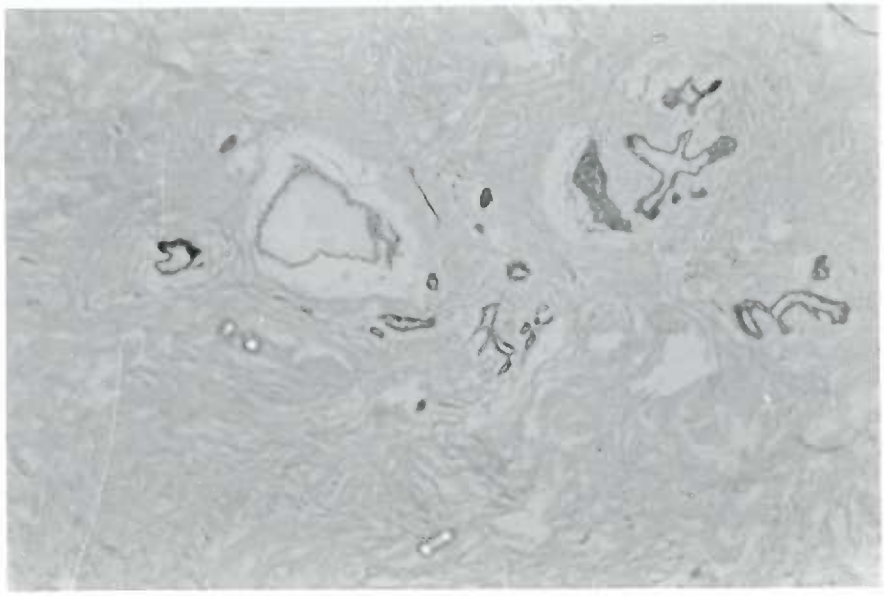

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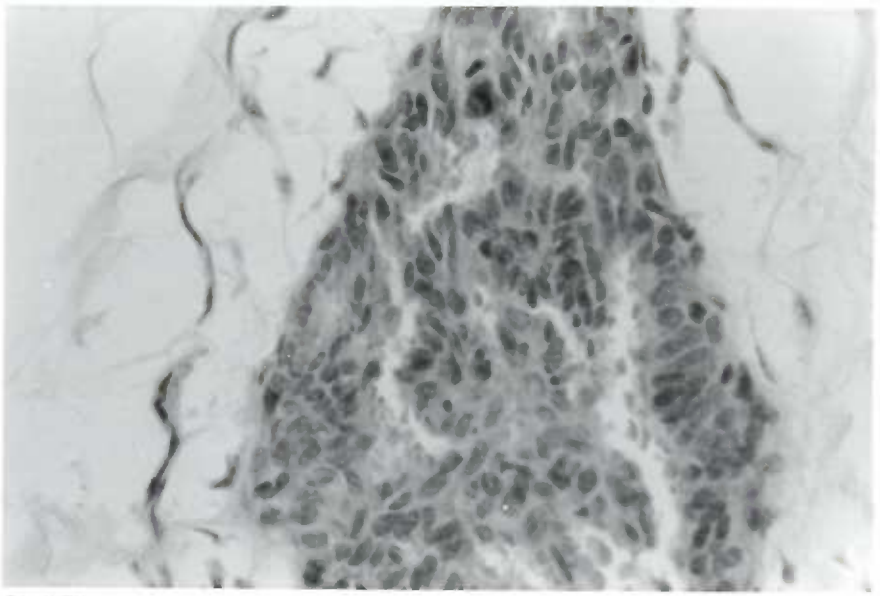
Figure 242:

Corresponding histology of Figure 240. Note the nuclear pleomorphism and loss of cellular polarity. No mitoses are seen and the myoepithelium appears intact. Hematoxylin and eosin. 160X.



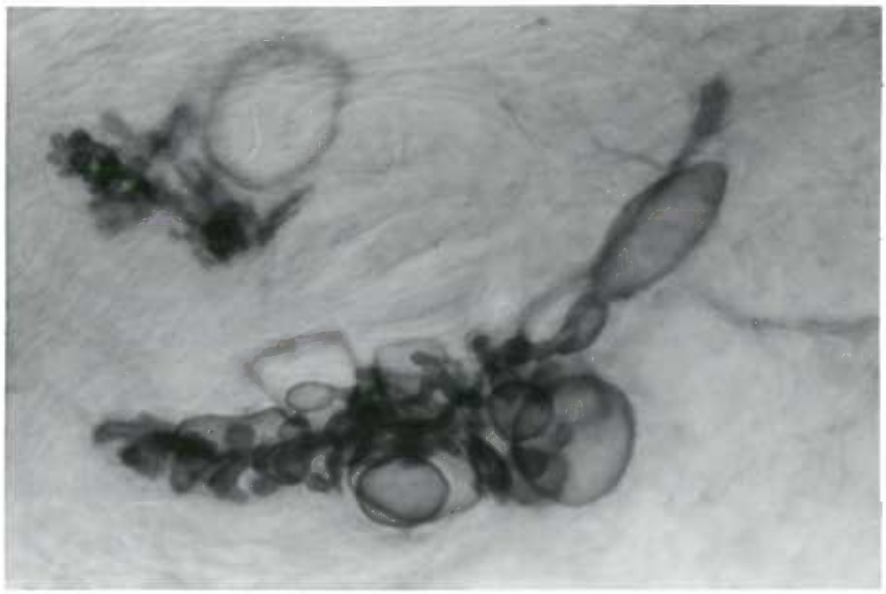
242

Figure 243:

Female, 19 years, normal breast (M-66-8). Subgross. A lobule composed of smooth walled, dilated ductules is illustrated. No areas of wall thickening are identified at this focal plane. Hematoxylin. 10X.

Figure 244:

Corresponding histology of Figure 243. Note the cystic ductules partly filled with epithelial cells. Hematoxylin and eosin. 10X.



243

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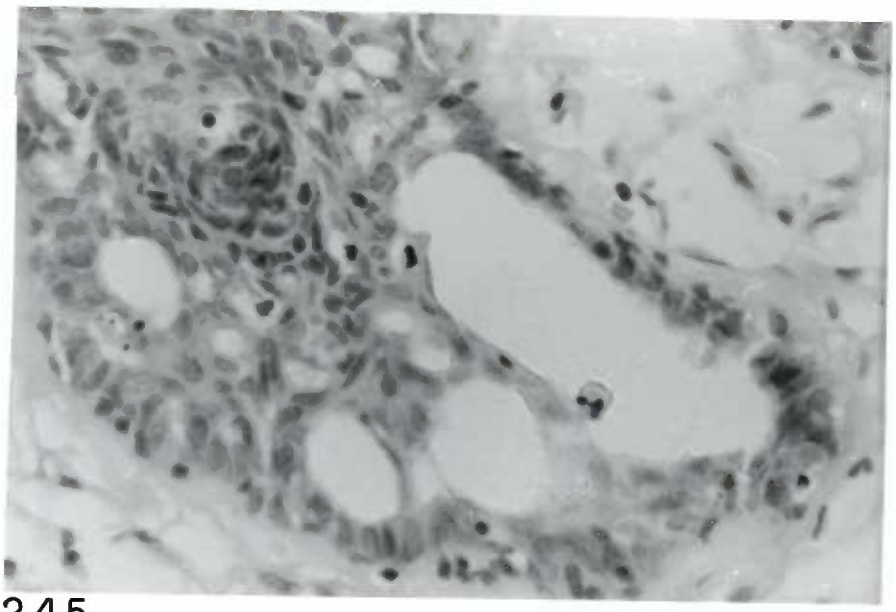
Figure 245:

Corresponding histology of Figure 243. The ductal epithelium forms a cribriform pattern. Note loss of cell polarity, nuclear pleomorphism, and hyperchromatic nuclei. This is severe epitheliosis with atypism. Hematoxylin and eosin. 160X.



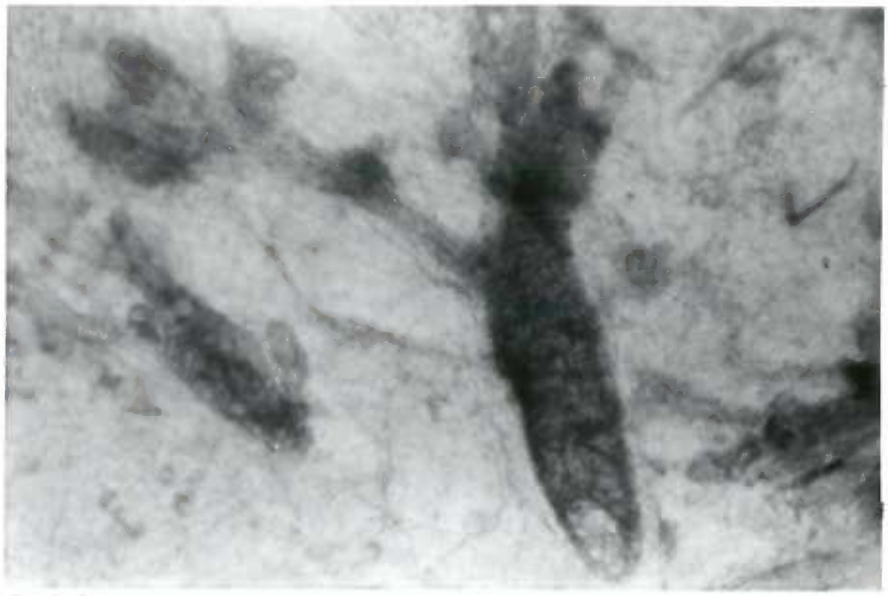
245

Figure 246:

Female, 70 years, breast with infiltrating ductal carcinoma (M-66-10). Subgross. A dilated duct has thickened walls and distinct circular translucencies, reminiscent of bubbles, in its lumen. Hematoxylin. 10X.

Figure 247:

Corresponding histology of Figure 246. Note the severe epitheliosis and cribriform pattern. Some necrotic debris is in the lumen. Hematoxylin and eosin. 40X.



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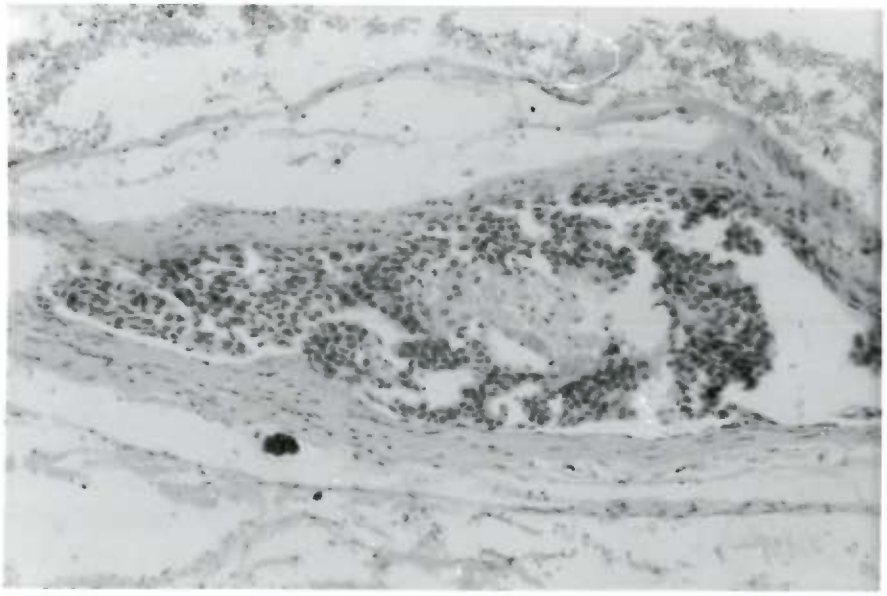


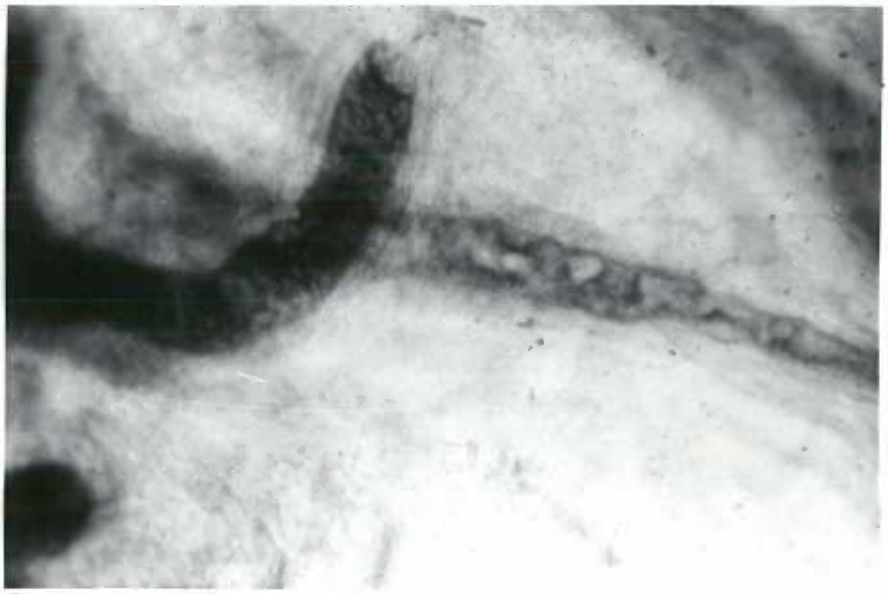
247

Figure 248:

Female, 70 years, breast with infiltrating ductal carcinoma (M-66-10). Subgross. Two ducts are visible, both having irregular linear densities in the lumen. They are causing luminal translucent areas. Hematoxylin. 10X.

Figure 249:

Corresponding histology of Figure 248. Solid type of epitheliosis is noted. There is loss of cellular polarity, distention of the duct wall, and nuclear pleomorphism. Hematoxylin and eosin. 40X.



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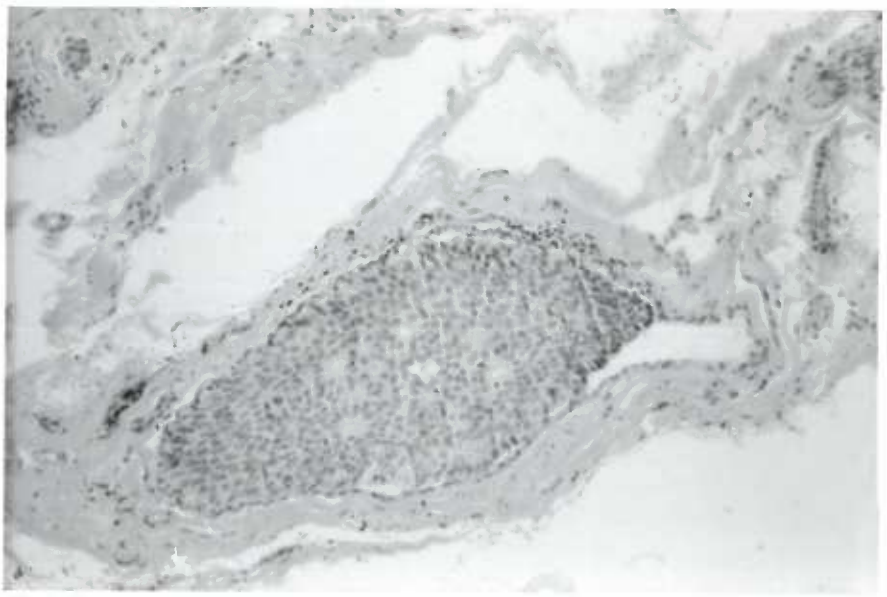


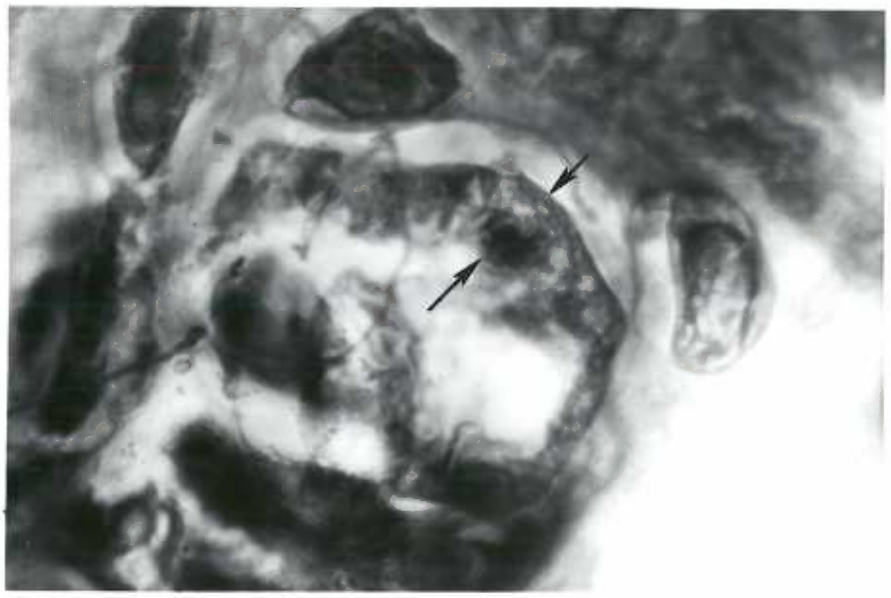
249

Figure 250:

Female, 70 years, breast with infiltrating ductal carcinoma (M-66-10). Subgross. A large dilated duct has thickened duct walls (between arrows). The luminal border is irregular and indistinct. Hematoxylin. 10X.

Figure 251:

Corresponding histology of Figure 250. Severe epitheliosis in a cribriform pattern exhibits cytological atypism. Hematoxylin and eosin. 160X.



