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A Stereomicroscopic Study of the Mastopathic Human Breast

I. Three-Dimensional Structures of Abnormal Duct Evolution and their Histologic Entity

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Stereomikroskopische Studie der durch Mastopathie veränderten menschlichen Mamma

I. Dreidimensionale Strukturen abnormer Milchgangsevolution und ihre histologischen Besonderheiten

Zusammenfassung. Mit der durch Dabelow eingeführten stereomikroskopischen Technik und einem sogen. Lochverfahren wurde eine dreidimensionale Untersuchung von Morphologie und Histogenese der durch Mastopathie veränderten menschlichen Brustdrüse ermöglicht. Die Hauptveränderung besteht demnach in Evolution und Involution abnormer Milchgänge, hervorgerufen durch ungewöhnliche hormonelle Stimulation des Organes. Die Morphologie der menschlichen Mastopathie wird wie folgt postuliert:

1. Abnorme Milchgänge werden differenziert und erzeugen eine Involution der Lobuli mit begleitender Stromafibrose.

2. Die abnorme Milchgangsproliferation wird am deutlichsten in ausgereiften Adenoseknoten. Die sogen. sklerosierende Adenose besteht aus Bündeln von Kanälchen, welche teilweise parallel angeordnet, teilweise geknotet sind.

3. In den meisten Fällen findet sich eine aus blind endigenden Kanälchen aufgebaute sogen. Adenose. Jene findet sich auch in perikanalikulären Fibroadenomen und bei Gynäkomastie.

4. Die stereomikroskopische Analyse des Verzweigungsmusters der Kanälchen erinnert an das Bauschema einer Gladiolenwurzel. Fibroadenomknoten entsprechen denmach überwiegend dem Typus einer sogen. Adenose; sie besitzen nicht die Charaktere echter Geschwülste.

Summary. With the stereomicroscopic technique of Dabelow in combination with punch sampling method, a three-dimensional approach to the morphology and histogenesis of human mastopathic breast was made possible. This afforded evidence that the key alteration is the evolution and involution of abnormal ducts (ductules) which were induced by a dyshormonal stimulation of the organ. The morphogenesis of human mastopathia is postulated as follows:

1. Abnormal ducts may develop and differentiate to form lobules and involute with stromal fibrosis.

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2. Abnormal duct proliferation is seen best in the florid type of nodular adenosis in which typical sclerosing and blunt-duct adenosis are common. Stereomicroscopically, sclerosing adenosis consists of bundles of ductules that run parallel forming whorls and knots. Lobular formation is seen rarely in this lesion.

3. For the most part blunt duct adenosis is composed of irregularly extended ductules and they were noted frequently in the florid type of adenosis. Organized dichotomous branching observed in the pericanalicular type of fibroadenoma and gynecomastia may also be recognized as blunt-duct adenosis histologically.

4. Stereomicroscopically the intracanalicular type of fibroadenoma resembles gladiola bulbs. These structures were interpreted histologically as complexly folded, multilayered ducts with a peculiar mesenchymal reaction. A similar structure was noted at the periphery of milk ducts. The three-dimensional structure of peripheral intracanalicular fibroadenoma suggests that the lesion is related to adenosis rather than to a neoplasm.

Because of its prevalence and high mortality rate among females past middle age, carcinoma of the breast and its closely related disorders have been investigated extensively (Geschickter, 1947; Haagensen, 1956). Among the latter conditions, the mastopathic lesion is regarded generally as the most important disorder since the lesion is clinically considered as precancerous and there is morphological resemblance to cancer. The condition is known under many synonyms which include mastopathia cystica chronica, chronic cystic mastitis, cystic disease, mammary dysplasia, etc. The pathologic anatomy of mastopathic breast consits of unbalanced proliferation of both epithelial and stromal elements (Geschickter, 1947; Haagensen, 1956), and Foote and Stewart (1945) classified eleven types of basic alteration in this lesion. Histologically three subtypes are recognized (Geschickter, 1947; Kuzma, 1966); mastodynia, adenosis and cystic disease. They are of similar composition in basic histologic units but are quantitatively different in the proportion of cysts for example. Because of the variegated histology in any given specimen, the key alteration of mastopathic breast is not clearly understood.

The three-dimensional approach, frequently used in the study of mammary glands of small animals (Nandi, 1958; Prop, 1966), is claimed to be superior to the ordinary, paraffin-embedding technics for the analysis of physiological responses of the human breast (Ingleby, 1942; Dabelow, 1957). However, the method has not been widely applied in the study of pathologic human breast (Ingleby, 1942; Ingleby and Gershon-Cohen, 1954; Goldschmidt and Hueck, 1953). The reconstruction of mastopathic breast has been successfully accomplished only with simpler structures such as cysts (Loeschcke, 1930) and fibroadenoma (Fraenkel, 1934; Demetrakopoulos, 1958).

For further analysis of this controversial lesion, we have employed a stereomicroscopic technique on human breasts according to the method described by Dabelow (1957). For the histopathologic confirmation of the specific changes in thick sections, the punch technique and serial sectioning were used. The results of these studies have already been published in abstracts (Oota and Tanaka, 1959, 1961). Our observation showed that the pathological evolution and involution of lactiferous ducts are the key alteration of the mastopathic breast. The present paper provides full information on the three-dimensional features of the mastopathic breast and discusses the significance of duct evolution for the morphogenesis of adenosis.

Material and Methods

Eleven cases of typical mastopathic breasts were selected for this study from biopsy samples obtained at the Cancer Institute, Japanese Foundation for Cancer Research, Tokyo, Japan from 1958 to 1960. The ages of patients and histologic evaluation of mastopathic lesions in each case are listed in the table. There was no selection based either on age distribution nor was the endometrium examined at the time when the breast tissues were submitted for analysis. For controls, breasts from four autopsies of non-pregnant adult females, 18 to 25 years old who died of acute illness were used. One of these patients died of cerebral hemorrhage complicated by acute leukemia, two of acute infection and in one the death occurred during operation for abdominal angiothrombosis. At autopsy the whole breasts were dissected from the skin. After fixation in fresh 10% formalin for a few weeks, the specimens were serially sectioned and the topographical findings were schematically recorded.

All surgical specimens and the selected pieces of autopsy samples were cut serially with a frozen-section microtome. The sections were about 1 mm in thickness. All slices were threaded in sequential order and were washed in running water for 24 to 48 hours to remove formalin. Some of them were bleached in a 10% hydrogen-peroxide solution if the tissues were yellowish. The bleached samples were rewashed in running water for 24 hours. Before staining, all slices were treated with 70% ethanol for a few days to remove excess fat which may interfere with the staining. Samples were stained with either hematoxylin or 1% alum-carmin acid solution (Dabelow, 1957). The staining times varied from one to several hours. After proper differentiation, the specimens were rewashed in running water and dehydrated by ethanol. The whole process of dehydration took nearly three weeks.

Table. *Ages of patients and histology of specimens*

Case No.	Age	A	B	C	D	E	F	Diagnosis
R-35270	43	+++	+++			++	++	Severe adenosis nodular type
R-35292	45	+	+		+++	+		Fibroadenoma, intracanalicular type
R-39652	51	+	+					Mastopathy, diffuse, slight
R-39717	22	++	++	+++		++	++	Mastopathy, cystic disease
R-39912	35	++	+++	+		++	+	Severe adenosis nodular type
R-42621	31	+++	++	++			+	Mastopathy, cystic disease
R-42804	39		+		+++			Fibroadenoma, pericanalicular type
R-43065	43	+	++	+	+			Mastopathy adenosis
R-45953	25		+++	+		++	++	Mastopathy, cystic disease
R-46042	32		+	+				Mastopathy, adenosis
R-49773	44	+	+					Severe adenosis, nodular type

A = Sclerosing adenosis; B = Blunt duct adenosis; C = Cysts; D = Fibroadenomatous lesion; E = Duct epithelial hyperplasia; F = Fibrosis. + = slight, ++ = moderate, +++ = severe.