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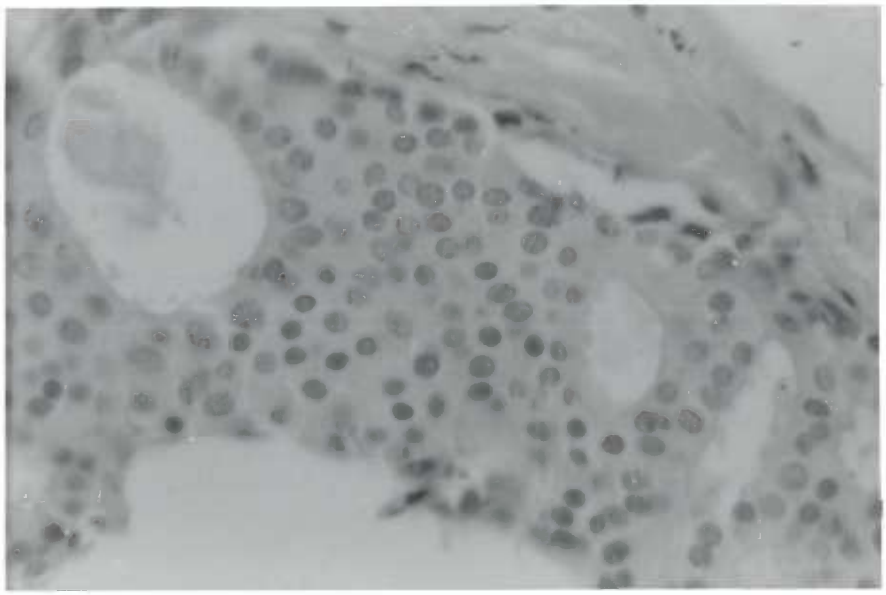


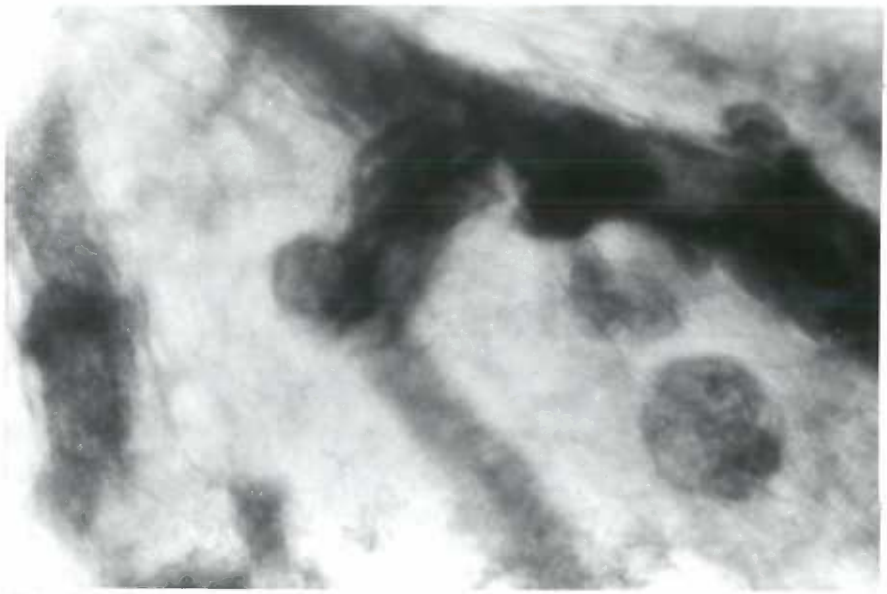
251

Figure 252:

Female, 70 years, breast with infiltrating ductal carcinoma (M-66-10). Subgross. A large branching duct appears to have a solid lumen in some segments (arrow). Hematoxylin. 10X.

Figure 253:

Corresponding histology of Figure 252. Severe atypical epitheliosis is observed. Hematoxylin and eosin. 40X.



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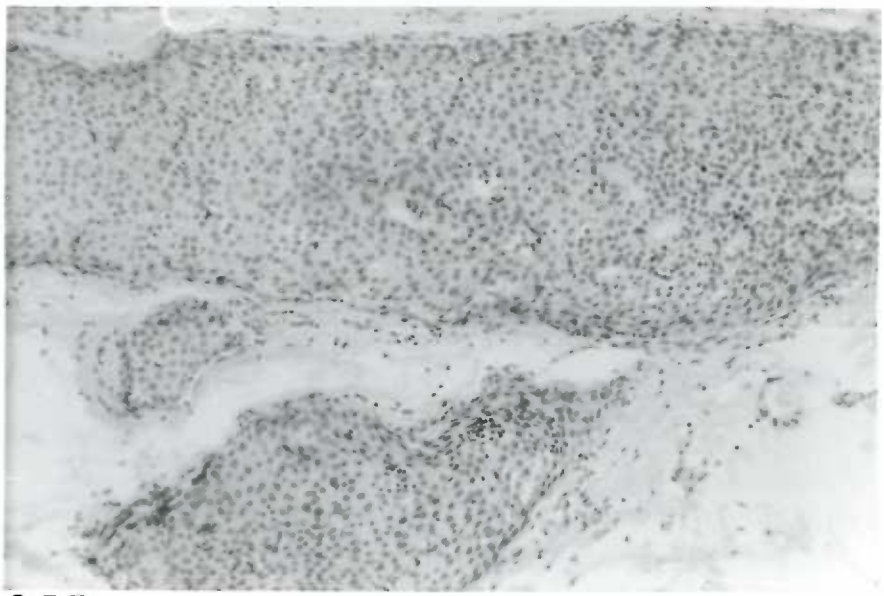


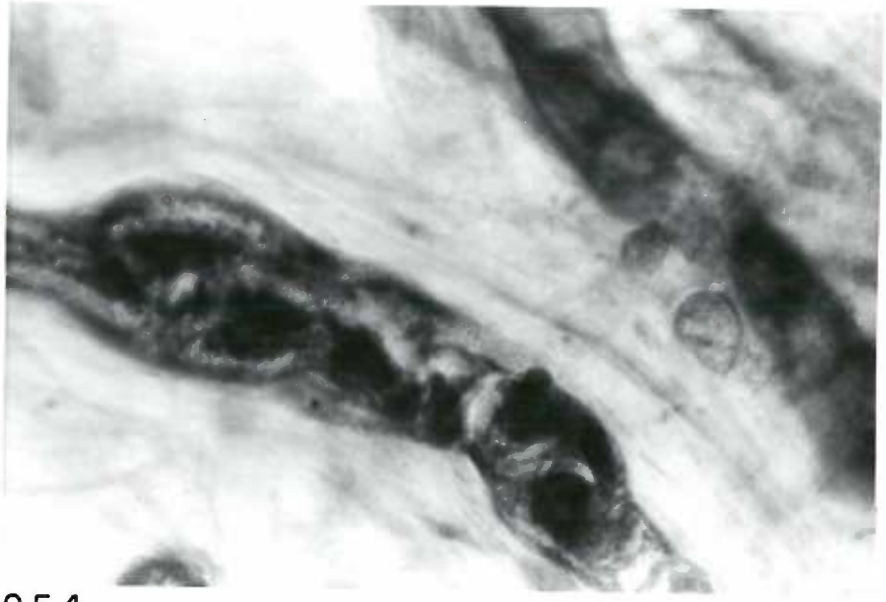
253

Figure 254:

Female, 70 years, breast with infiltrating duct carcinoma (M-66-10). Subgross. A segmentally dilated duct in the foreground has easily discernible intraluminal densities. Hematoxylin. 10X.

Figure 255:

Corresponding histology of Figure 254. Severe atypical epitheliosis is present, showing solid (arrow 1), cribriform (arrow 2), and papillary (arrow 3) patterns. Hematoxylin and eosin. 40X.



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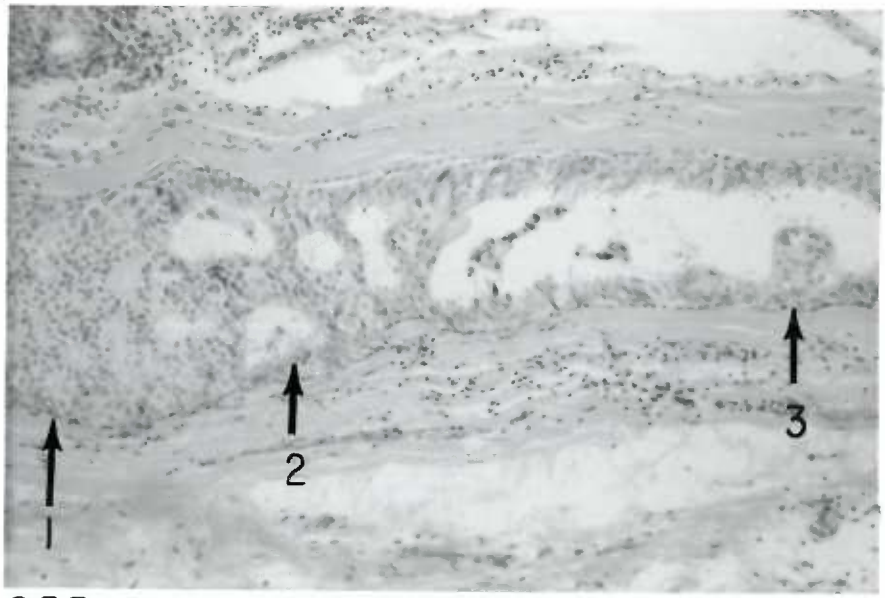


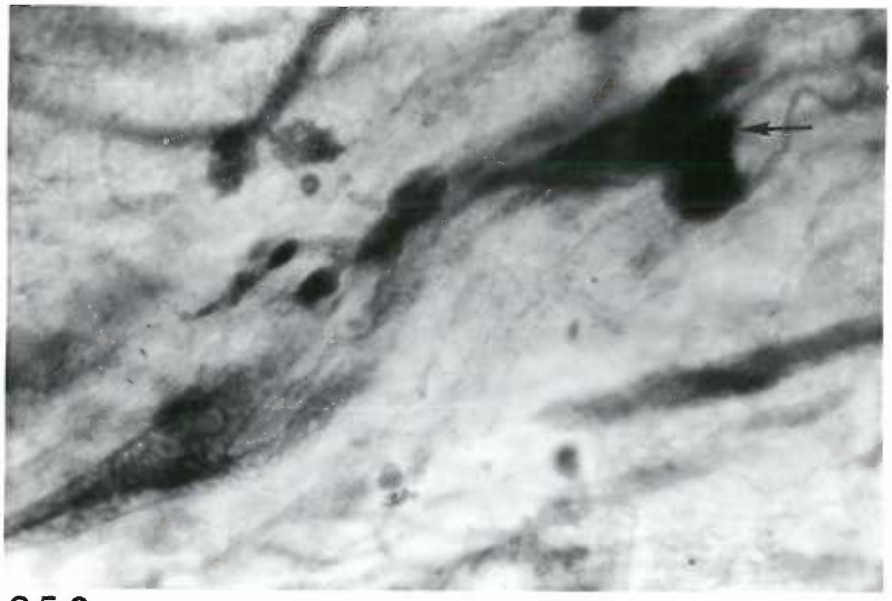
255

Figure 256:

Female, 70 years, breast with infiltrating ductal carcinoma (M-66-10). Subgross. Duct with solid zone (arrow). Hematoxylin. 10X.

Figure 257:

Corresponding histology of Figure 256. Severe atypical epitheliosis is noted. No stromal invasion is visible. Hematoxylin and eosin. 40X.



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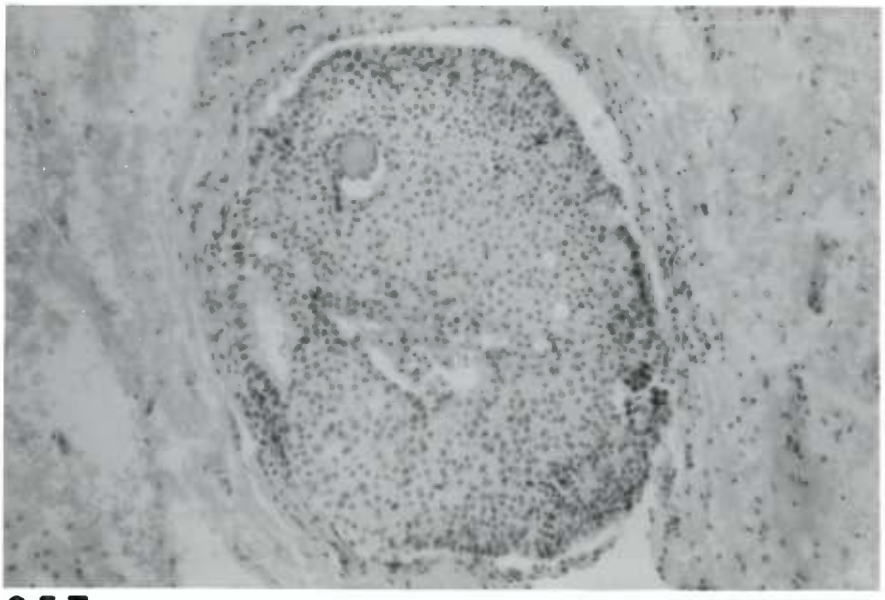
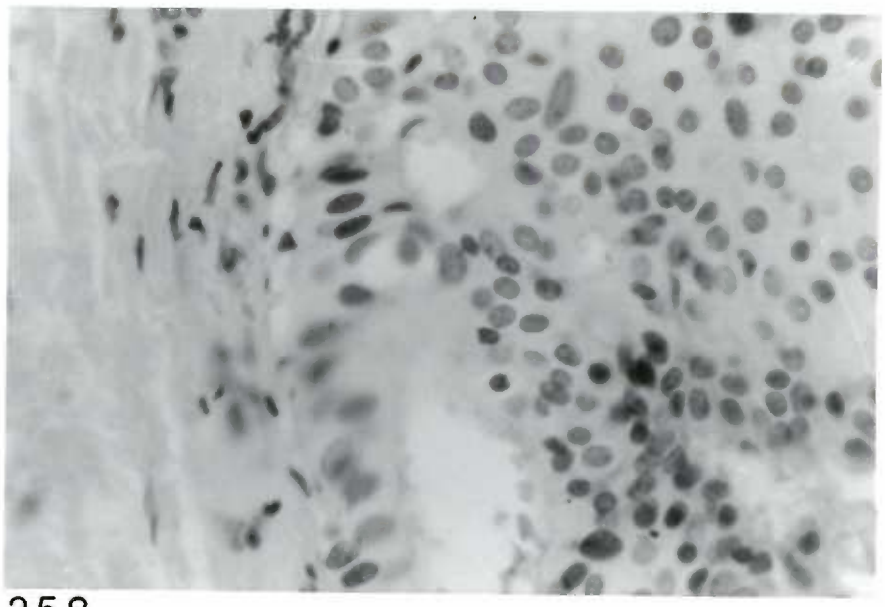


257

Figure 258:

Corresponding histology of Figure 256. A higher power exhibits the nuclear pleomorphism, hyperchromatism, loss of cellular polarity, increased nuclear size, and absence of nucleoli. Hematoxylin and eosin. 160X.



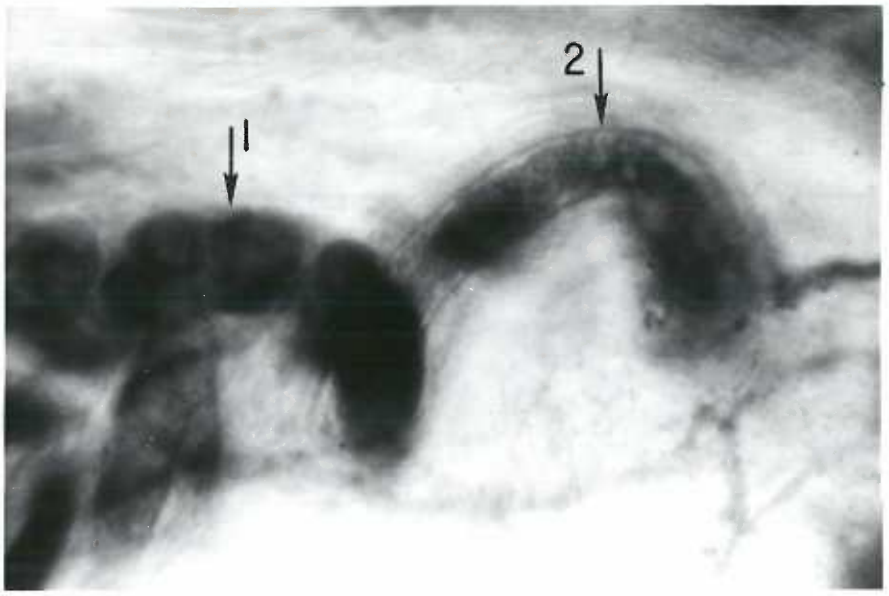
258

Figure 259:

Female, 70 years, breast with infiltrating ductal carcinoma (M-66-10). Subgross. A large tortuous duct has areas where the lumen is solid (arrow 1) and subtotally filled (arrow 2). Hematoxylin. 10X.

Figure 260:

Corresponding histology of Figure 259. The histologic correlation is evident. Moderate stromal inflammation is noted. Hematoxylin and eosin. 10X.



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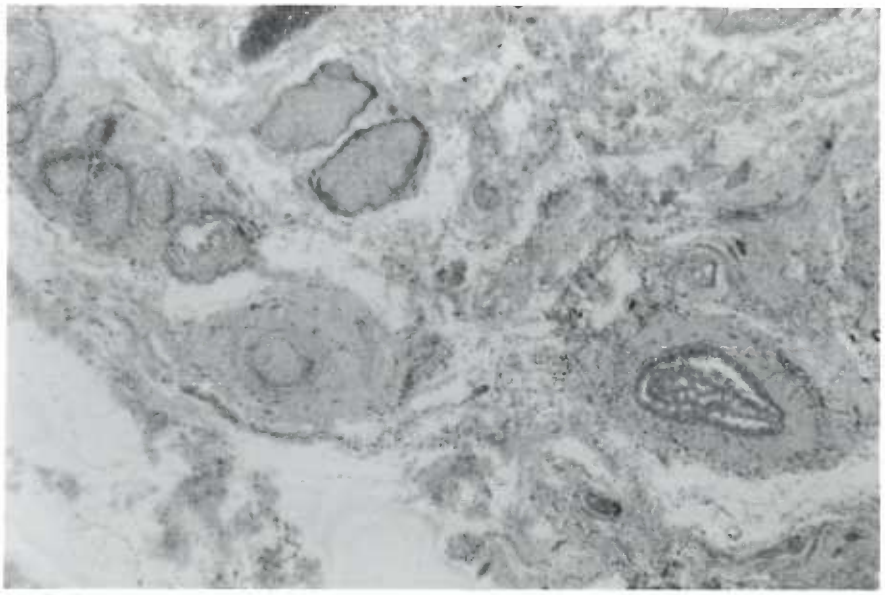


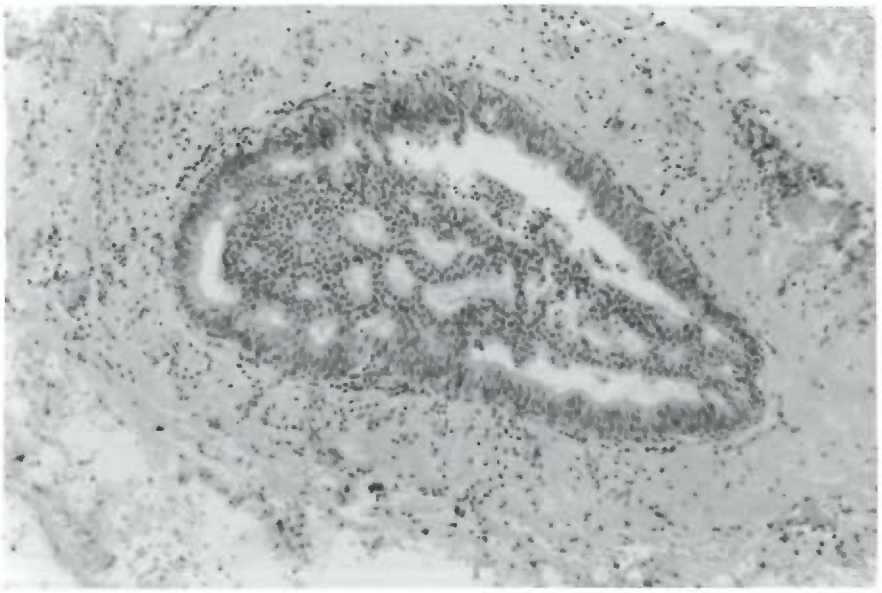
260

Figure 261:

Corresponding histology of Figure 259. The tissue from the partially filled duct shows atypical epitheliosis in the cribriform pattern. Note the marked chronic inflammation in periductal stroma. Hematoxylin and eosin. 40X.