The thick preparations were cleared in a mixture consisting of four parts of each of chloroform and cedar oil, two parts of origanum oil, one part each of absolute alcohol and carbol crystal (Romeis, 1948). Finally, thick preparations were embedded in canada balsam within plastic frames about one millimeter in thickness on the clean microscopic slides. Mounted specimens were kept overnight in a 25° C incubator with a weight placed on the coverlips to flatten the tissues. They were kept at room temperature for several weeks before examination. Complete views of the mounted specimens were recorded on films using a close-up attachment.

Punch sampling of specimens was accomplished by means of circular steel blades of two different diameters, 0.5 and 1.0 cm. In the process of applying this technic, embedding media were removed by xylene. The punch specimens were treated with celloidin and embedded in paraffin. The whole specimens embedded in celloidin-paraffin were cut serially at a thickness of about 10 μ. Sections were stained with hematoxylin and eosin. On occasion, the periodic acid Schiff reaction was used.

Small but typical foci of blunt duct and sclerosing adenosis were reconstructed in wax models. Serial sections were enlarged photographically, up to 140 times, and the images were transferred on dental wax sheets of about 1.5 mm in thickness. This procedure created some longitudinal exaggeration (less than 8%); however, its was quite adequate to analyze three-dimensional relation of proliferating ductules.

Observations

1. Controls (Figs. 1—3)

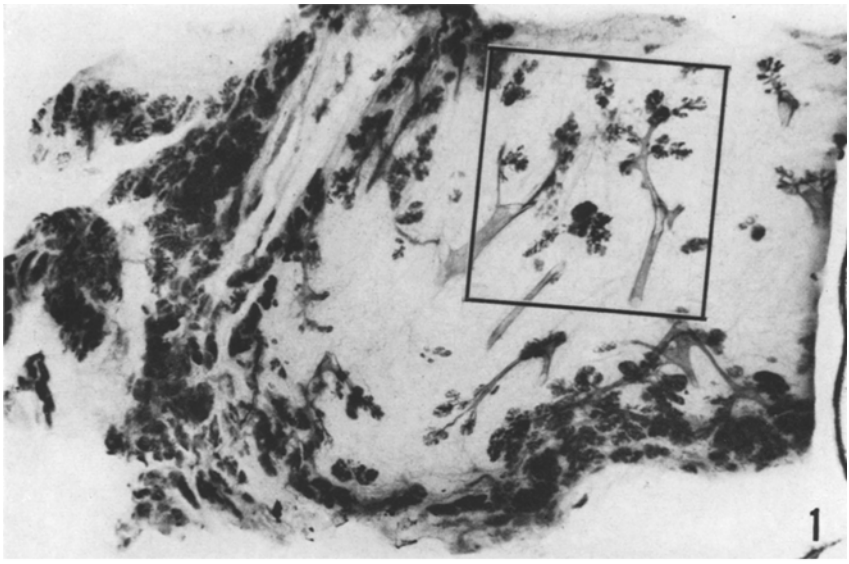
Mammary glands of four controls appeared to confirm all details of the previous observation reported by others (Ingleby, 1942; Ingleby and Gershon-Cohen, 1954; Goldschmidt and Hueck, 1953; Dabelow, 1957). The significant findings were the following: The mammary glands of non-pregnant adolescent females consisted of ducts and immature lobules (Figs. 1, 2). The main lactiferous ducts originated from the nipple and extended in stroma with organized dichotomous divisions until they ended in terminal ductules which formed lobules (Figs. 1, 2). The ductal walls of the young adult female breast were highly infolded or ridged along the longitudinal axis, and the luminal dilatation common in breasts of aged subjects was noted rarely.

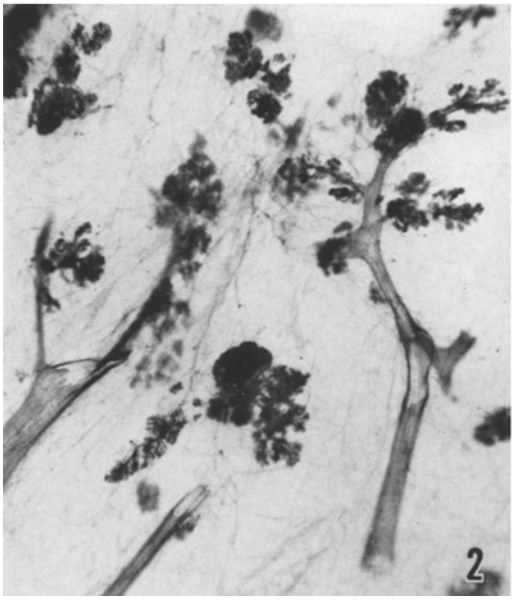
The lobules consisted of dichotomous divisions of short ductules (Fig. 3), whose diameter was smaller than that of terminal ductules, and ended blindly (Fig. 3). The terminations were slightly dilated. In non-pregnant subjects, a few divisions of ductules were seen in lobules (Fig. 3). The distribution and sizes of lobules varied considerably from one place to another in a given breast, but they were most prominent at the periphery (Fig. 1). In pregnancy or the progesterone dominant phase of menstrual cycle, lobules became hypertrophic due to increasing numbers of ductules.

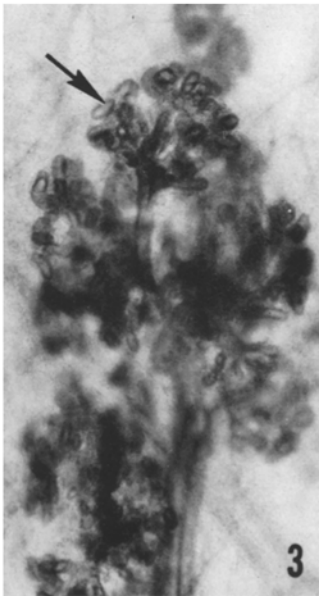
The gland became atrophic being replaced by the stromal fibrosis when the breast underwent involution in old age and abnormal distention of ducts was seen commonly. The involution of ductules proceeded retrogressively leaving no epithelial elements in the stroma.

2. Mastopathic Breasts (Figs. 4—34)

Under the stereomicroscope, the most significant feature of the mastopathic breast was proliferation of abnormal ducts (Goldschmidt and Hueck, 1953; Oota and Tanaka, 1959, 1961). A typical example of such alteration was well seen in a nodular lesion (Figs. 4, 5). Such specimens were often diagnosed as florid type of







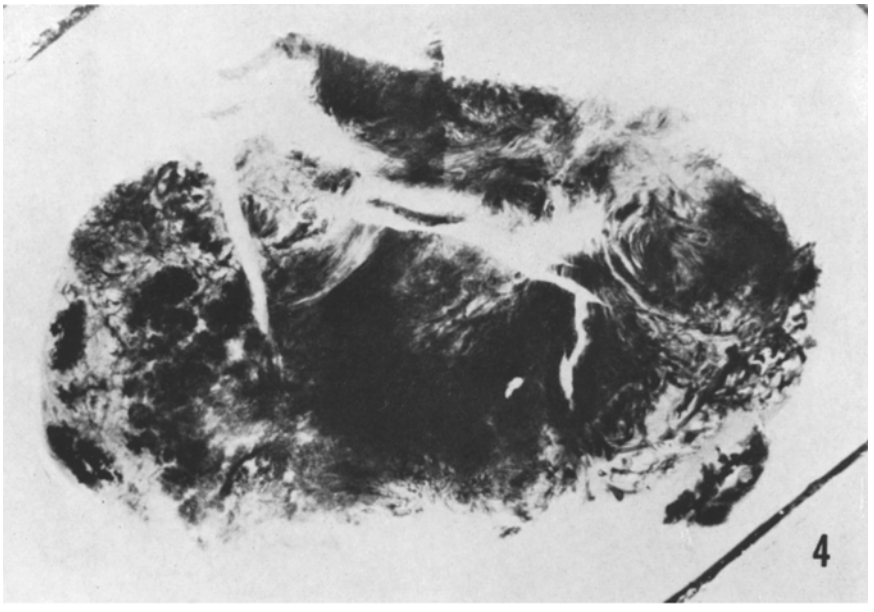
Cases used for illustrations: R-35270, Figs. 4—12 and 15—17; RA-35292, Figs. 26—30; R-39652, Figs. 13, 14; R-46621, Figs. 18—22; R-42804, Figs. 33, 34, 35; R-43065, Figs. 24, 25, 31, 32; R-46042, Fig. 23. Abbreviation: (H) hematoxylin stain, (C) Carmin acid stain, (HE) hematoxylin-eosin stain

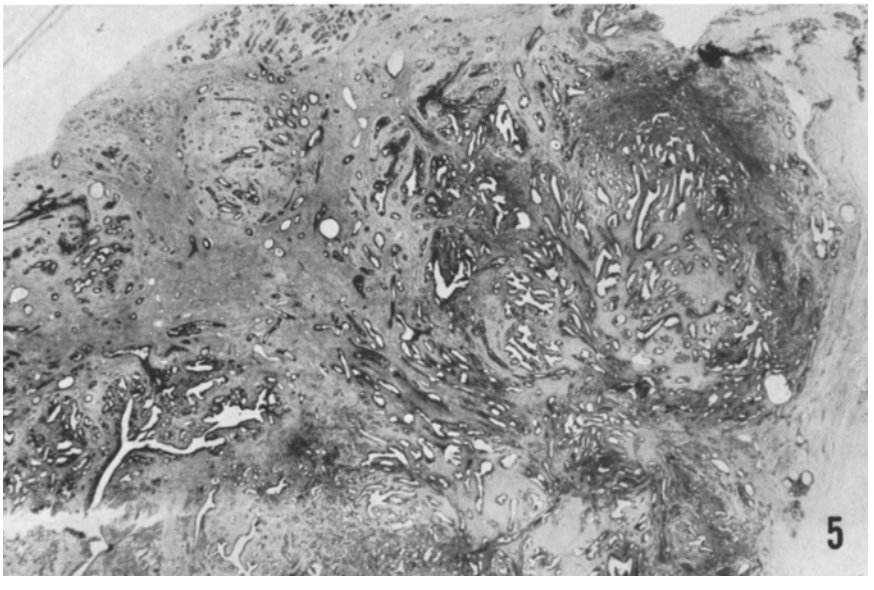
Figs. 1—3. Normal breast. A thick preparation from a 22 year old female. Death following postoperative abdominal bleeding

Fig. 1. A low-power view of the breast showing lactiferous ducts and lobules which predominate at the margin (H) $\times 3.7$

Fig. 2. A high-power view of the area marked in Fig. 1 showing details of normal lactiferous ducts. (H) $\times 6.1$

Fig. 3. Details of a lobule composed of dichotomous divisions of ductules which end bluntly (arrow). (H) $\times 100$





Figs. 4—8. Nodular lesion, general view

Fig. 4. General view of a thick preparation diagnosed as a nodular adenosis demonstrating abnormal proliferation of ductules. No lobules are seen. (H) ×4.4

Fig. 5. Histology of the section adjacent to that of Fig. 4 confirms stereomicroscopic interpretation (HE) ×6.5

adenosis and showed an admixture of various histologic alterations (Foote and Stewart, 1945; Haagensen, 1956; Kuzma, 1966) including sclerosing adenosis, blunt duct adenosis and fibroadenomatous lesion, particularly of intracanalicular type.

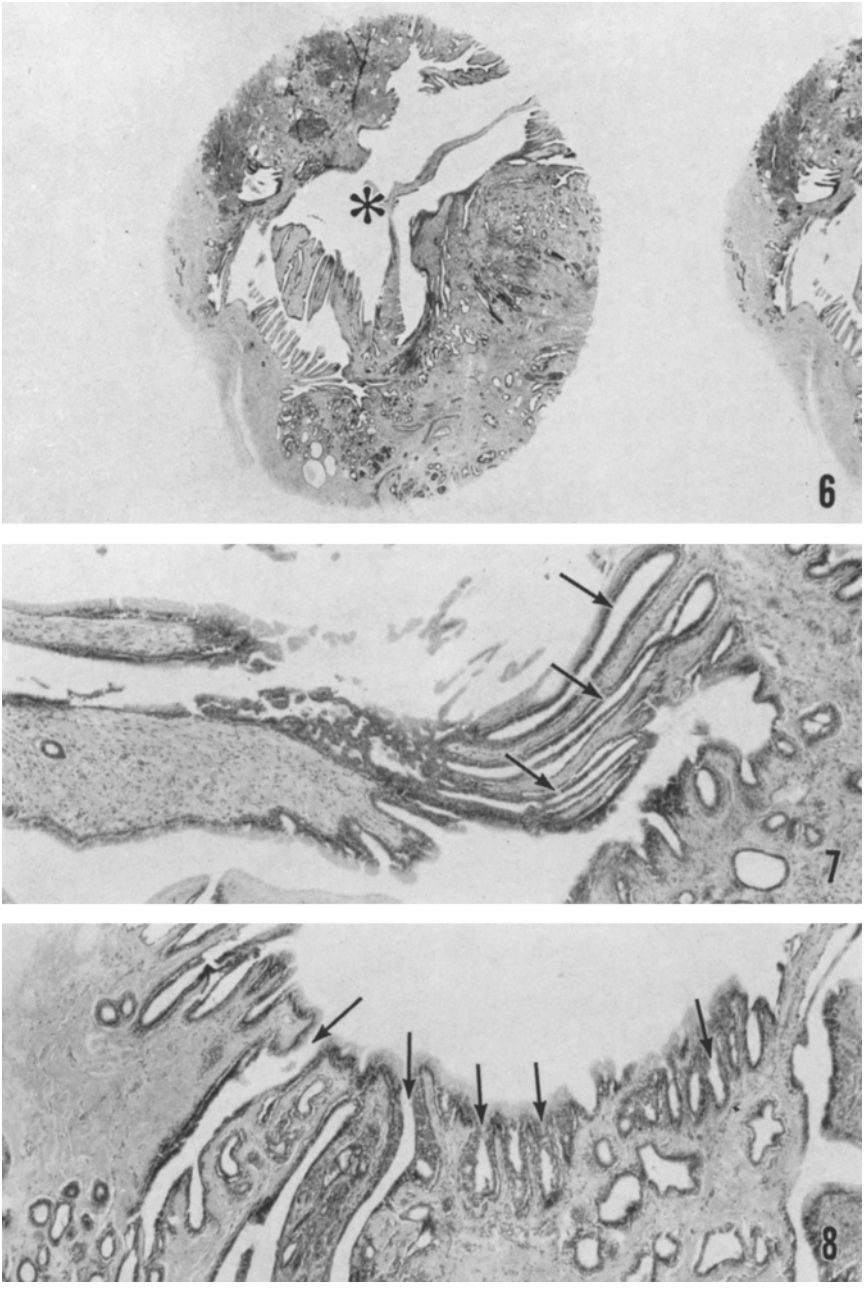
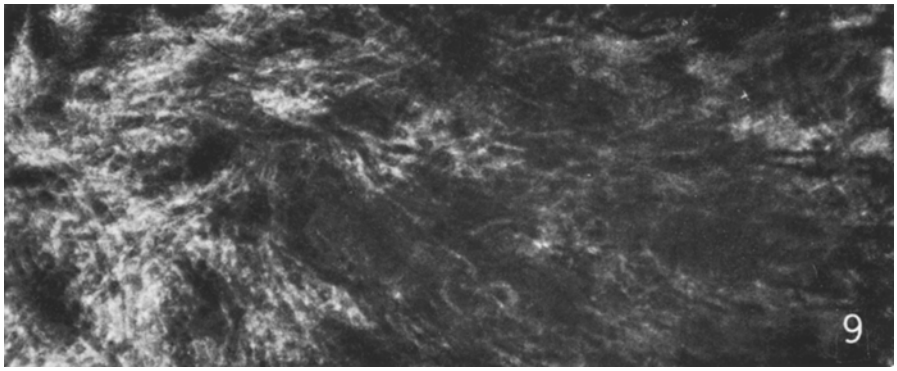
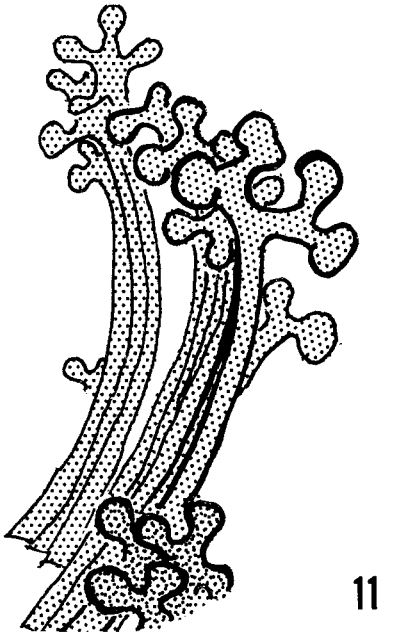
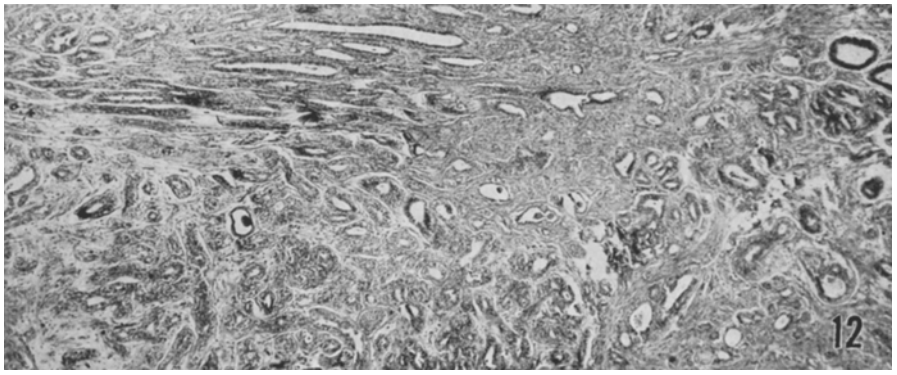