Figure 262:

Corresponding histology of Figure 259. The atypical epitheliosis of solid type is from the area of the duct which possessed a solid lumen in the subgross preparation. Hematoxylin and eosin. 40X.



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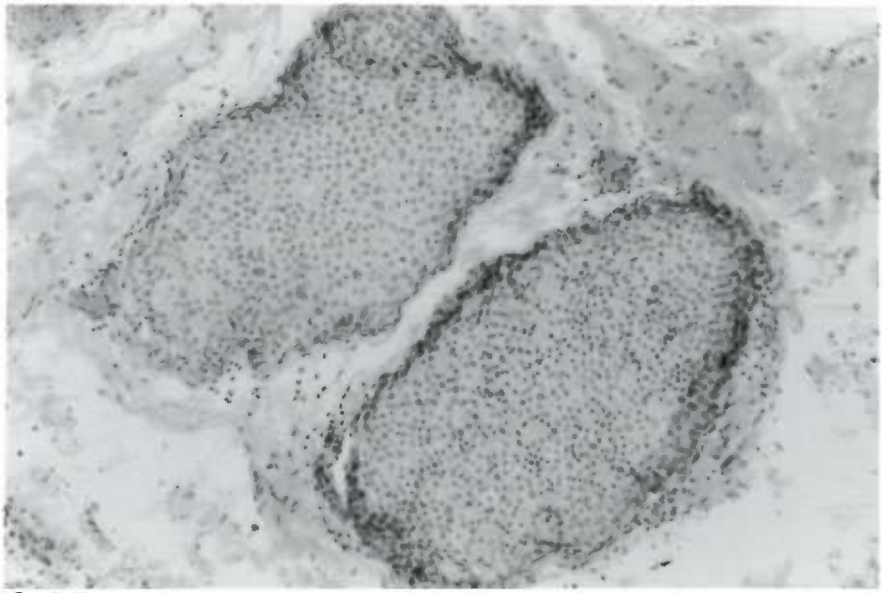


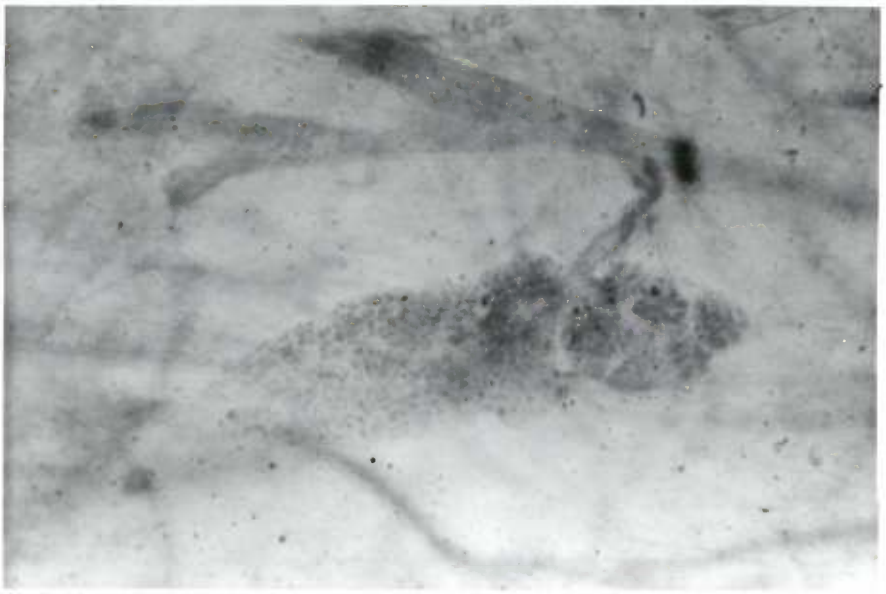
262

Figure 263:

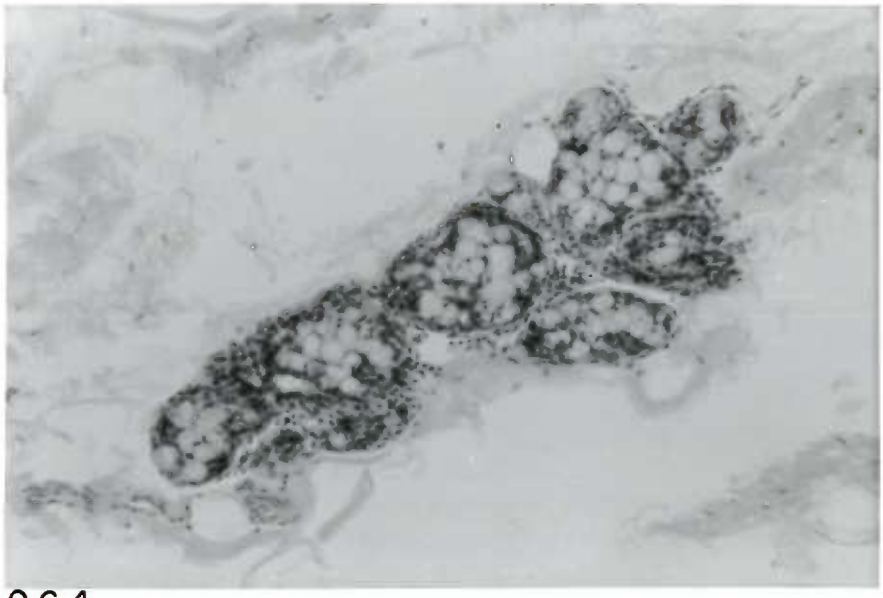
Female, 88 years, normal breast (M-66-15). Subgross. A pale, well circumscribed lobule with entering ducts is noted. Hematoxylin. 10X.

Figure 264:

Corresponding histology of Figure 263. The ductules are filled by large vacuolated cells. The surrounding stroma is normal. Hematoxylin and eosin. 40X.



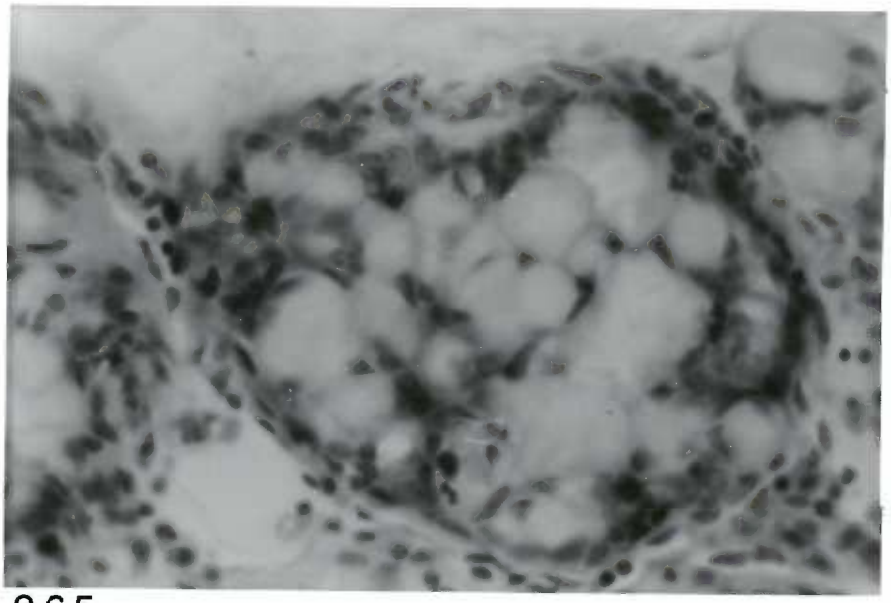
263



264

Figure 265:

Corresponding histology of Figure 263. The large vacuolated cells have peripherally located nuclei. Normal epithelial cells are dispersed among them. This is cystophorous desquamative epithelial hyperplasia, as described by Cheatle and Cutler (13). Hematoxylin and eosin. 160X.



265

INFILTRATING DUCTAL CARCINOMA

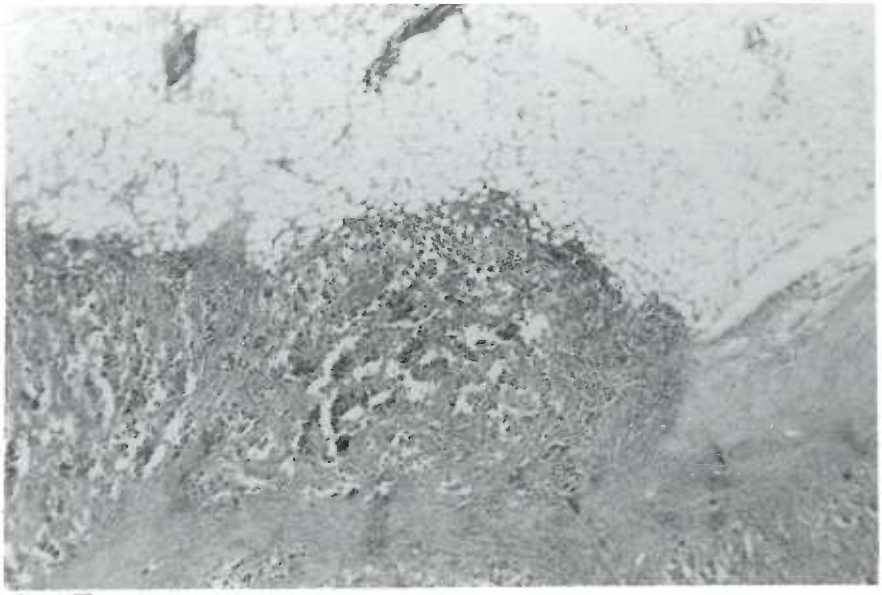
Figure 266:

Female, 70 years, breast with infiltrating ductal carcinoma (M-66-10). Subgross. A diffuse density with "streaming" edges is seen. Note the sharply defined fat cells at the leading edge of the tumor (arrow). Hematoxylin. 10X.

Figure 267:

Corresponding histology of Figure 266. The correlation between microscopy and subgross configuration is demonstrated. Note the tumor infiltrating between the fat cells. Hematoxylin and eosin. 10X.

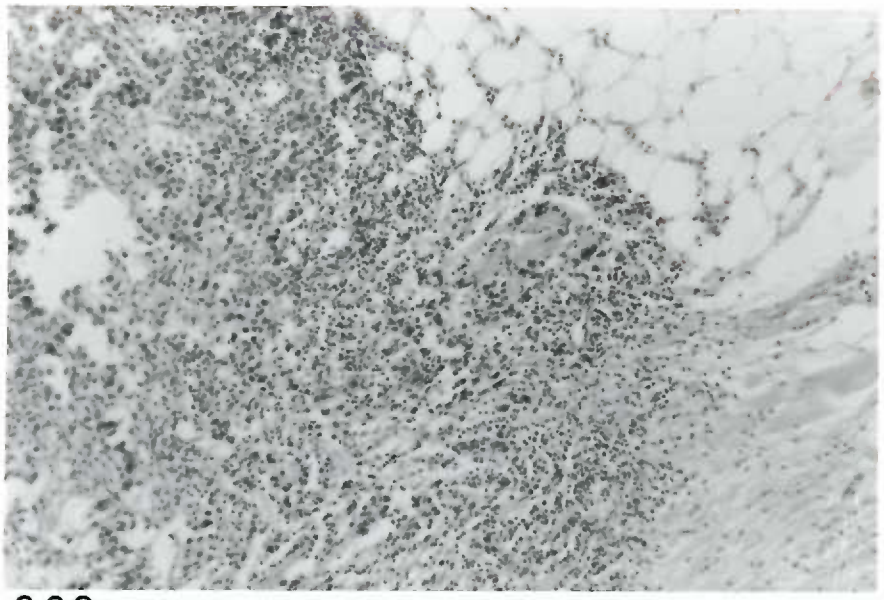
266



267

Figure 268:

Corresponding histology of Figure 266. A higher power shows tumor cells infiltrating the fat and fibrous stroma. Hematoxylin and eosin. 40X.



268

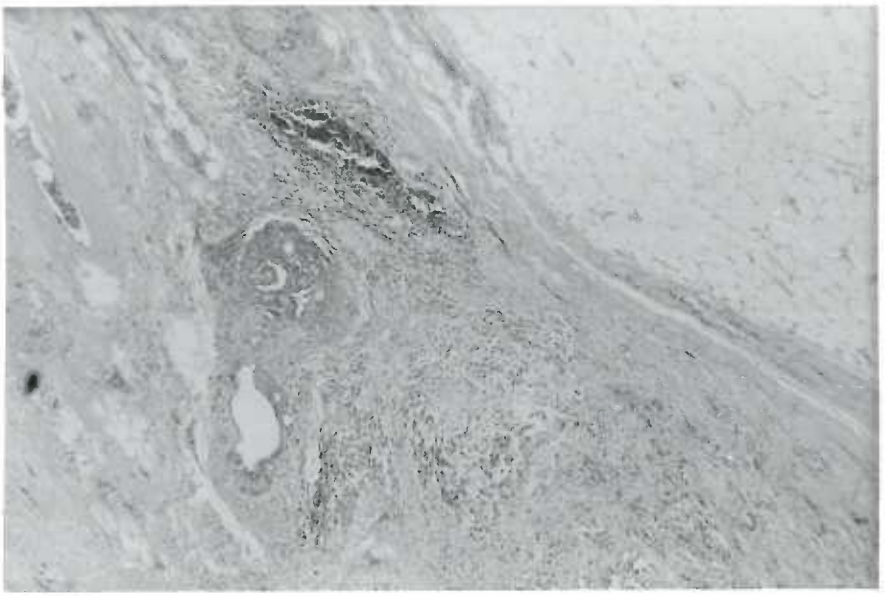
Figure 269:

Female, 70 years, breast with infiltrating ductal carcinoma (M-66-10). Subgross. A large field of irregular density is seen. A duct is located at the arrow. Hematoxylin. 10X.

Figure 270:

Corresponding histology of Figure 269. The microscopy confirms the above. Hematoxylin and eosin. 10X.

269



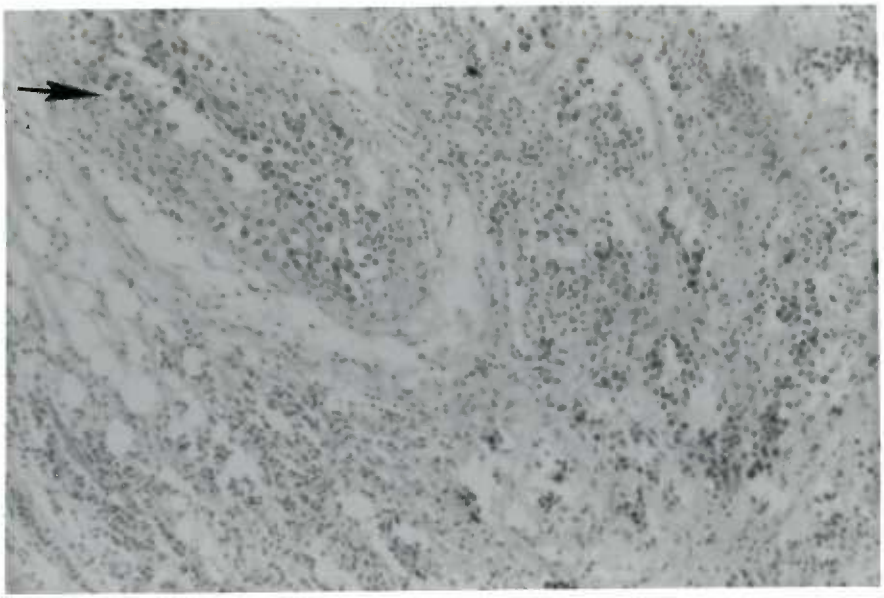
270

Figure 271:

Corresponding histology of Figure 269. A duct (arrow) is surrounded by nests of tumor cells invading the fibrous and fatty stroma. Hematoxylin and eosin. 40X.

Figure 272:

Corresponding histology of Figure 269. A higher power shows the character of the individual invading cells. Note the pleomorphism. No mitoses are recognized in this field. Hematoxylin and eosin. 160X.



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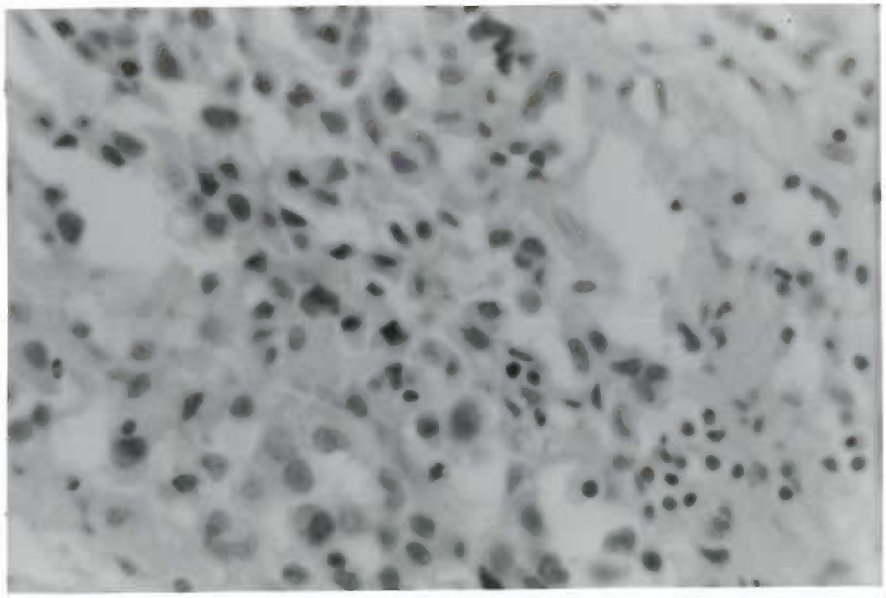


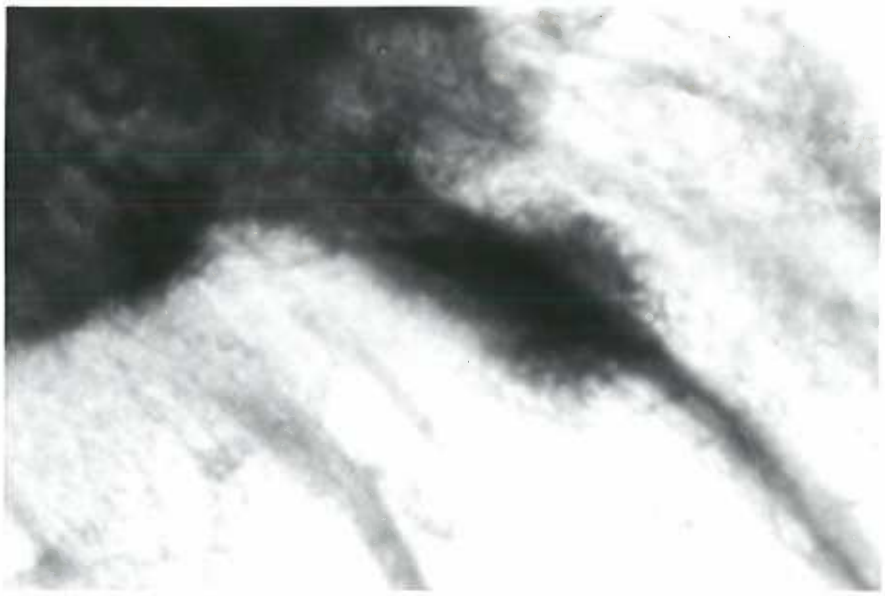
272

Figure 273:

Female, 70 years, breast with infiltrating ductal carcinoma (M-66-10). Subgross. A large density representing cancer is seen infiltrating along a duct and into the surrounding fat. Hematoxylin. 10X.