Fig. 6. Serial sections of a punch specimen from the same case. Note the presence of a large duct in the middle with serrated wall (Asterisk). (H) ×6.0

Figs. 7 and 8. These two photographs of serial sections of the same specimen used in Fig. 6 show evolution of multiple lactiferous ductules (arrows) from the large duct seen in Fig. 6. (HE) ×100. Axial section in Fig. 7 and cross section in Fig. 8







Figs. 9—14. Sclerosing adenosis

Fig. 9. Sclerosing adenosis in a thick preparation. In this picture, details are not resolved but the presence of abnormal ductules forming bundles is seen. (H) ×25

Stereomicroscopically, tissues were replaced by numerous ducts and ductules which had proliferated with insignificant organization or lobular formation (Figs. 4, 5). At the center of these specimens, several large, flattened ducts were seen (Fig. 6). These ducts must have originated from the stem duct. However, confirmation of such relationship was hardly possible in surgically resected specimens. Details of duct arrangement were difficult to analyze by stereomicroscopy particularly at the center of specimens mainly because of the presence of closely packed, proliferating elements (Fig. 4). At the periphery, structure and arrangement of proliferating ducts were frequently discernible. From comparison of the stereomicroscopic appearance of the lesion with histology of the same site in the punch specimens, the following became evident: 1. The typical *sclerosing adenosis* (Figs. 9 to 12) consisted of a parallel array of ductules which sprouted abruptly from large, flattened ducts (Figs. 7, 8). Abnormal ductules ran straight or curved over or under other bundles of the same or different stem duct (Figs. 9, 10). The general appearance of this abnormal proliferation may be described as "bundles of noodles' forming whorls or knots (Oota and Tanaka, 1959, 1961). The end of each ductule ended in a flask or digital shape (Figs. 10, 11) resembling an acinus ending. The whole structure created by parallel ductules with club-shaped endings is reminiscent of a bouquet (Figs. 10, 11). The contribution of parallel ductules in forming sclerosing adenosis was confirmed by the reconstruction of a small focus demonstrated in Figs. 13 and 14. 2. The stereomicroscopic structure of *blunt duct adenosis* (Figs. 15—17) was a ductal proliferation of unorganized pattern (Figs. 15, 16). The shape of ducts and pattern of ductal arrangement varied considerably and intermediate forms between blunt duct adenosis and sclerosing adenosis or intracanalicular fibroadenoma were noted. Under high magnification, a lacy appearance or dentation was seen within ductal lumina (Fig. 16). These changes were identified as either epithelial hyperplasia or duct papillomatosis histologically. 3. Abnormal duct proliferation was also noted near the terminal branching of lactiferous ducts (Figs. 18—22). The pathological evolution may be multiple or single, but typical lobules are seldom formed. Ductal evolution of this type was observed most frequently in specimens diagnosed as cystic disease. This alteration is considered to be important for the morphogenesis of cystic disease and will be described separately (Tanaka and Oota, 1969). 4. In specimens diagnosed as florid adenosis, significant alterations of acini were occasionally noted. Examples of such alteration are illustrated schematically in Figs. 23—25. A unique lesion illustrated in Fig. 25 has been described by Dabelow (1957) in a pregnant breast. Histologically, it may be interpreted as blunt duct adenosis or microcyst formation.

Fibroadenoma of both intra and peri-canalicular types, was also subjected to study by this method. The *intracanalicular type* (Figs. 26—30) consisted of flattened large ducts without typical lobules (Fig. 26, 29). The wall of all flattened ducts were

Figs. 10 and 11. A high-power view of ductules with club-shaped endings noted in the previous specimen. (H) ×75. The schematic interpretation of abnormal ductules in the previous two pictures is shown in Fig. 11

Fig. 12. Histology of the punch specimen which includes the lesion shown in Figs. 9 and 10. Ductules cut through the axial plane are seen at the upper left corner and those met in cross section are at the bottom. The histology is compatible with that of sclerosing adenosis. (H) ×25