Figure 274:

Corresponding histology of Figure 273. Microscopy confirms the above. Hematoxylin and eosin. 10X.



273

274

Figure 275:

Female, 70 years, breast with infiltrating ductal carcinoma (M-66-10). Subgross. A large dense area with a stringy border is noted. Hematoxylin. 10X.

Figure 276:

Corresponding histology of Figure 275. Infiltrating tumor cells give the same pattern as seen above. Hematoxylin and eosin. 10X.

275

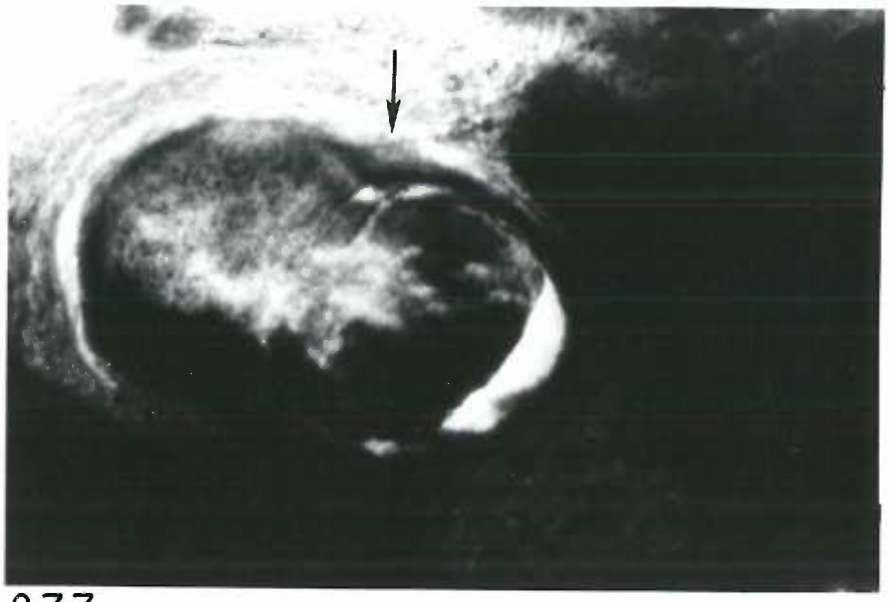
276

Figure 277:

Female, 56 years, breast with mammary dysplasia (M-66-4). Subgross. A large duct with material in the lumen (arrow) is surrounded by very dense tissue similar to that seen in Figure 266. Hematoxylin. 11X.

Figure 278:

Corresponding histology of Figure 277. The duct is filled with exfoliated cells and necrotic debris. The surrounding stroma has large hemorrhagic areas, secondary to surgical trauma, which correspond to the dense areas seen on subgross. Hematoxylin and eosin. 10X.



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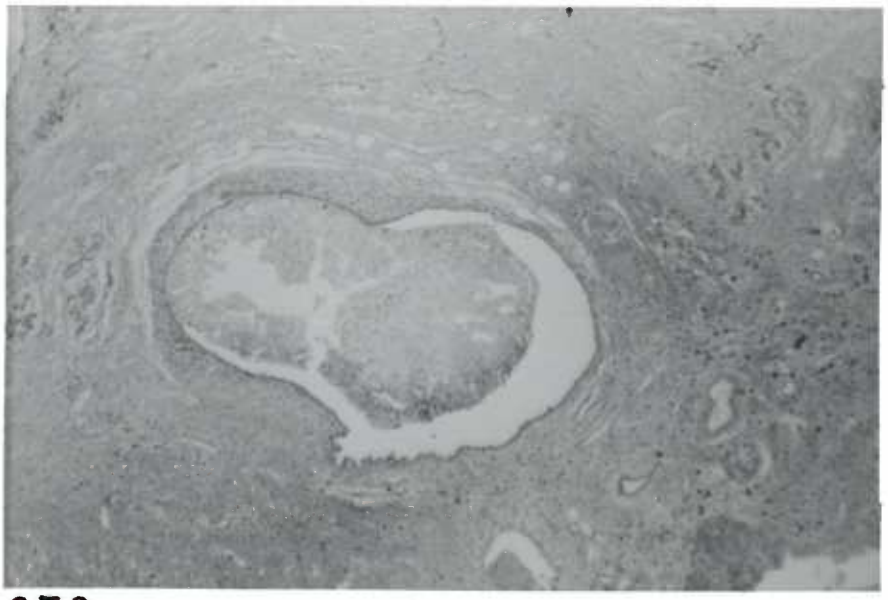


278

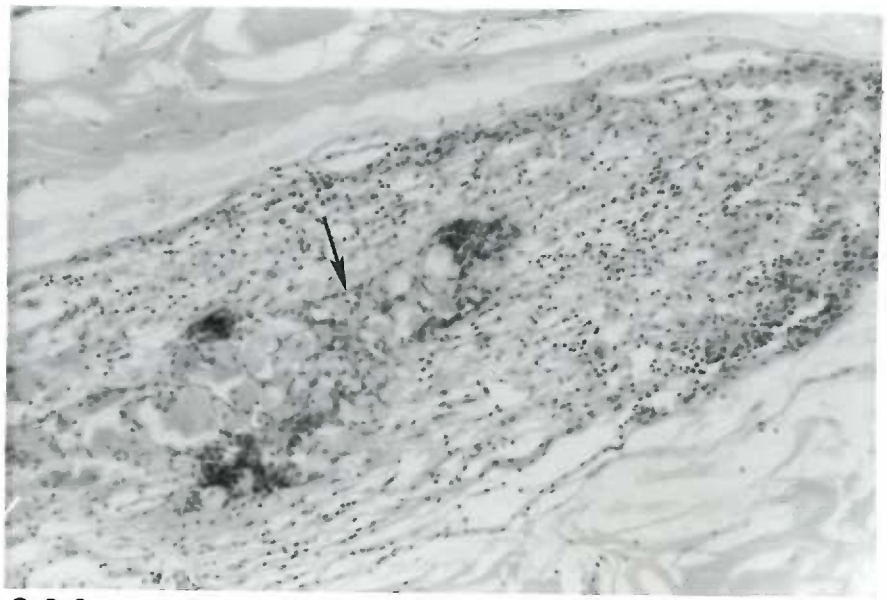
Figure 279:

Female, 53 years, normal breast (M-66-21). Subgross. A large lobular density is arising directly from a duct. It bears a resemblance to subgross formations of carcinoma seen earlier. Hematoxylin. 10X.

Figure 280:

Corresponding histology of Figure 279. A moderate chronic inflammatory infiltrate is noted in the proliferated periductal fibrous tissue. Duct lumen (arrow) is filled by macrophages. Hematoxylin and eosin. 40X.

279



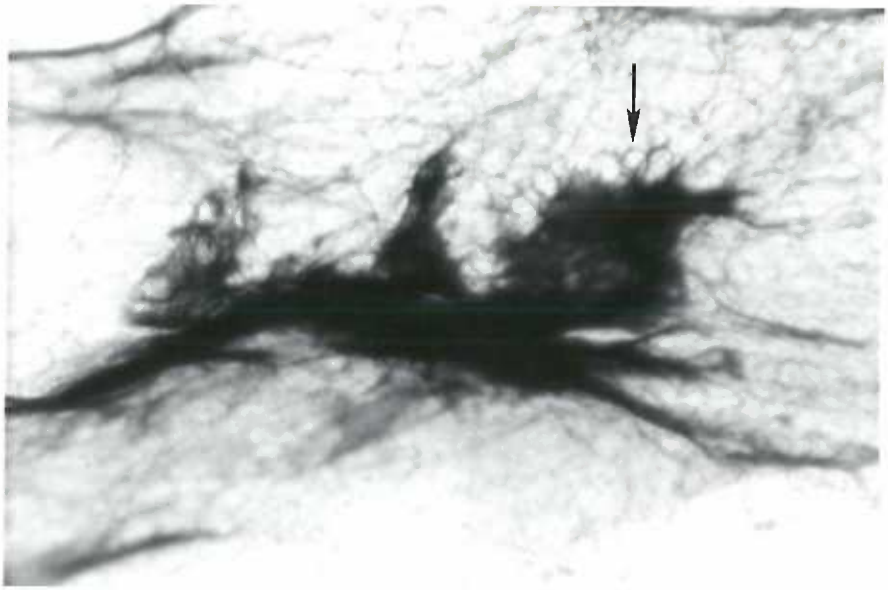
280

Figure 281:

Female, 55 years, normal breast (M-66-19). Subgross. An irregularly shaped density appears to be infiltrating fat, as evidenced by scalloping (arrow). Hematoxylin. 10X.

Figure 282:

Corresponding histology of Figure 281. A small irregular lobule is attached to a fibrous band. Ductules are visible (arrow). No atypism is noted. Hematoxylin and eosin. 40X.



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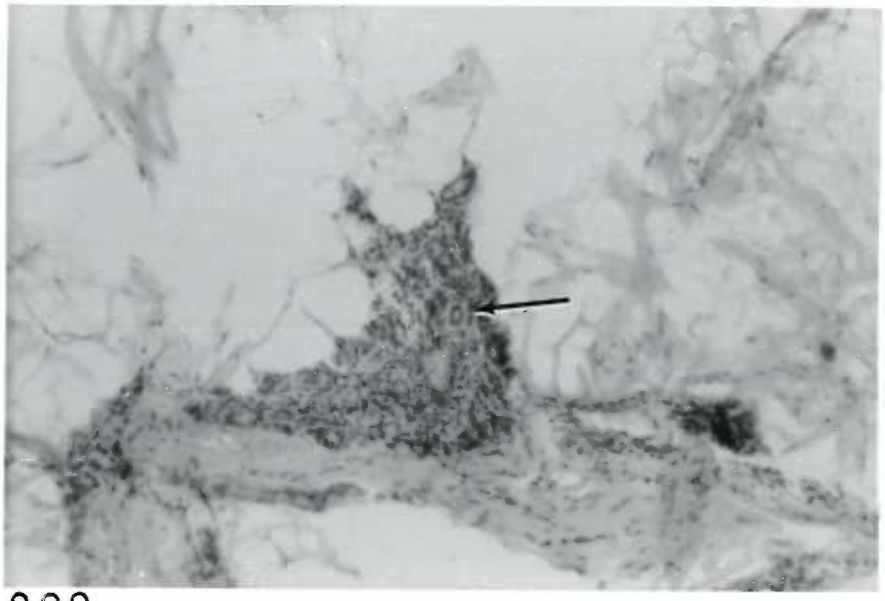


282

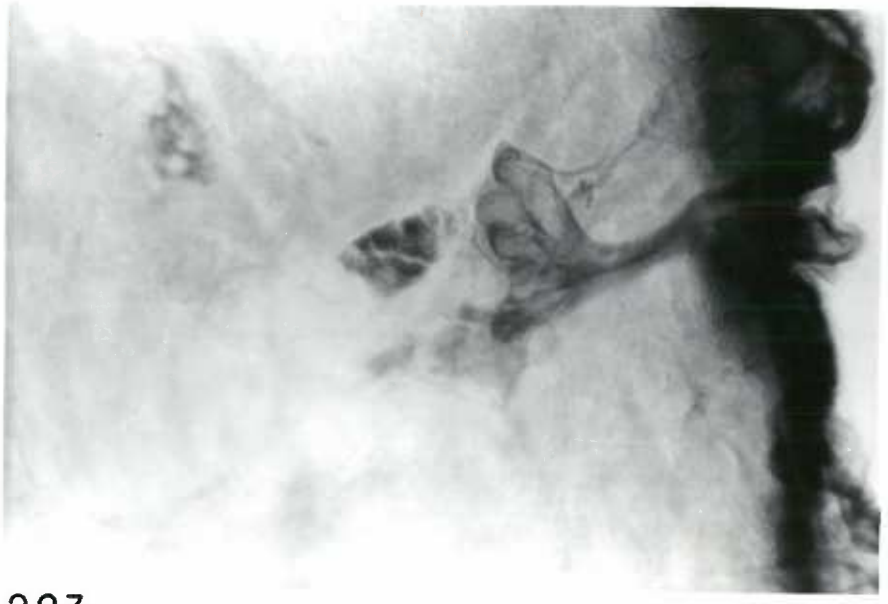
OTHER NORMAL BREAST STRUCTURES

Figure 283:

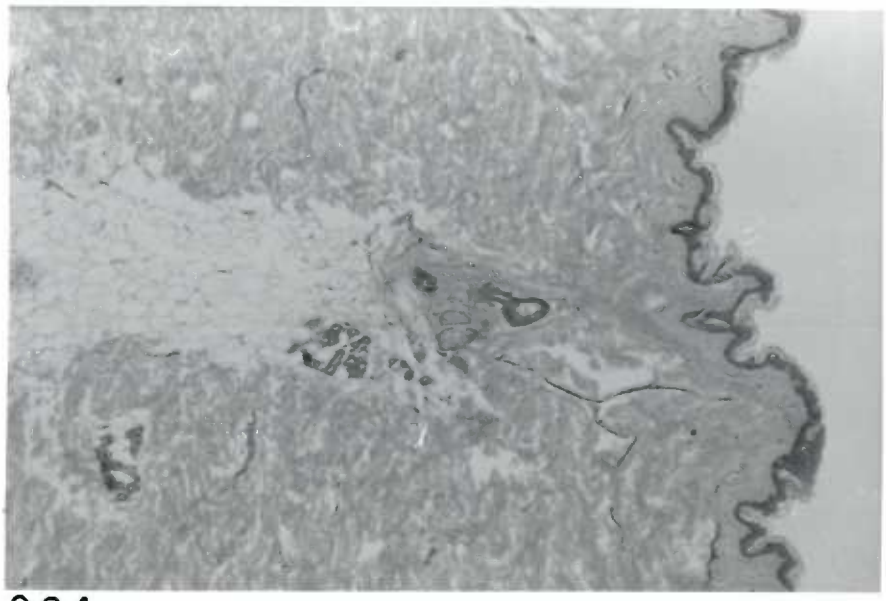
Female, 53 years, normal breast (M-66-21). Subgross. The epithelial surface is to the right. Two gland structures with ducts can be seen projecting into the dermis. Hematoxylin. 10X.

Figure 284:

Corresponding histology of Figure 283. Note sweat gland and sebaceous gland which are also visible in Figure 283. Hematoxylin and eosin. 10X.



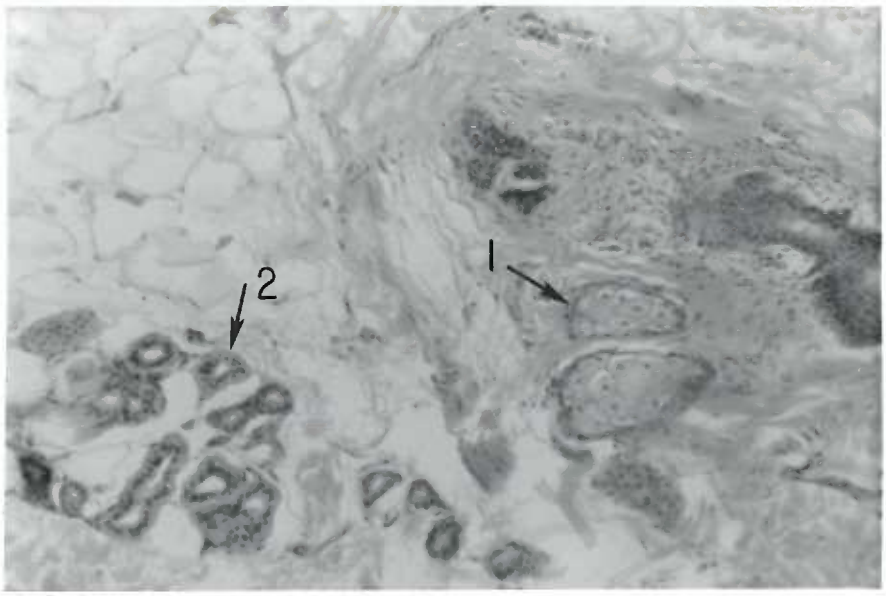
283



284

Figure 285:

Corresponding histology of Figure 283. The gland structures are identifiable as sebaceous gland (arrow 1) and sweat gland (arrow 2). Hematoxylin and eosin. 40X.



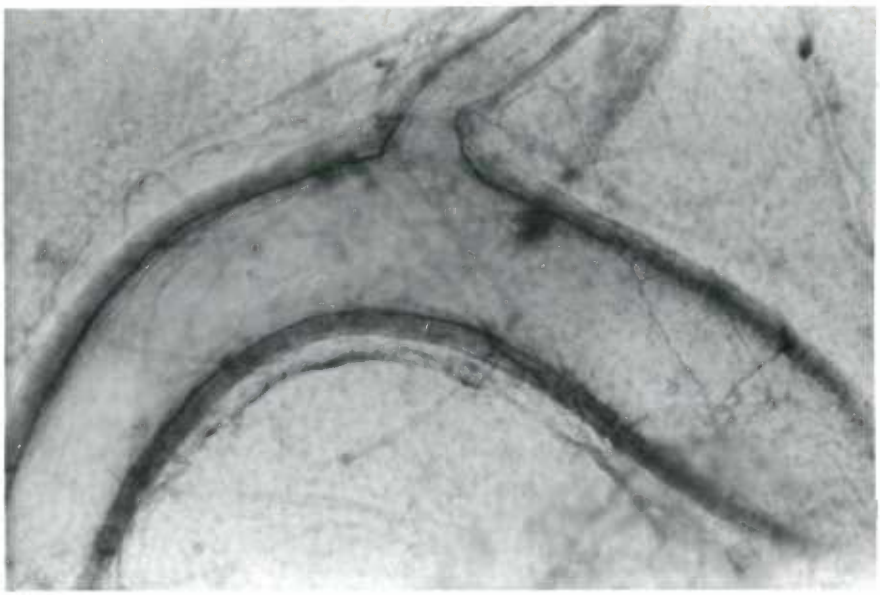
285

Figure 286:

Female, 41 years, normal breast (M-66-26). Subgross. This is the appearance of a normal blood vessel. Note the smooth even walls. Hematoxylin. 10X.

Figure 287:

Corresponding histology of Figure 286. Microscopy confirms the above. Hematoxylin and eosin. 40X.