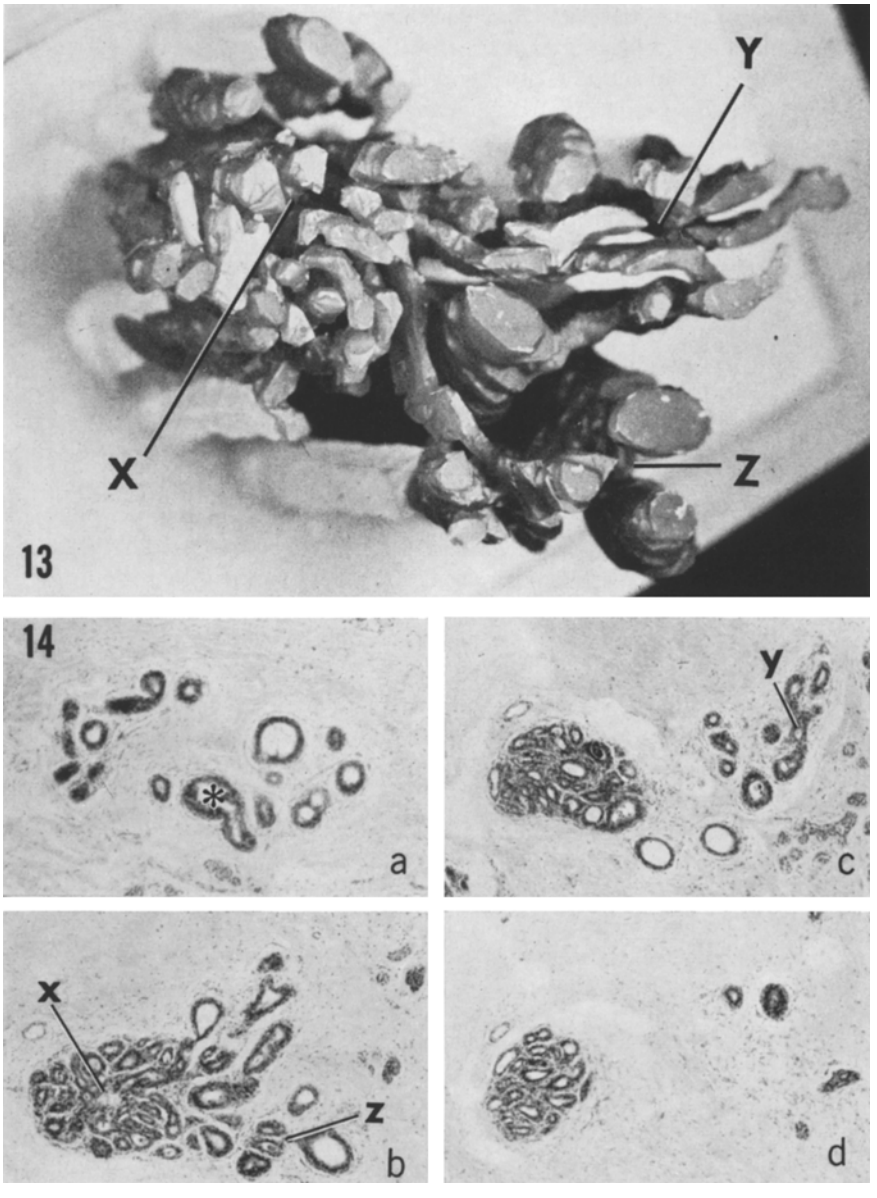
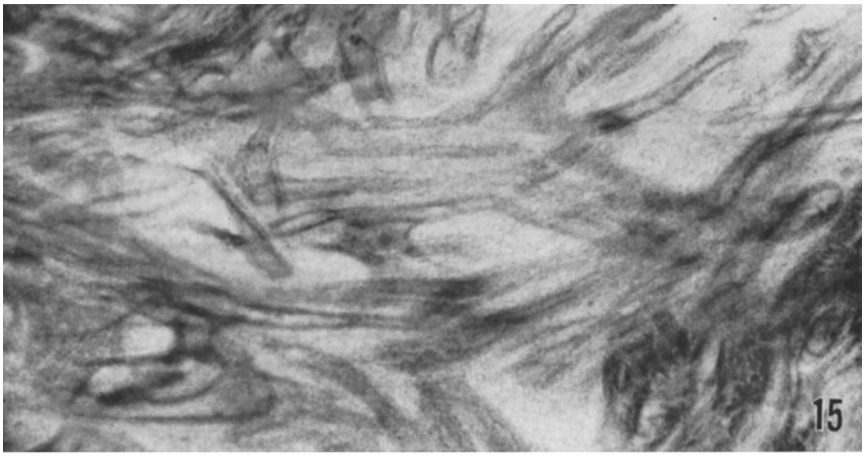
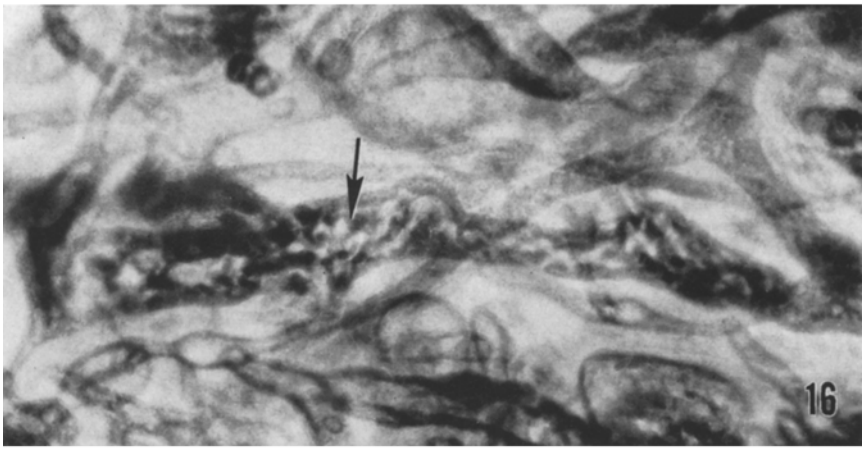
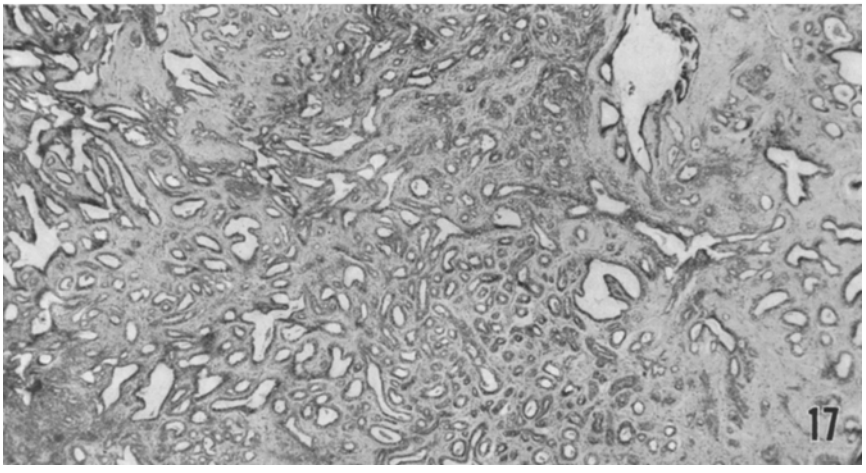


Fig. 13. A wax-reconstruction model of a minute focus of sclerosing adenosis. Details of duct configuration cannot be appreciated but it is clear that the lesion is composed of packed ductules at the left (*X*), elongated tubules at the right (*Y*) and ductules with cystic dilatation (*Z*)

Fig. 14a—d. Histology of serial sections used for reconstruction. (HE) ×100. Photographs a to d are arranged so that sequence corresponds to the order from the bottom to the top of the model. The ductules at the left (*x*) may be an abortive lobule. The ductule (asterisk) in Fig. 14a is responsible for creation of this lesion. Letters (*x*, *y*, *z*) correspond to the sites marked by the same letters in Fig. 13