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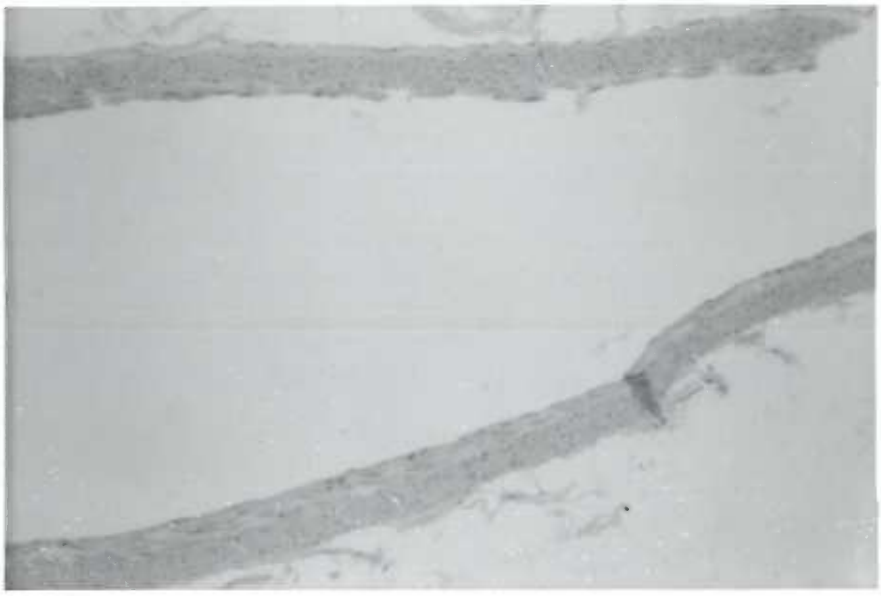


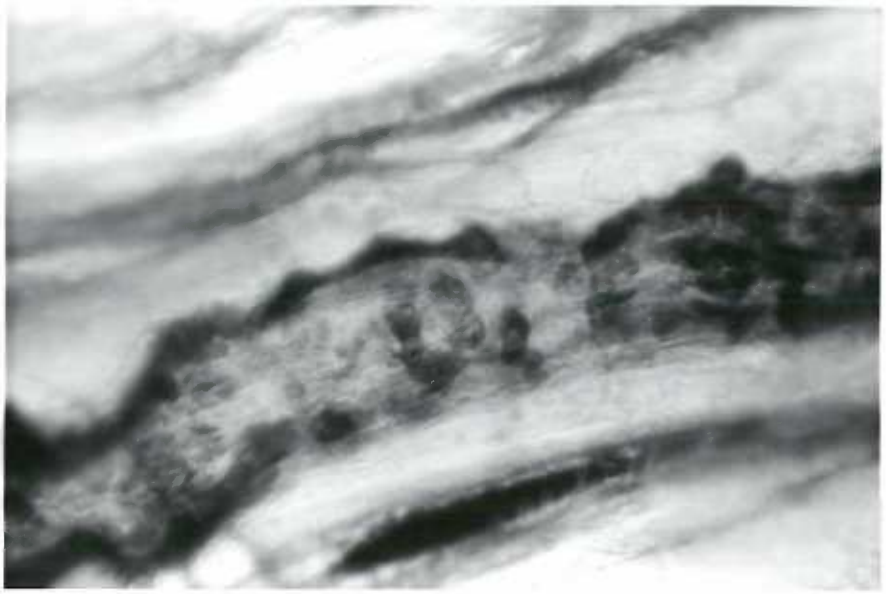
287

Figure 288:

Female, 79 years, normal breast (M-66-18). Subgross. The subgross appearance of a calcified blood vessel shows irregular densities protruding from its walls. Hematoxylin. 10X.

Figure 289:

Corresponding histology of Figure 288. Note the deposits of calcium in the media of this small artery. Hematoxylin and eosin. 40X.



288

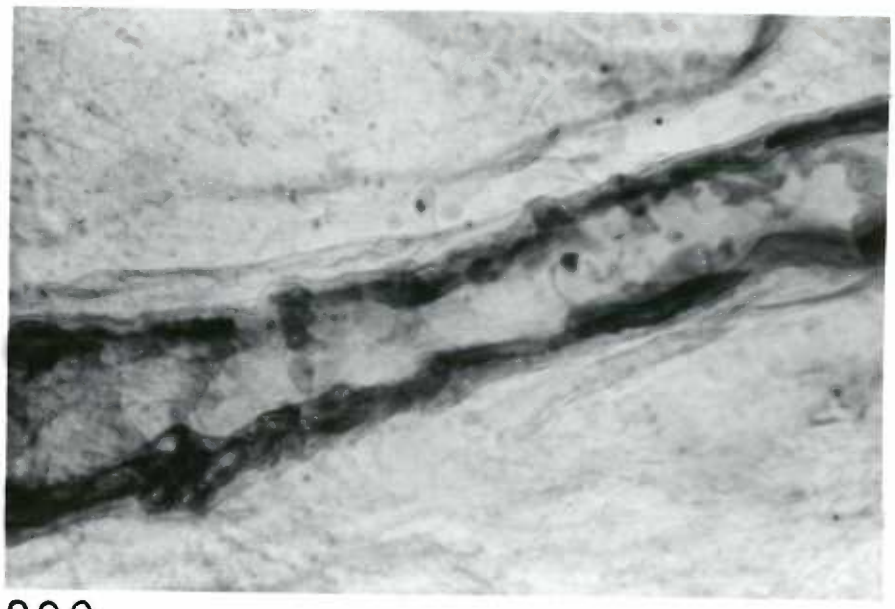
289

Figure 290:

Female, 88 years, normal breast (M-66-15). Subgross. Another blood vessel with calcium deposited in the walls. Hematoxylin. 10X.

Figure 291:

Corresponding histology of Figure 290. Microscopy confirms the above. Hematoxylin and eosin. 40X.



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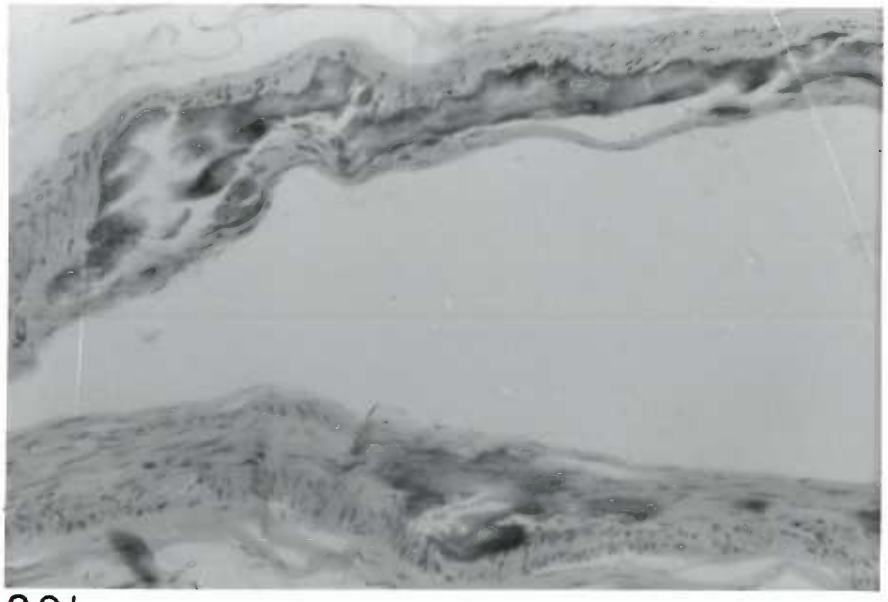


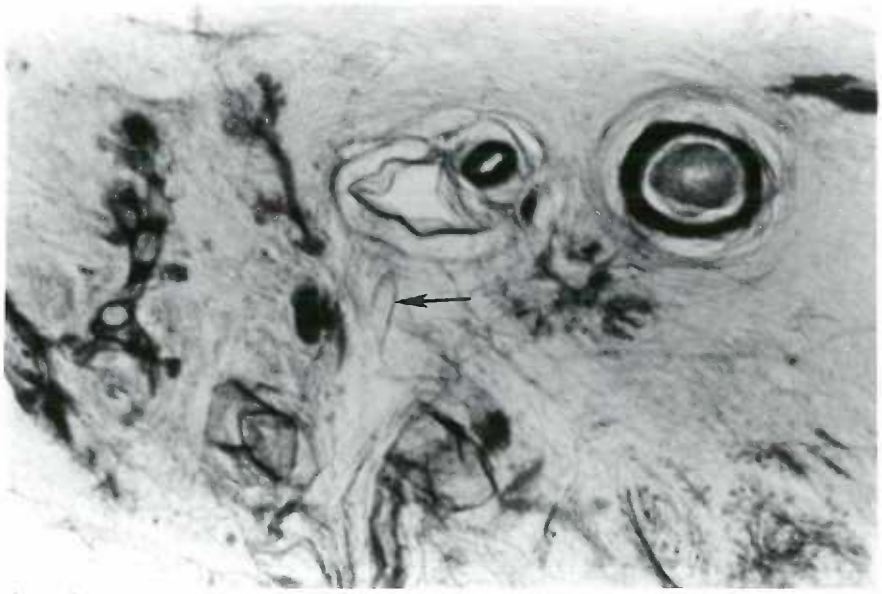
291

Figure 292:

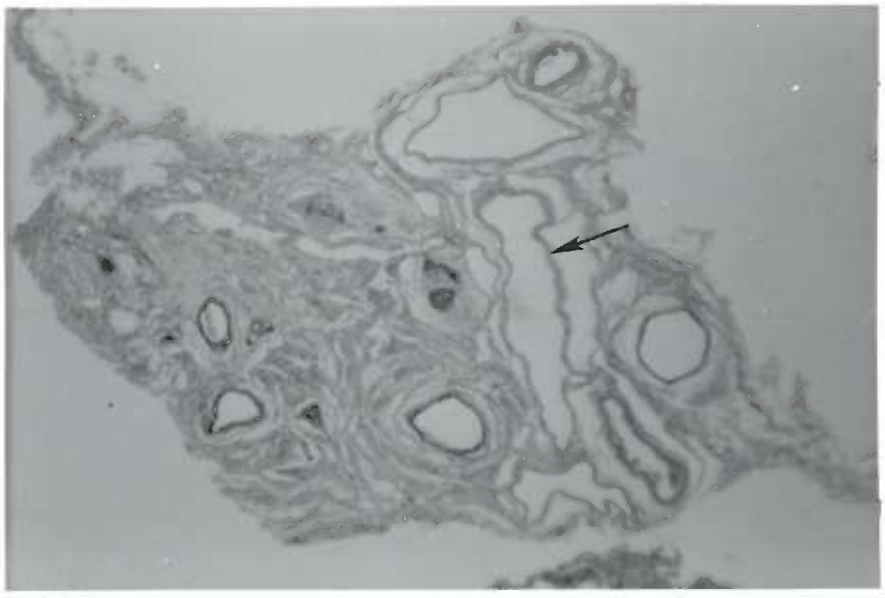
Female, 56 years, breast with mammary dysplasia (M-66-4). Sub-gross. Note the ducts and lobules as well as the thin-walled channel (arrow). Hematoxylin. 8.5X.

Figure 293:

Corresponding histology of Figure 292. Note the correlations with the thin-walled structure above being represented by this vessel (arrow). Hematoxylin and eosin. 10X.



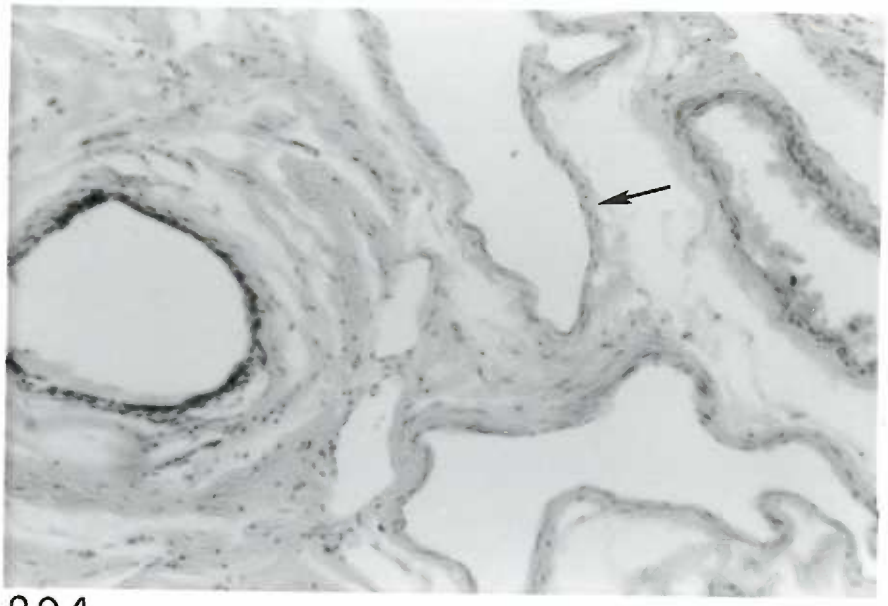
292



293

Figure 294:

Corresponding histology of Figure 292. The endothelial lined spaces are lymphatic vessels (arrow) and correspond to the subgross structure at the arrows in Figure 292. Hematoxylin and eosin. 40X.



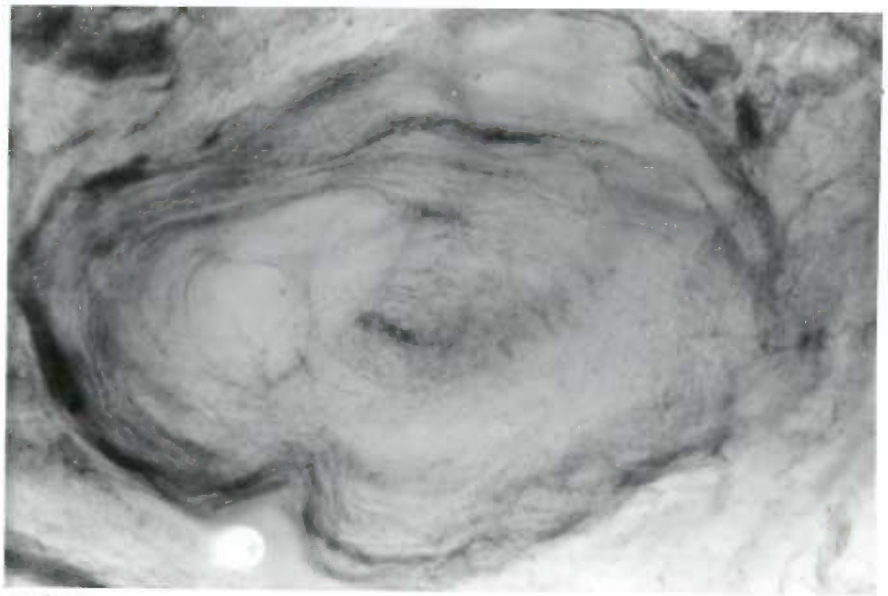
294

Figure 295:

Female, 78 years, normal breast (M-66-27). Subgross. This is the subgross configuration of a Paccinian corpuscle. Hematoxylin. 10X.

Figure 296:

Corresponding histology of Figure 295. Hematoxylin and eosin. 40X.



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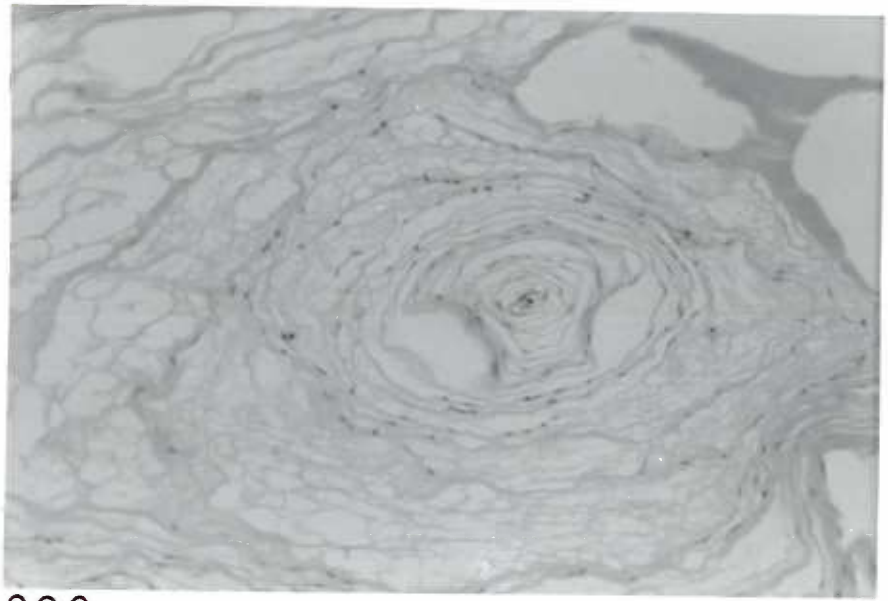


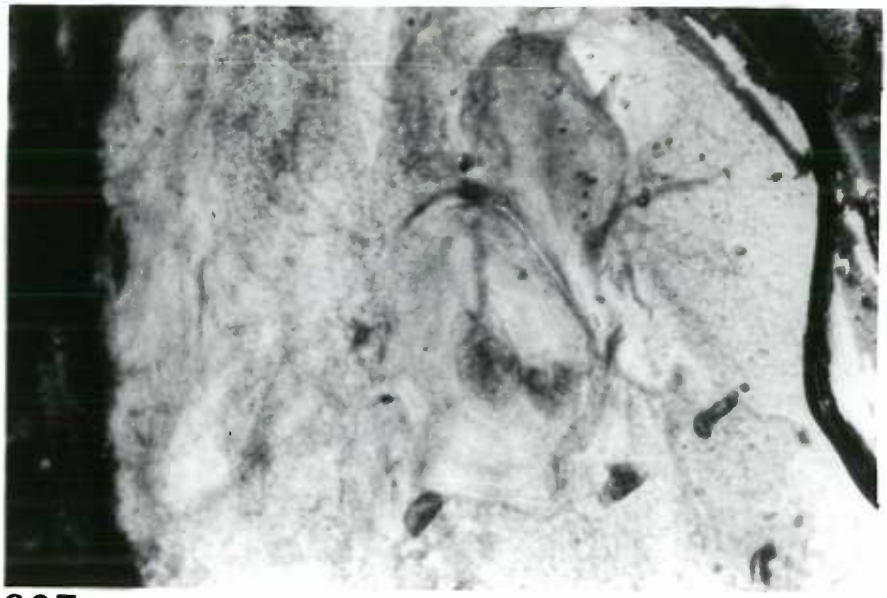
296

Figure 297:

Female, 56 years, breast with mammary dysplasia (M-66-4). Another Paccinian corpuscle is in the center of the field. Hematoxylin. 7X.

Figure 298:

Corresponding histology of Figure 297. Hematoxylin and eosin. 40X.