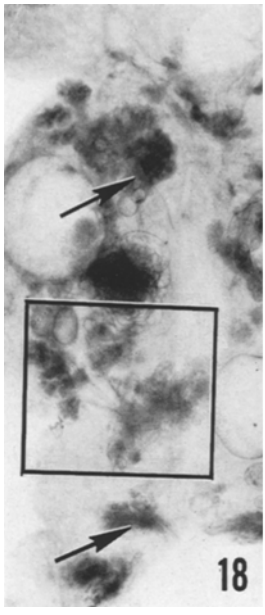


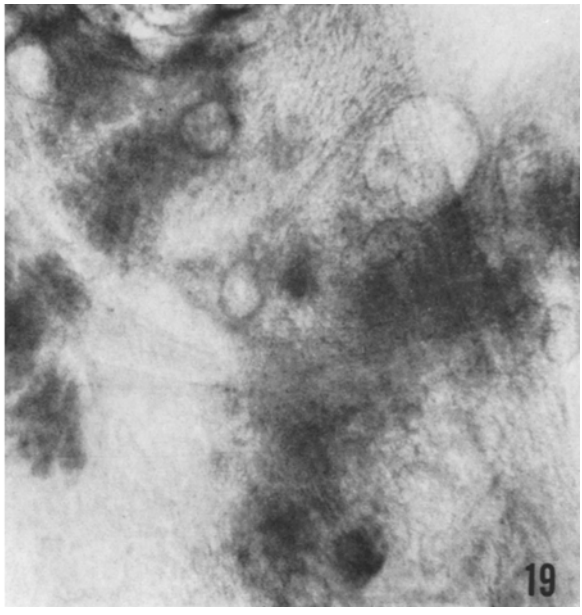
Figs. 15—17. Blunt duct adenosis

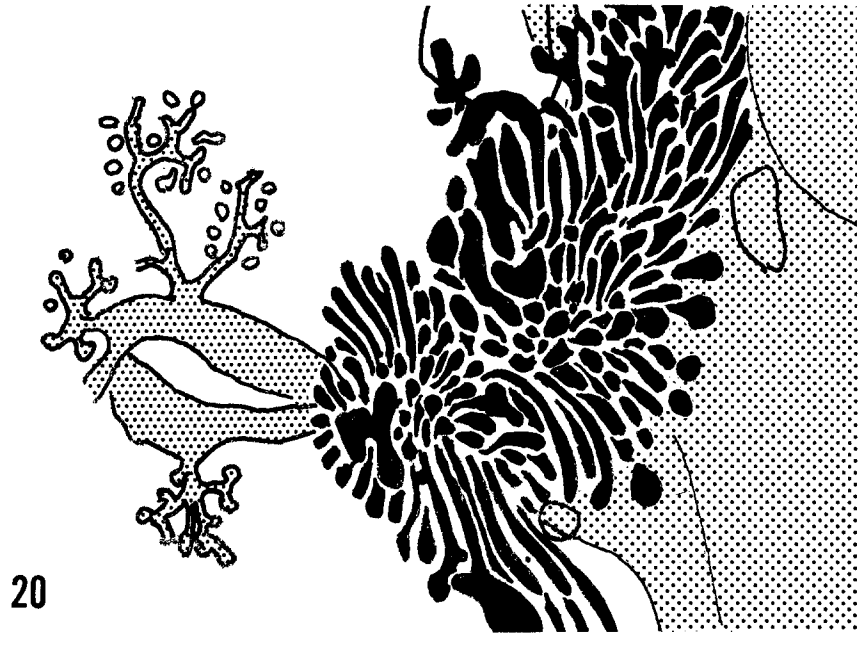
Fig. 15. Irregularly distended ductules in a nodular lesion (H) ×100

Fig. 16. Epithelial hyperplasia (arrow) in blunt duct adenosis. (H) ×100

Fig. 17. Histology of the same specimen confirms the presence of many ductules with no lobules. (HE) ×18



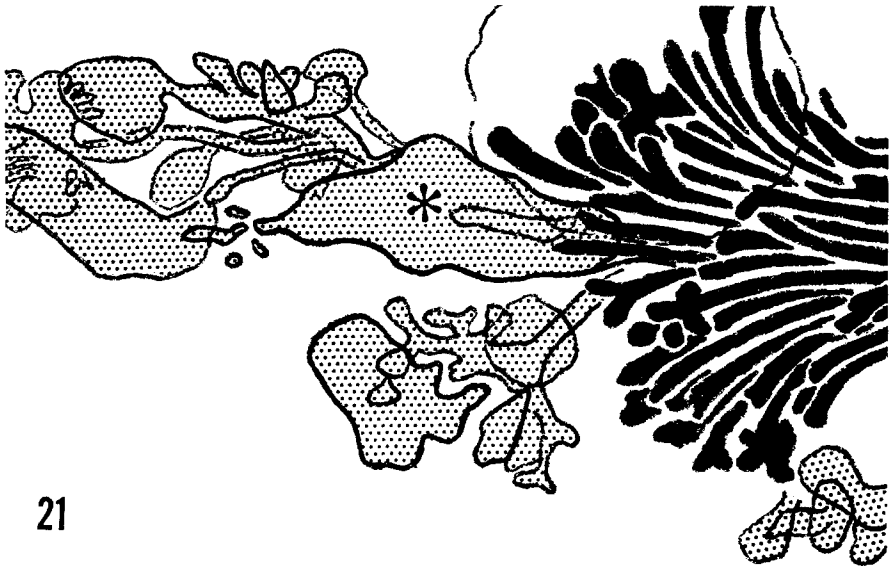


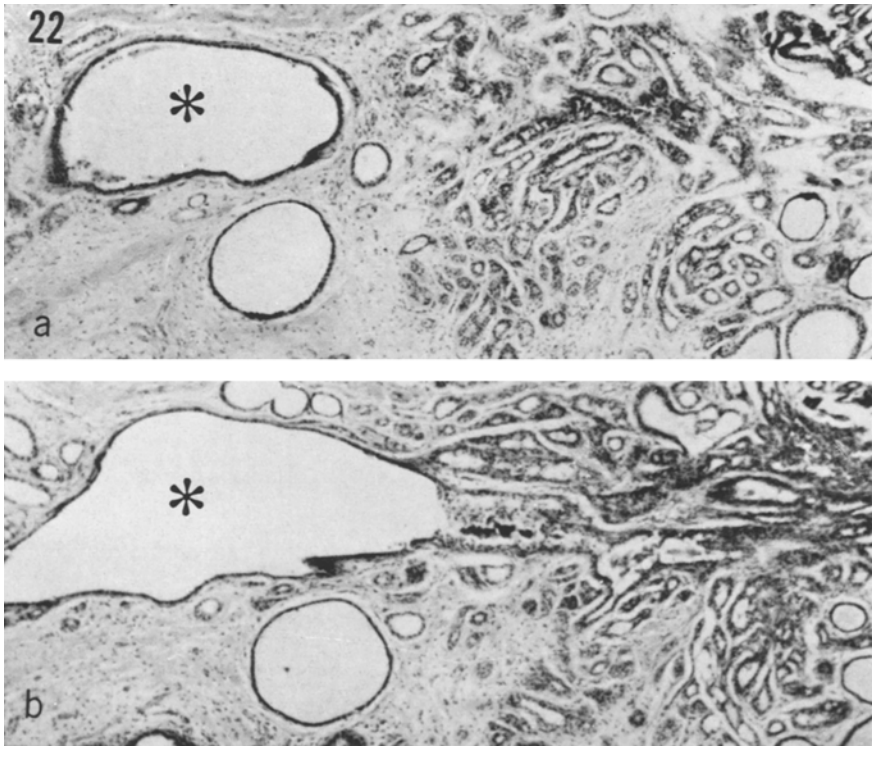


Figs. 18—22. Peripheral type of duct evolution noted in cystic disease

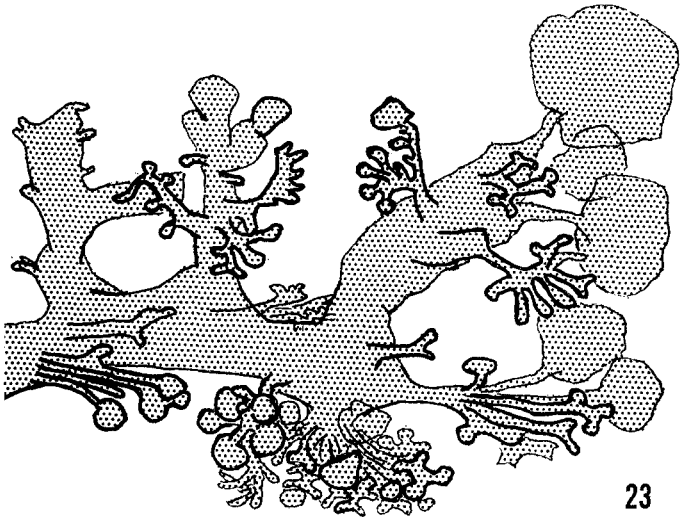
Fig. 18. A low-power view of a thick preparation shows a large duct in the middle and abnormal ductules at multiple sites (arrows). (C) ×7

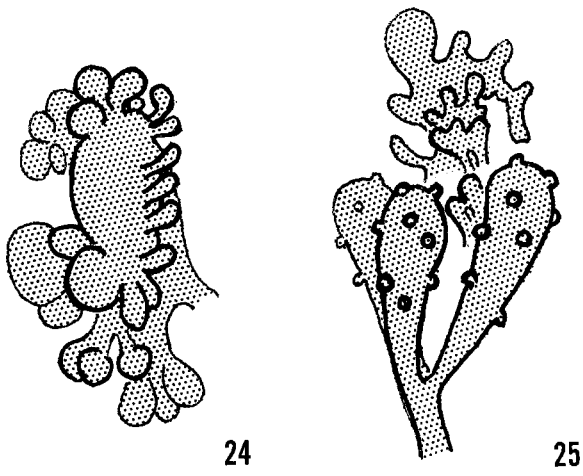
Figs. 19 and 20. A high-power view of the marked area in Fig. 18 shows the presence of abnormal proliferation near the branching of two lactiferous ducts. (C) ×35. This is illustrated schematically in Fig. 20. Black ductules represent abnormal ductules





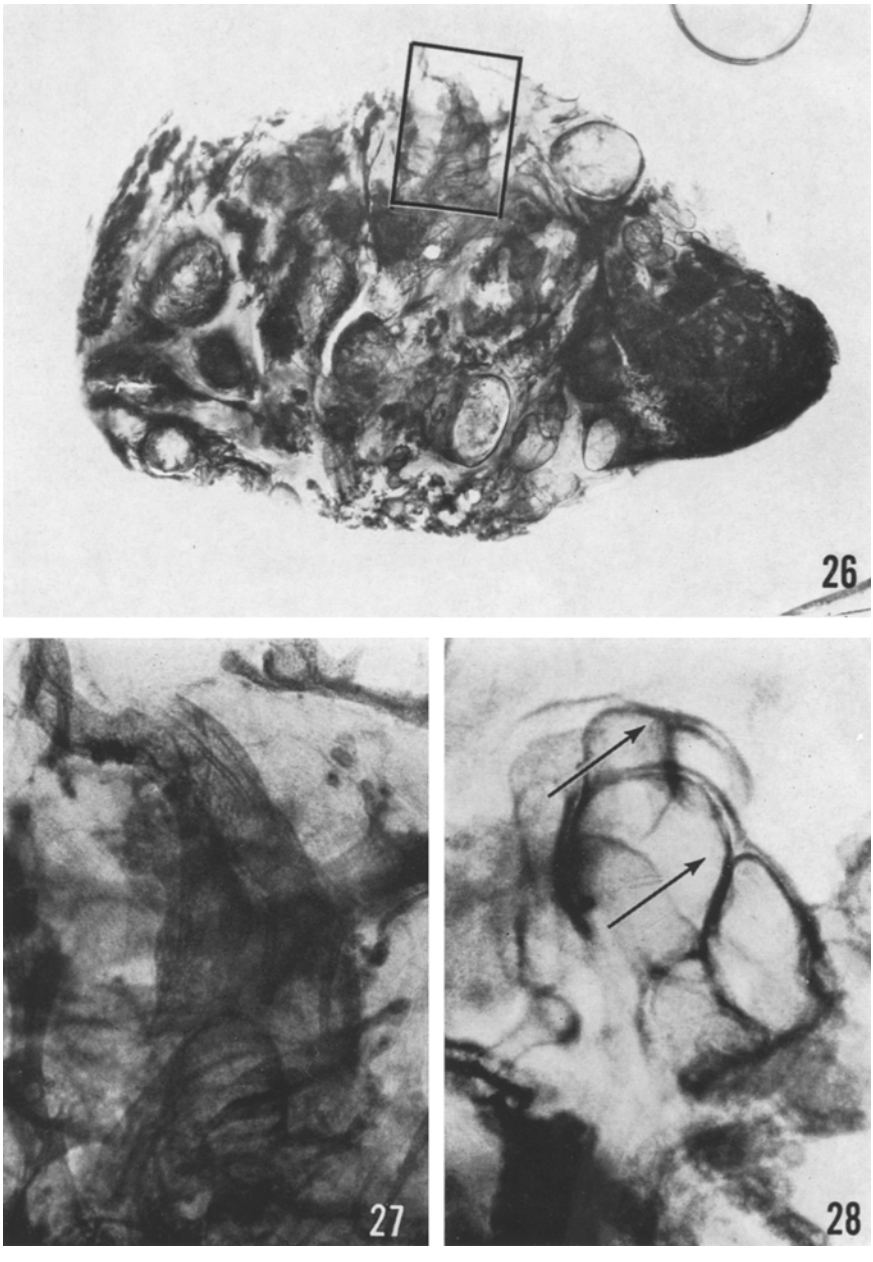
Figs. 21 and 22a and b. A schema of abnormal ductule proliferation noted in another specimen in Fig. 21. Black ductules are of abnormal type. Fig. 22a and b are taken from serial sections of the punch specimen which included the lesion shown in Fig. 21 and the photographic sequence a to b corresponds to the order from the surface to the bottom of the specimen under the observation. (HE) $\times 125$. These illustrations attest the presence of abnormal ductules in the pattern illustrated in Fig. 21. Asterisks in each picture indicate the same ductule





Figs. 23—25. Abnormal acinar endings in mastopathic breasts

deeply indented (Figs. 28). When the ducts formed a multilayered structure, they resembled gladiolus roots (Goldschmidt and Hueck, 1953). Abnormal ductal evolution resembling blunt duct adenosis or sclerosing adenosis may be associated with this lesion (Fig. 27). Minute foci resembling intracanalicular type of fibroadenoma have been described in the mastopathic lesion (Foote and Stewart, 1945). In our present study, the presence of such structures was recognized near the ends of normal-looking glands (Figs. 31, 32). The flattened ductules assumed a spherical shape (Fig. 31) and dichotomous divisions resembling rudimentary lobules were seen. These structures were identified as fibroadenomatous lesions by the punch technique (Fig. 32). In contrast to the unique morphology of intracanalicular fibroadenoma, the *pericanalicular type* was composed of ducts with organized divisions but failed to form typical lobules (Figs. 33—35). Stereomicroscopically, the