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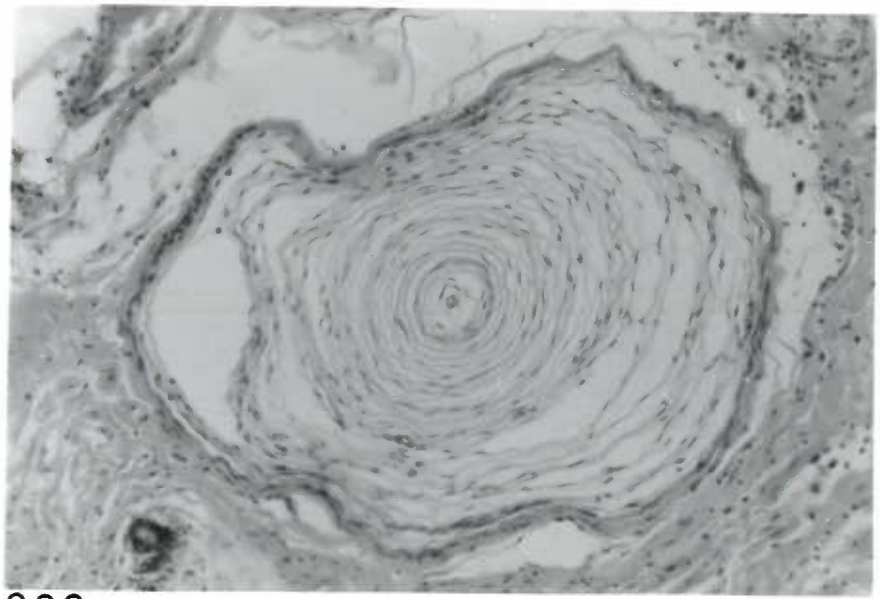


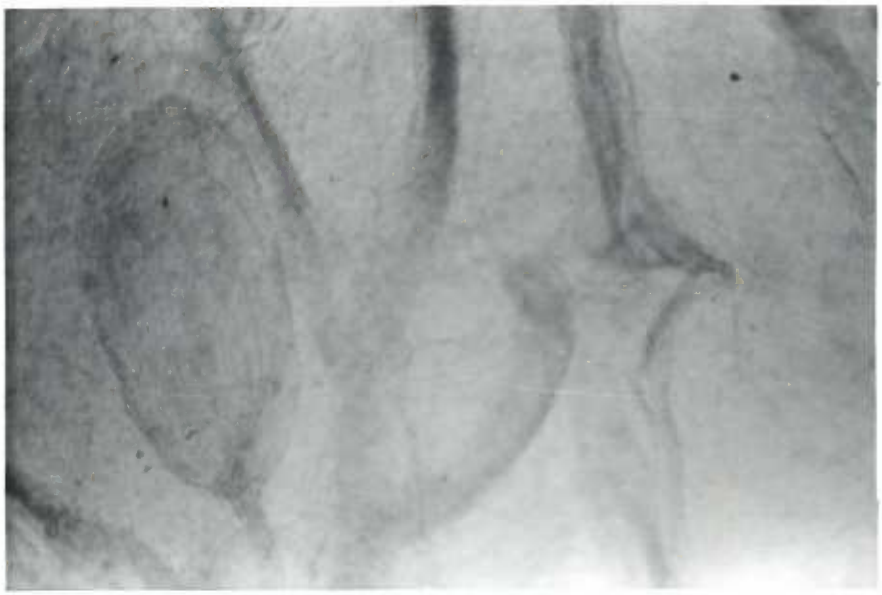
298

Figure 299:

Female, 53 years, normal breast (M-66-21). Subgross. A smooth regular structure is noted. It has an "onion-skin" appearance with a structure attached to one end. Hematoxylin. 10X.

Figure 300:

Corresponding histology of Figure 299. It is identified as a paccinian corpuscle. Hematoxylin and eosin. 40X.



299

300

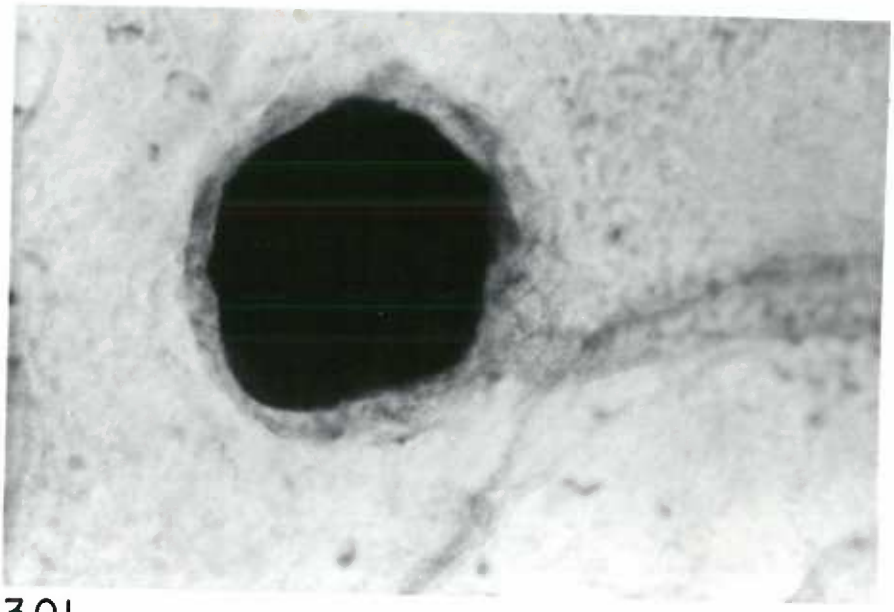
UNUSUAL BREAST STRUCTURES

Figure 301:

Female, 88 years, normal breast (M-66-15). Subgross. An extremely dense formation has a capsule and an entering duct-like structure. Hematoxylin. 10X.

Figure 302:

Corresponding histology of Figure 301. The dense nodule is basically composed of lymphocytes arranged in intersecting cords. There is a surrounding fibrous capsule which has a space separating it from the lymphoid mass. There are no follicles or other usual structures seen in this lymphoid mass. Hematoxylin and eosin. 10X.



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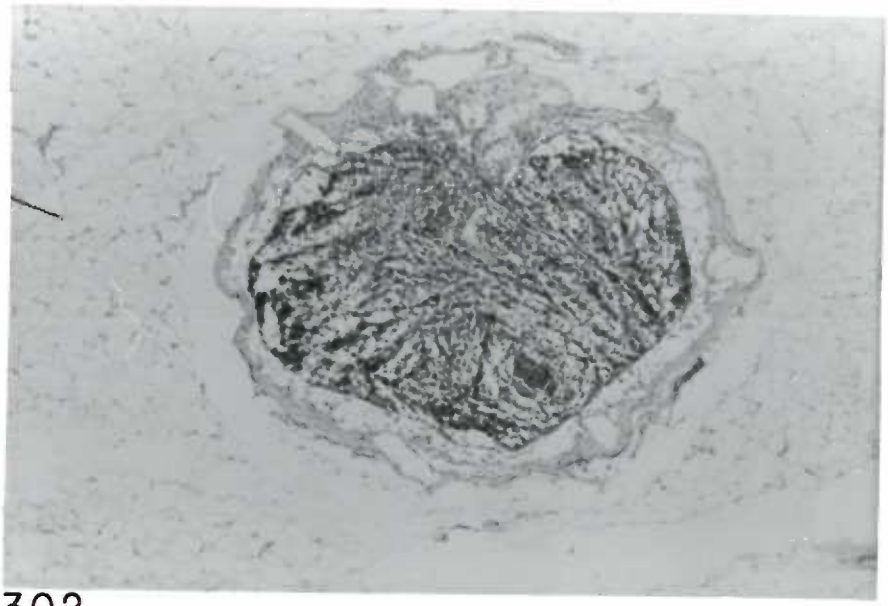


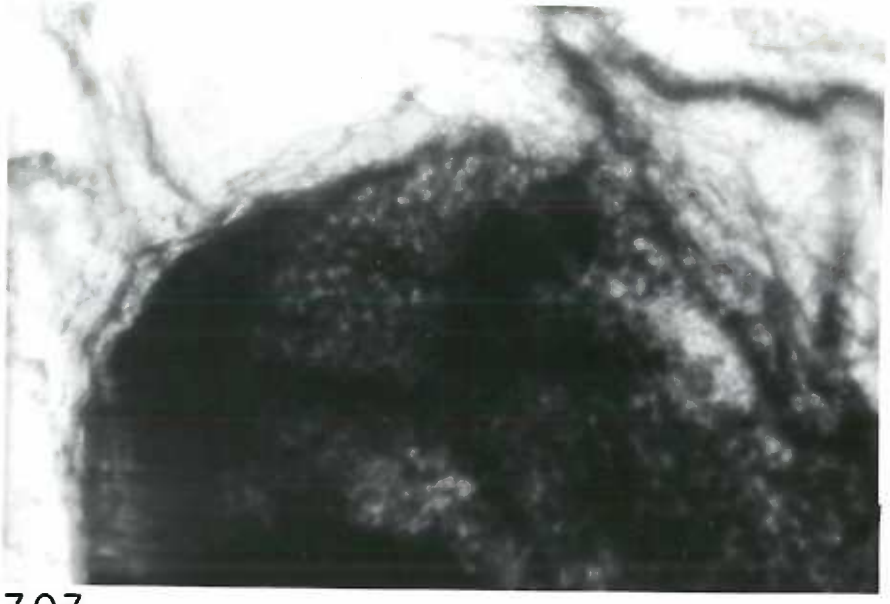
302

Figure 303:

Female, 55 years, normal breast (M-66-19). Subgross. A large dense mass has an irregular border and patchy translucencies. Hematoxylin. 10X.

Figure 304:

Corresponding histology of Figure 303. The lymphocytes are coursing between the fat cells and are partially encapsulated by a fibrous capsule. Hematoxylin and eosin. 10X.



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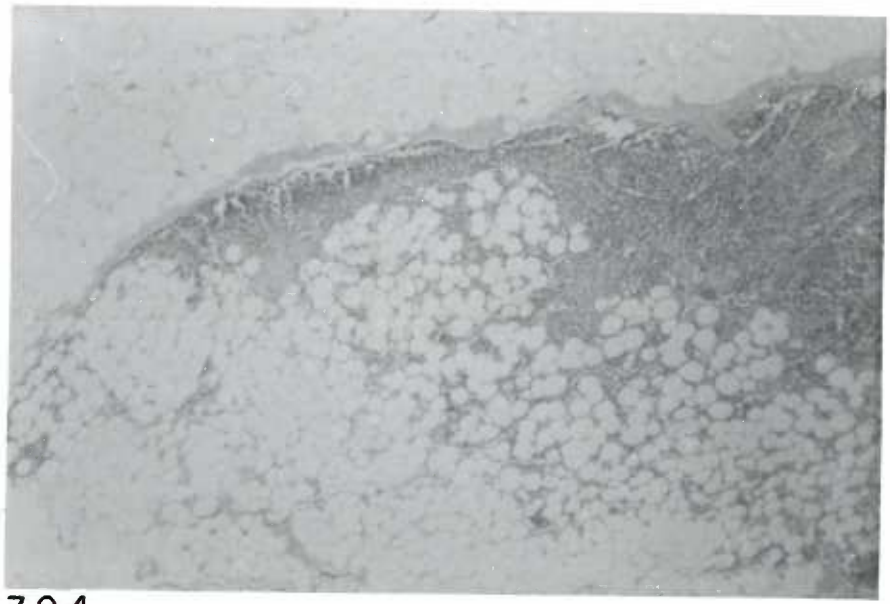


304

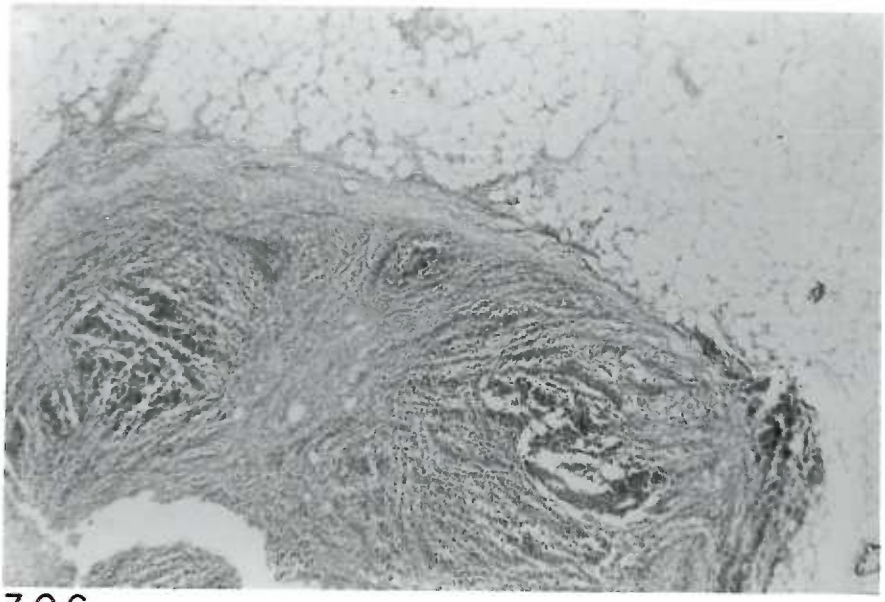
Figure 305:

Female, 70 years, breast with infiltrating ductal carcinoma (M-66-10). Subgross. Another large density is seen with poorly demarcated borders. Invasion of the fat causes sharp delineation of fat cells. Hematoxylin. 10X.

Figure 306:

Corresponding histology of Figure 305. Lymphocytes are arranged in strands and separated by cleft-like spaces. A poorly defined capsule encases the mass. Lymphocytes are infiltrating the surrounding fat. Hematoxylin and eosin. 10X.

305



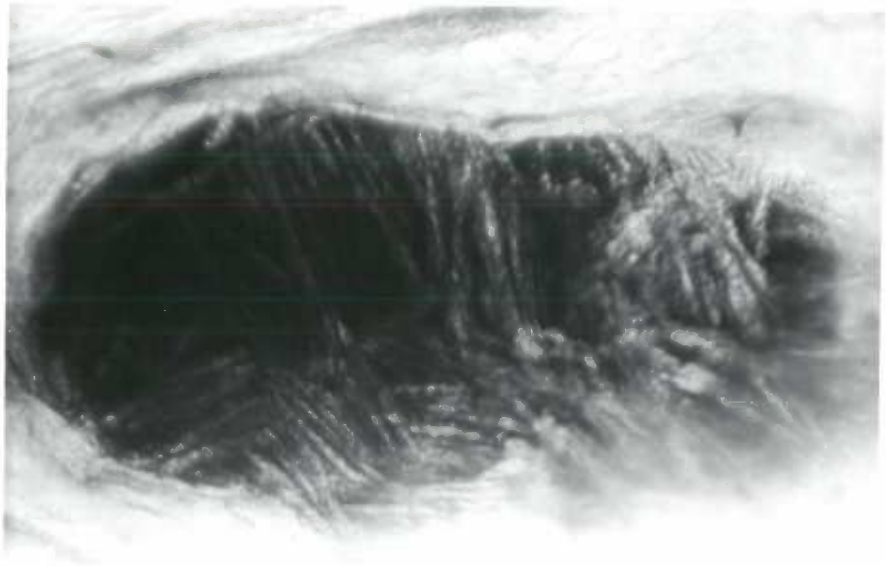
306

Figure 307:

Female, 48 years, normal breast (M-66-14). Subgross. A smoothly shaped density has elongate, "crystal-like" translucencies within its borders. Hematoxylin. 10X.

Figure 308:

Corresponding histology of Figure 307. An encapsulated structure with lymphocytes arranged in a linear fashion separated by empty spaces. Hematoxylin and eosin. 10X.



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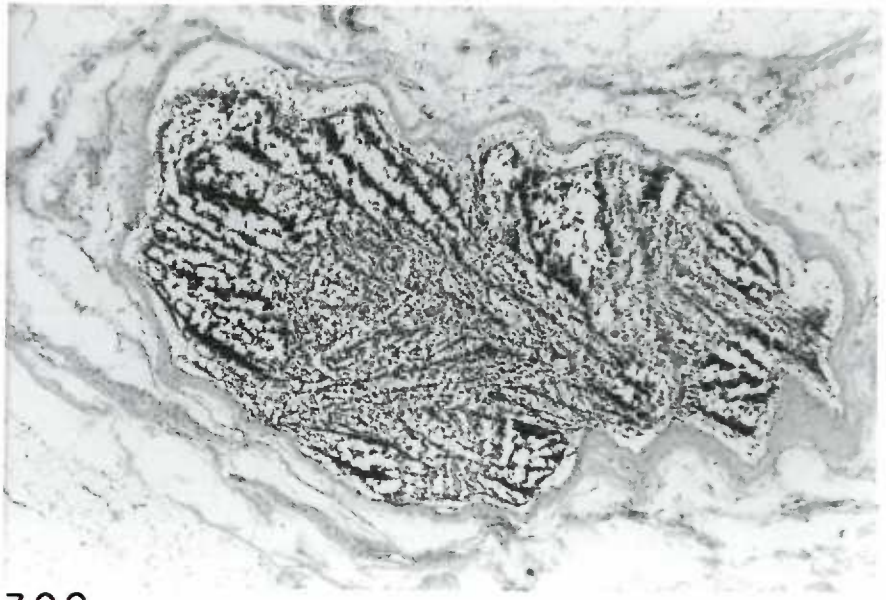


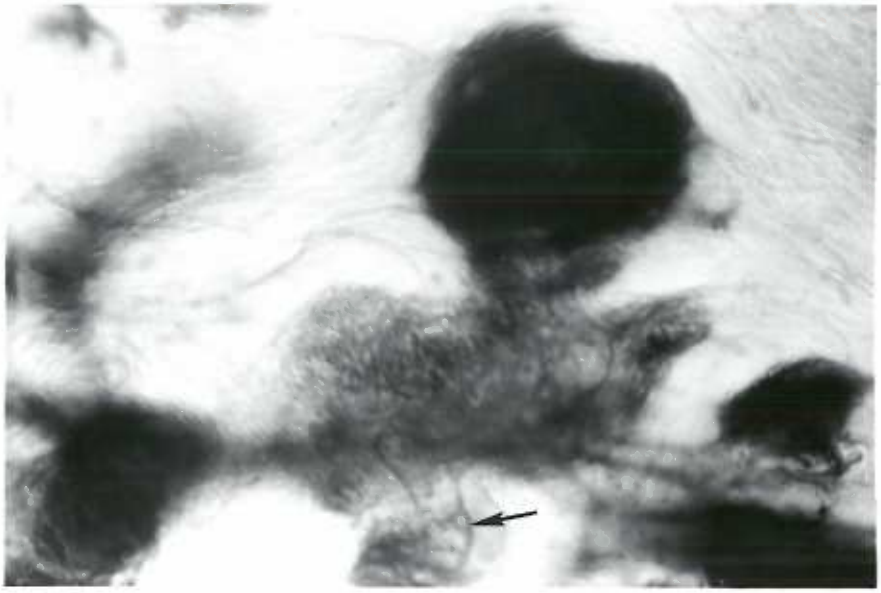
308

Figure 309:

Female, 53 years, normal breast (M-66-21). Subgross. A more lobulated structure is noted. A duct can be seen (arrow). Hematoxylin. 10X.

Figure 310:

Corresponding histology of Figure 309. Several ducts lined by breast duct epithelium can be seen (arrow). A marked inflammatory reaction is noted in the periductal tissue consistent with mastitis. It is similar to Figures 302, 304, 306, and 308. Hematoxylin and eosin. 10X.



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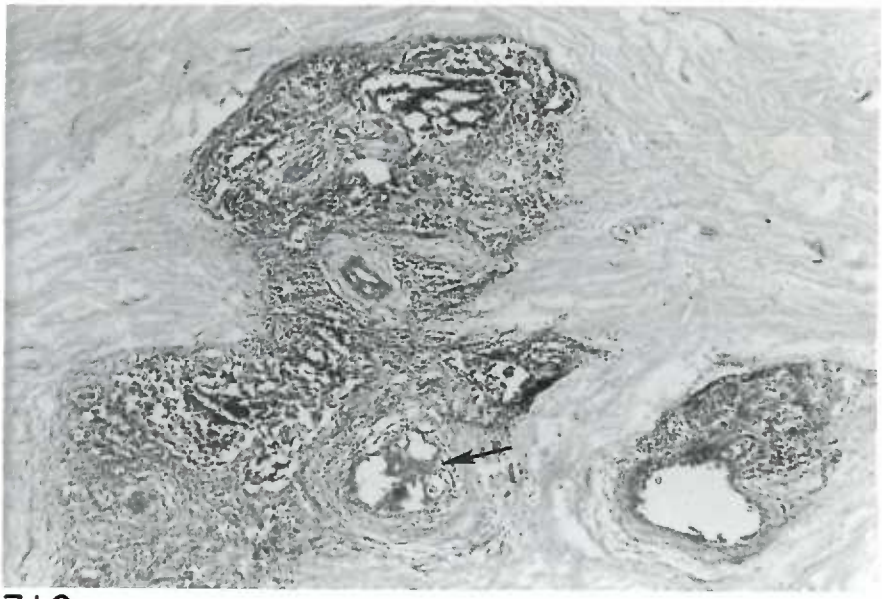
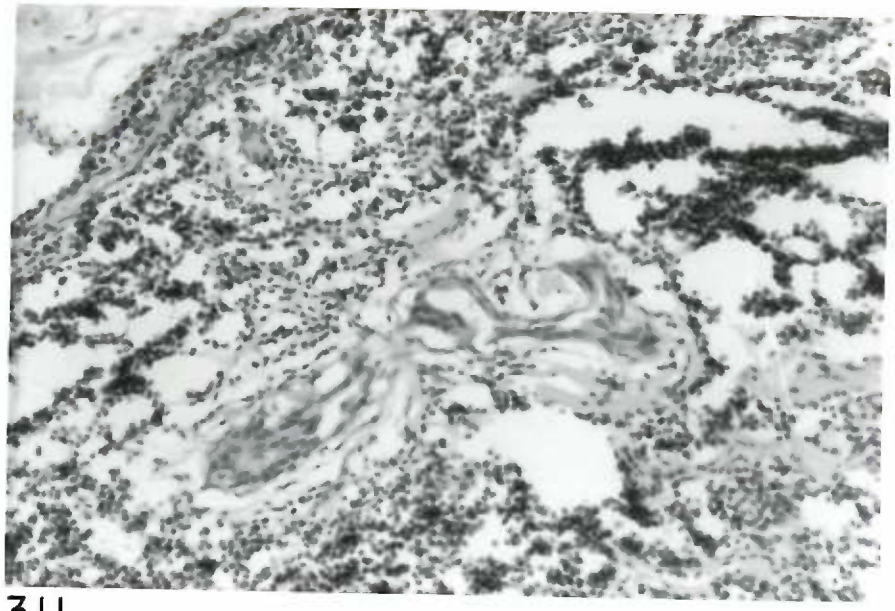


310

Figure 311:

Corresponding histology of Figure 309. A higher power shows a duct with abnormal epithelium. The character of the surrounding lymphocytes is evident. Hematoxylin and eosin. 40X.



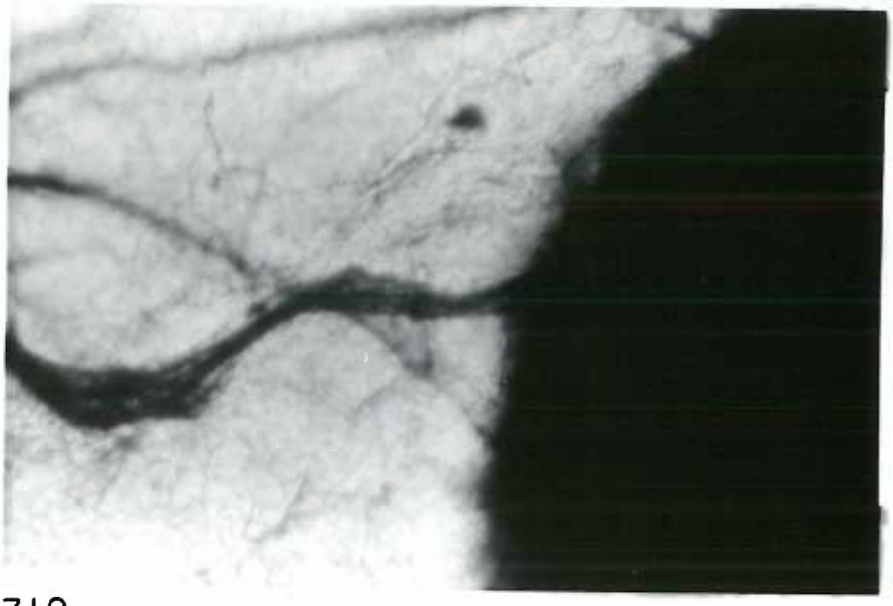
311

Figure 312:

Female, 55 years, normal breast (M-66-19). Subgross. A duct is seen entering one of the encapsulated lymphoid structures. Hematoxylin. 10X.

Figure 313:

Corresponding histology of Figure 312. Encapsulated lymphocytes have islands of epithelial cells in their midst. A vessel lined by endothelium is entering from the left. Hematoxylin and eosin. 40X.



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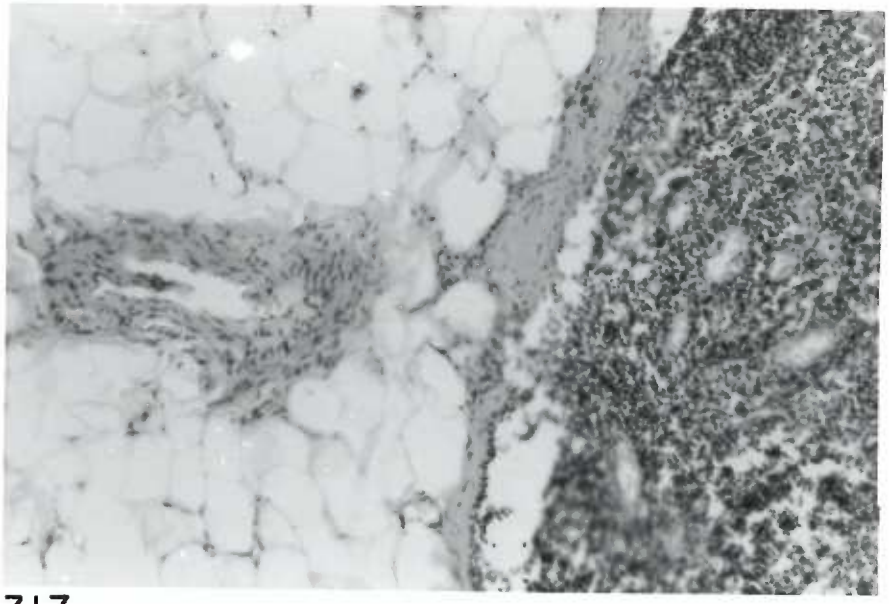


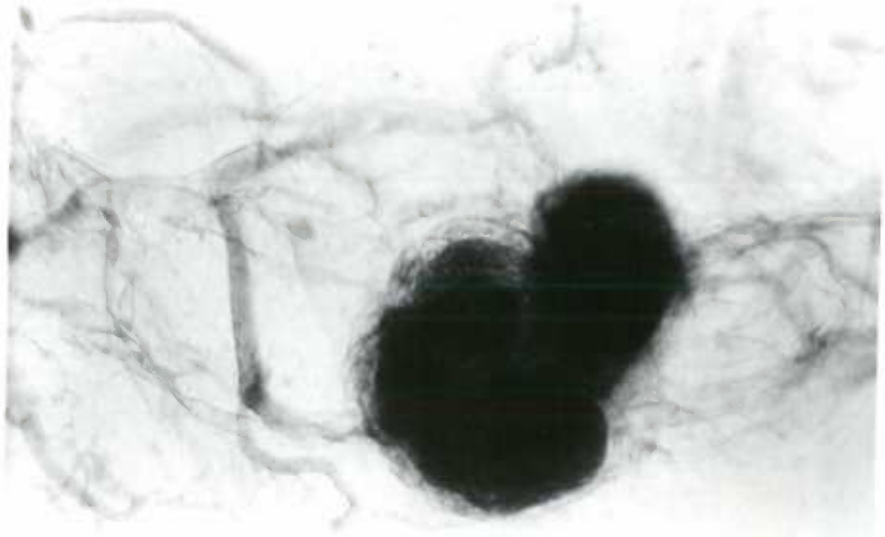
313

Figure 314:

Female, 53 years, normal breast (M-66-21). Subgross. A lobulated density with an entering duct is noted. Hematoxylin. 10X.

Figure 315:

Corresponding histology of Figure 314. The lymphocytes composing the above mass are clumped in groups of 2 to 10 cells which appear to be associated with strands of connective tissue. Hematoxylin and eosin. 40X.



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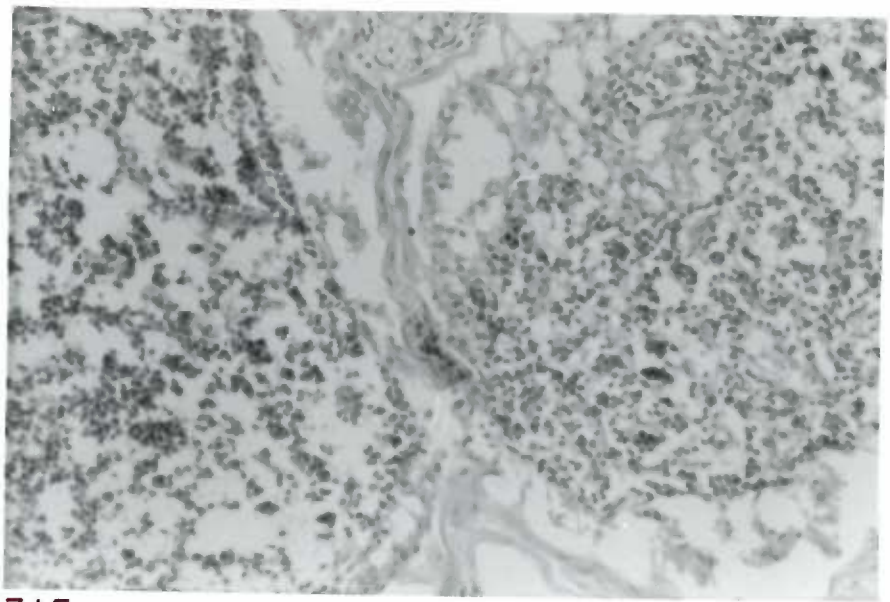


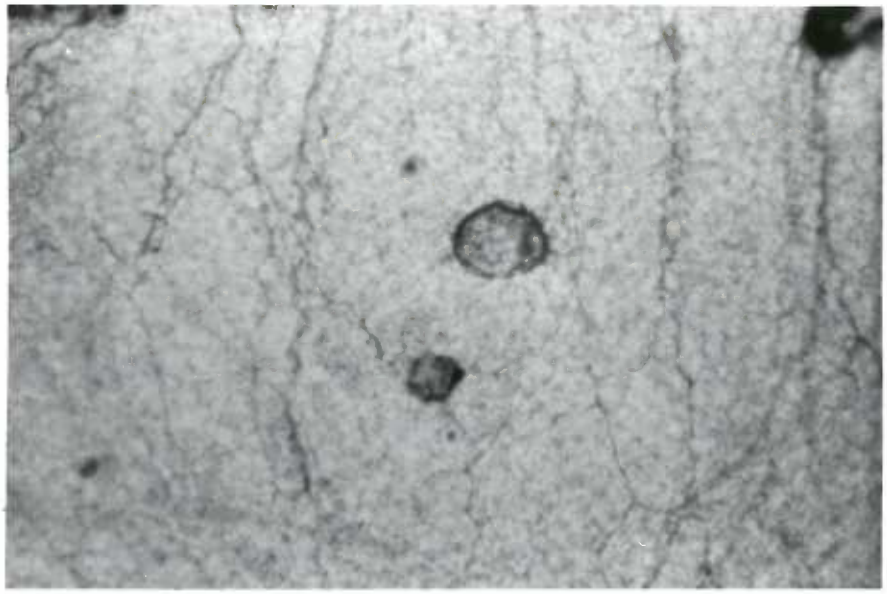
315

Figure 316:

Female, 55 years, normal breast (M-66-19). Subgross. Two small isolated cystic structures are located in a fat lobule. Hematoxylin. 10X.

Figure 317:

Corresponding histology of Figure 316. The wall of the empty cyst is composed of cells with dense nuclei of different sizes. Hematoxylin and eosin. 160X.



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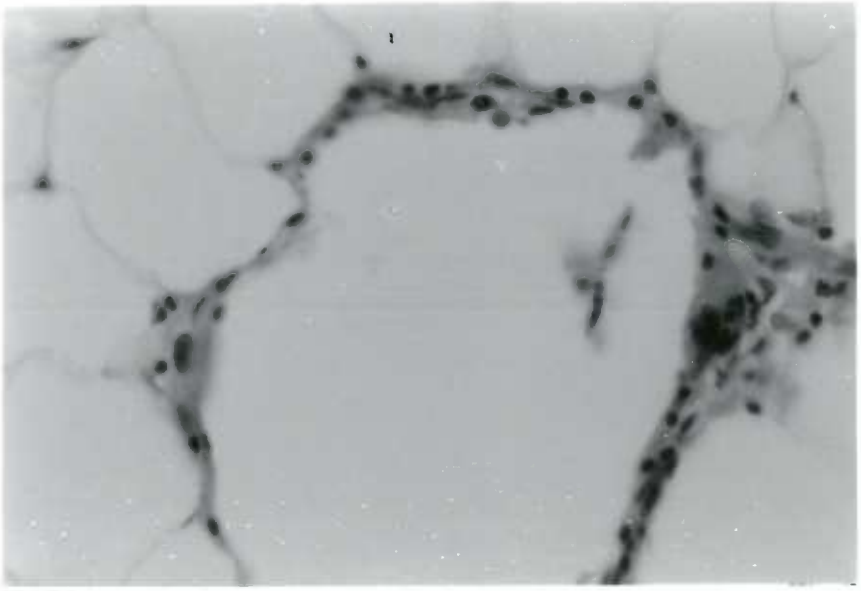


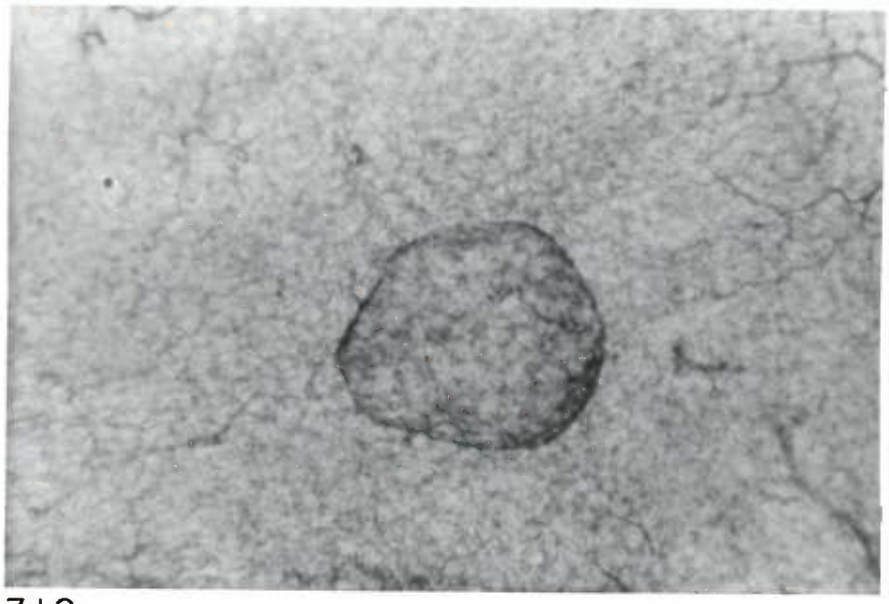
317

Figure 318:

Female, 55 years, normal breast (M-66-19). Subgross. An empty, isolated cystic structure is seen in a fat lobule. Hematoxylin. 10X.

Figure 319:

Corresponding histology of Figure 318. The cystic space is lined by the same type of cells noted in Figure 317. Hematoxylin and eosin. 40X.



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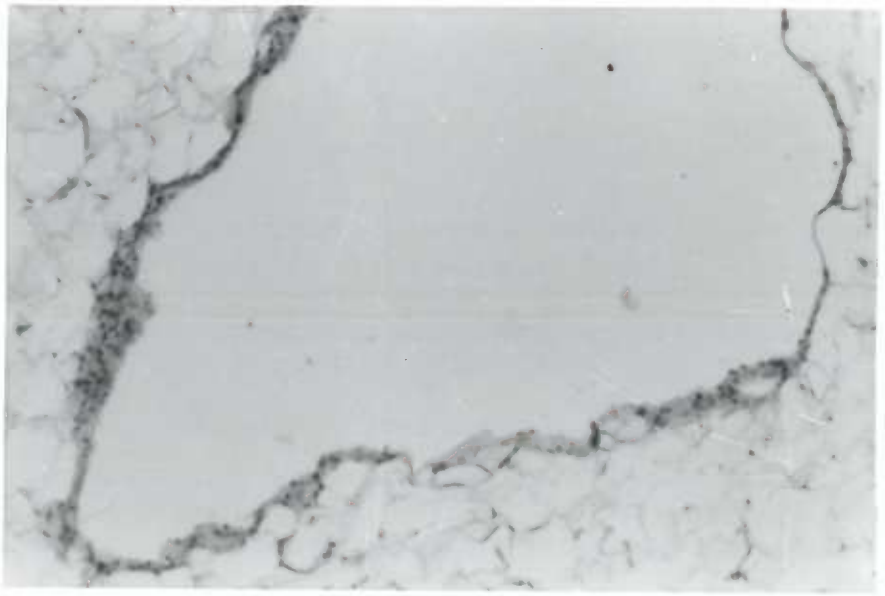


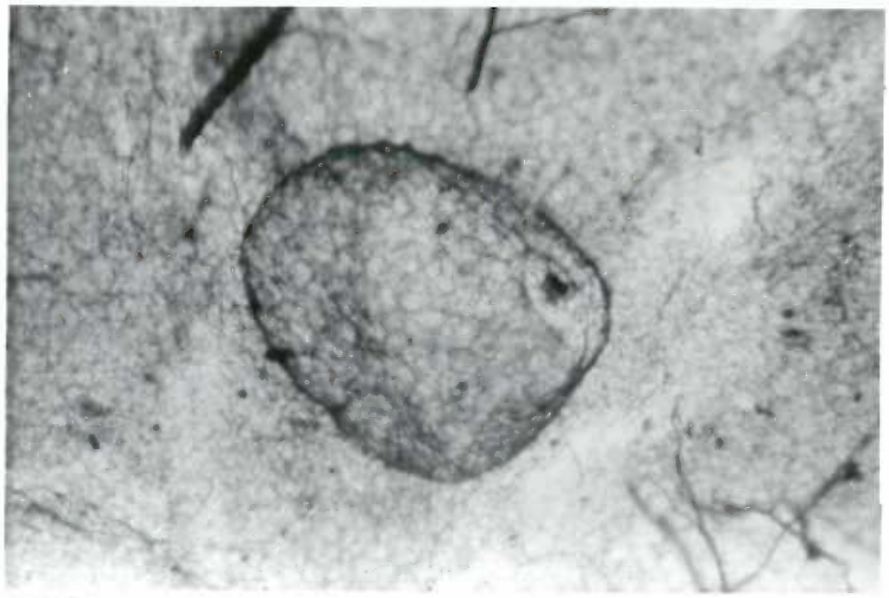
319

Figure 320:

Female, 55 years, normal breast (M-66-19). Subgross. Another cyst of the same type as seen in Figures 316 and 318. It appears to be empty. Hematoxylin. 10X.

Figure 321:

Corresponding histology of Figure 320. The cyst wall again is lined by the cells seen in Figures 317 and 319. A fatty stromal invagination is noted. There is a nest of cells (arrow) which differs from the other lining cells. Hematoxylin and eosin. 10X.



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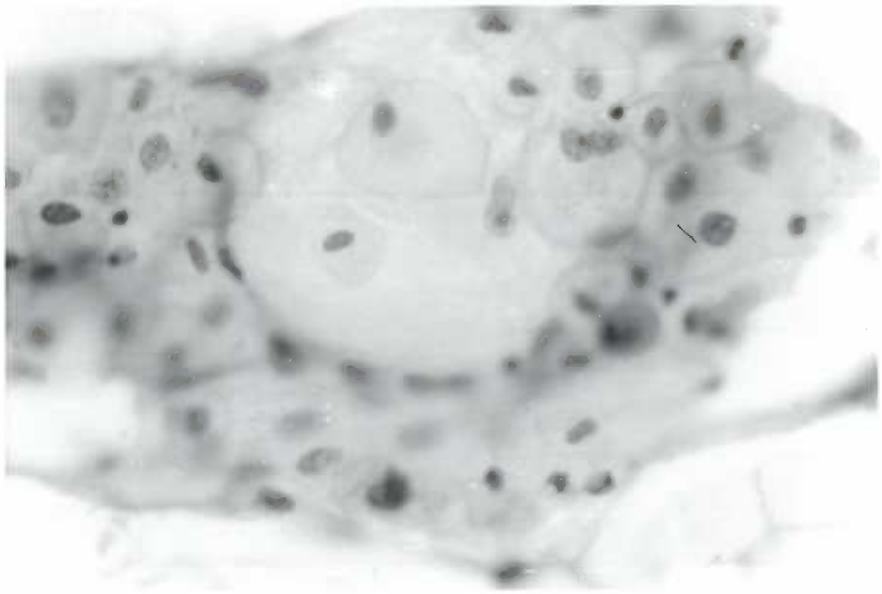
321

Figure 322:

Corresponding histology of Figure 320. The cells in the cell nest are large and foamy. They have abundant cytoplasm, sharp cell borders, and prominent nucleoli. Hematoxylin and eosin. 160X.

Figure 323:

Corresponding histology of Figure 320. The cells lining the remainder of the cyst suggest fat cells containing minimal fat (arrow). Hematoxylin and eosin. 160X.



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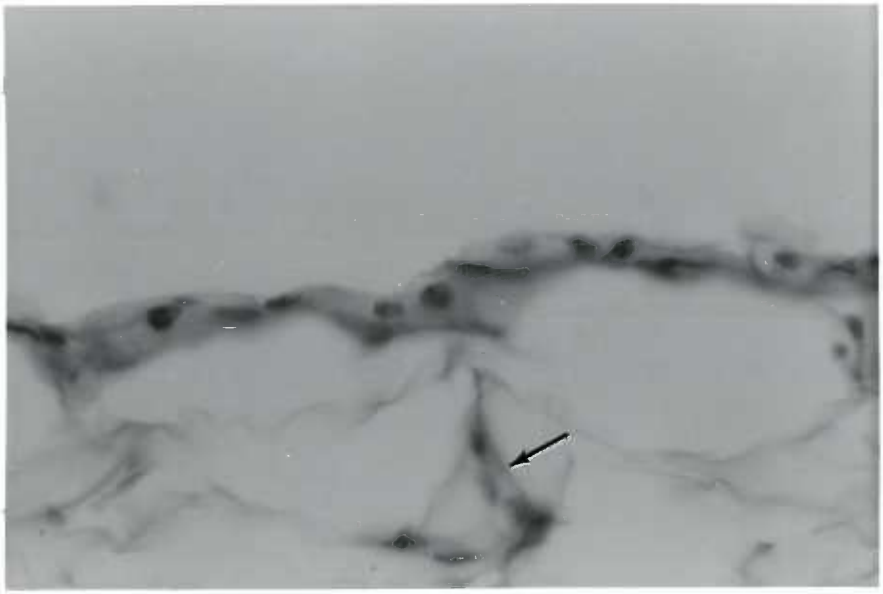


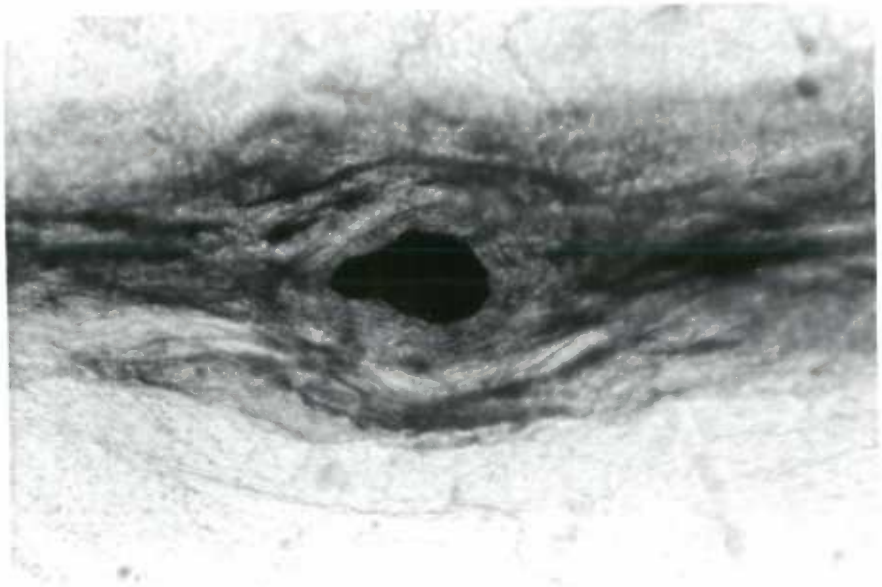
323

Figure 324:

Female, 69 years, normal breast (M-66-25). Subgross. A sharply demarcated, extremely dense structure is surrounded by fibrous tissue. Hematoxylin. 10X.

Figure 325:

Corresponding histology of Figure 324. A calcific center is surrounded by dense fibrous connective tissue. Hematoxylin and eosin. 40X.



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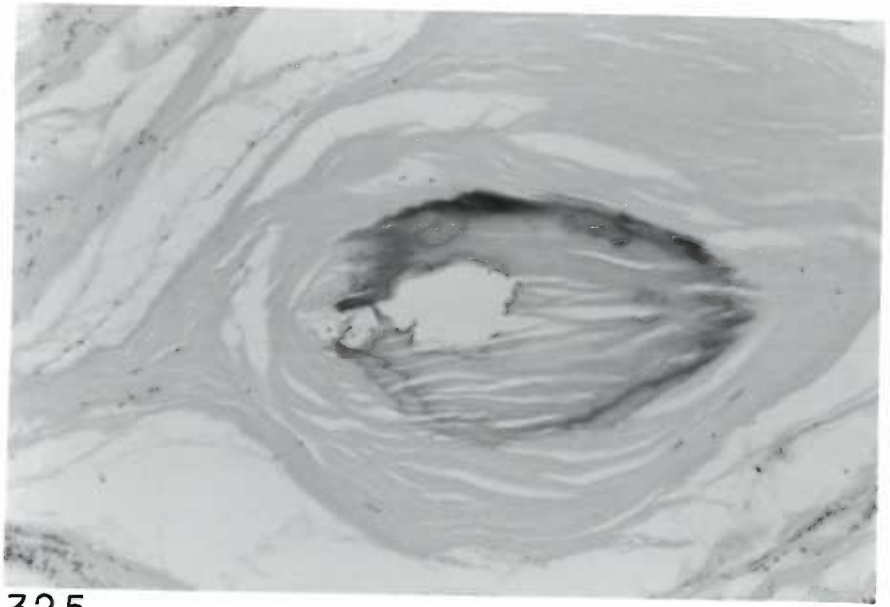


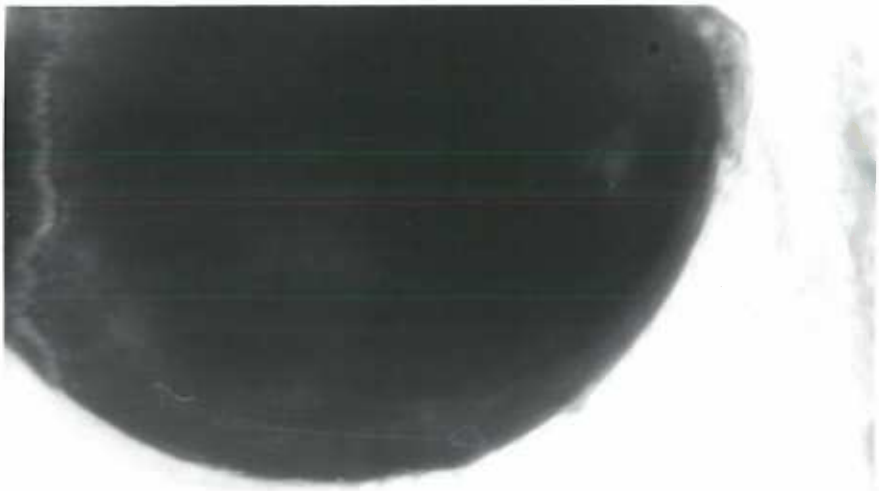
325

Figure 326:

Female, 78 years, normal breast (M-66-27). Subgross. A smooth dense calcific body, located in a fat lobule. Hematoxylin. 10X.

Figure 327:

Corresponding histology of Figure 326. Microscopy confirms the above. The mass appears smaller than in Figure 326 because it is not sectioned through its center. Hematoxylin and eosin. 10X.



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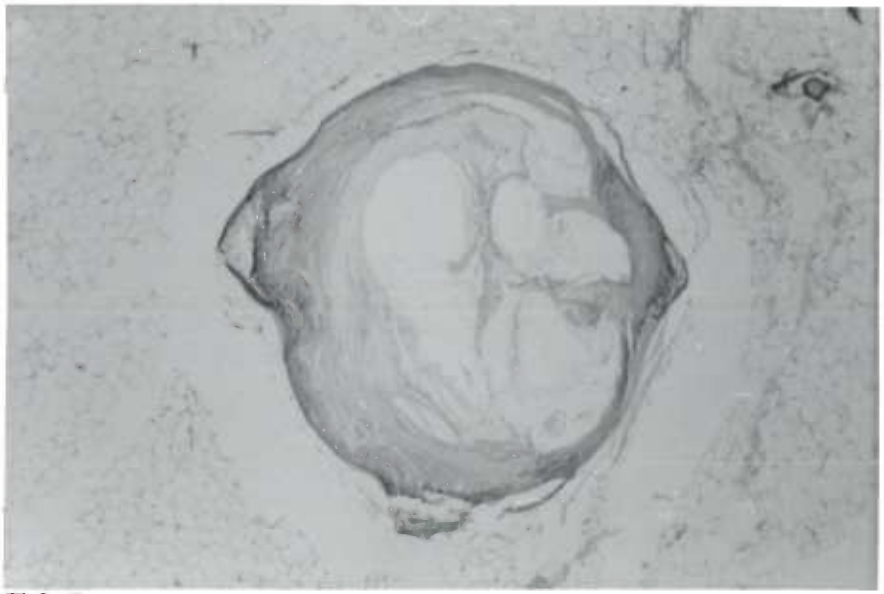


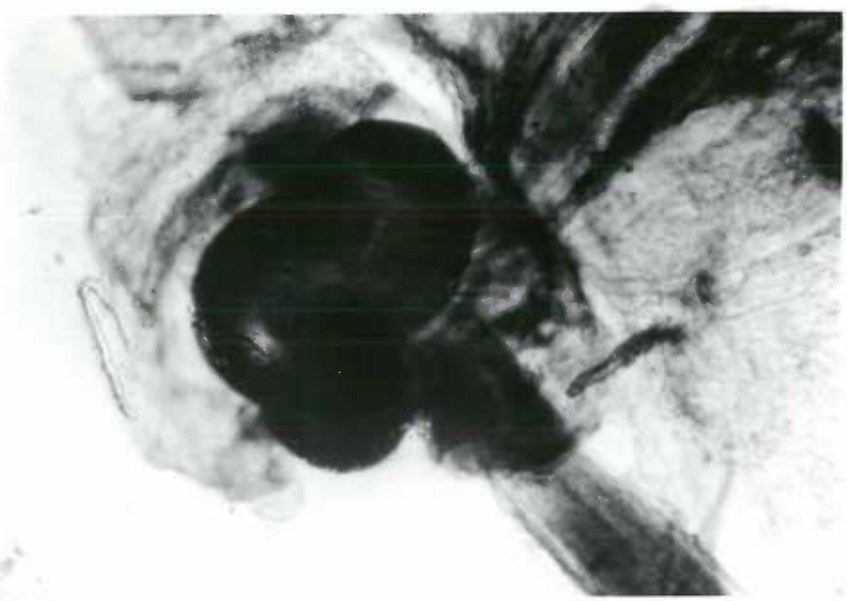
327

Figure 328:

Female, 56 years, breast with mammary dysplasia (M-66-4). Subgross. A smooth, lobulated mass with a translucent area has two entering bands of dense tissue. Hematoxylin. 9X.

Figure 329:

Corresponding histology of Figure 328. The lobulation is caused by broad bands of dense collagen. No surrounding tissue reaction is identified. Hematoxylin and eosin. 10X.



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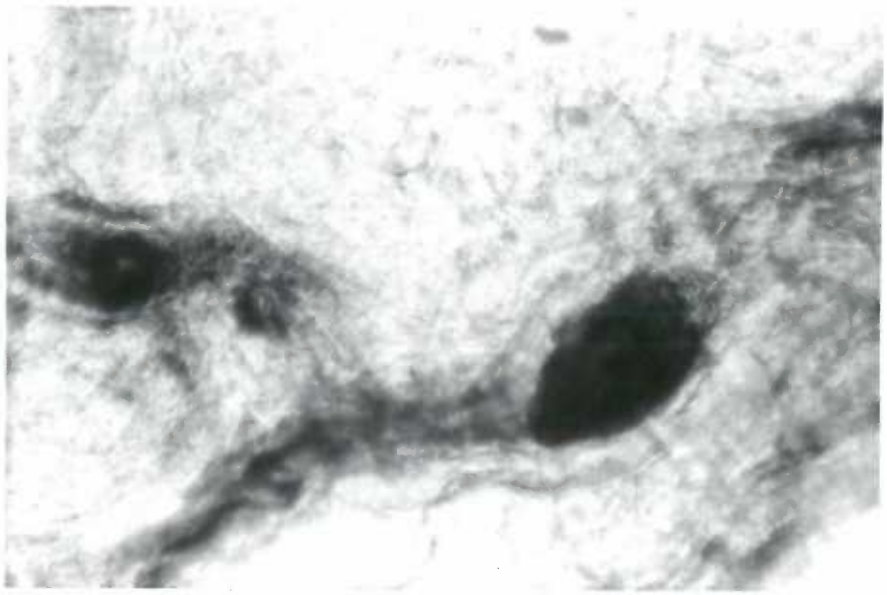
329

Figure 330:

Female, 47 years, normal breast (M-66-28). Subgross. A dense lobular structure has a large duct approaching it from the left. Hematoxylin. 10X.

Figure 331:

Corresponding histology of Figure 330. Centrally located ducts lined by normal epithelium (arrow) are surrounded by small vacuolated cells, each separated by dense staining material. A thin capsule is visible. The character of these cells and spaces is unknown, although they resemble lymphatic channels. Hematoxylin and eosin. 40X.



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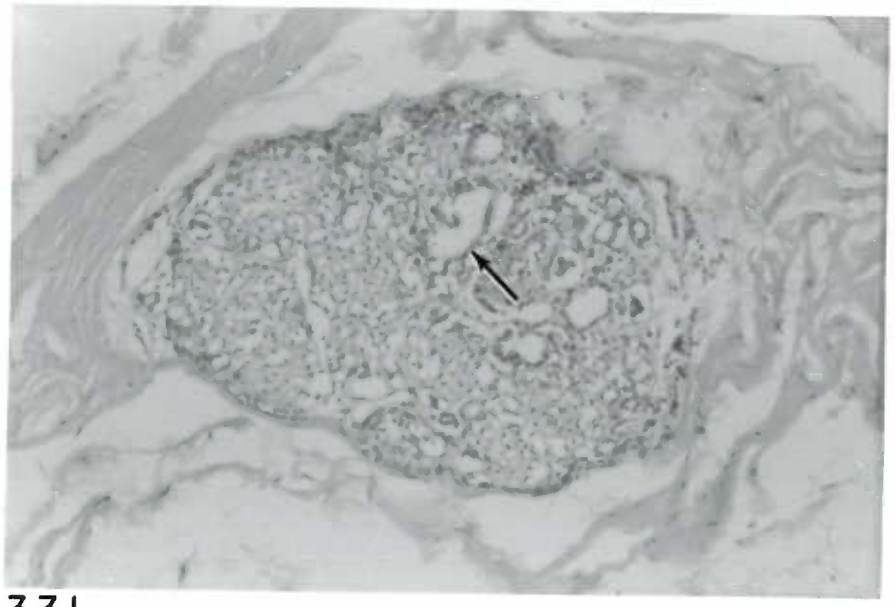

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