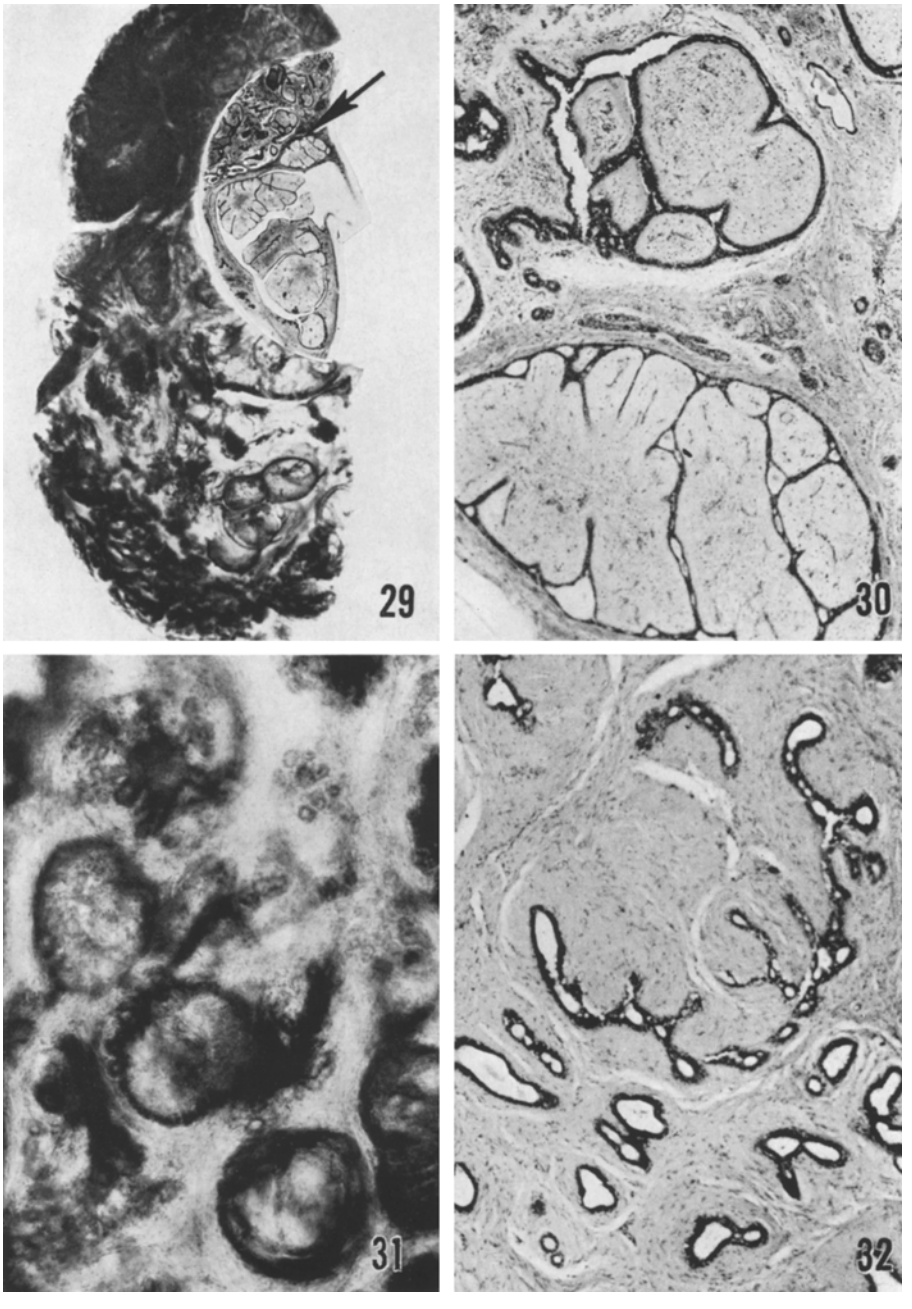


Figs. 26—31. Intracanalicular fibroadenoma

Fig. 26. A thick preparation showing peculiar arrangement of ductules and ducts. (H) ×6.0

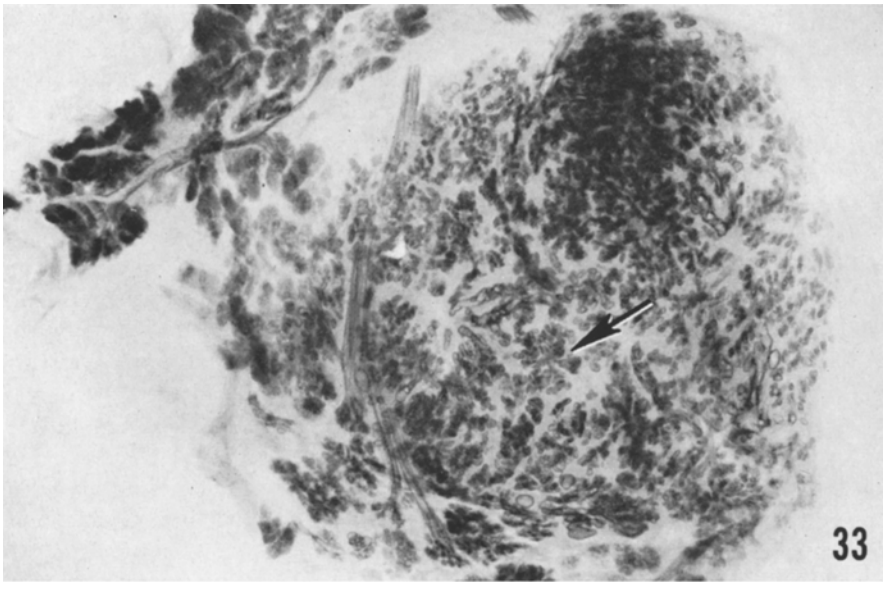
Fig. 27. A high-power view of the area marked in Fig. 26 showing a flattened duct, the most common structure in intracanalicula fibroadenoma. (H) ×24

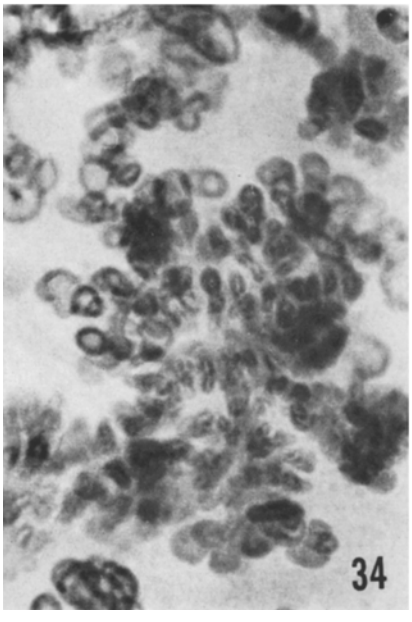
Fig. 28. A cross section of a flattened duct (arrows) shows highly idented wall. (H) ×95

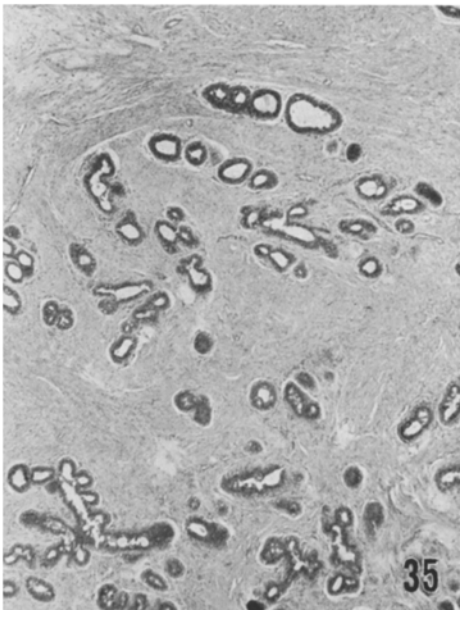


Figs. 29 and 30. Another example of intracanalicular fibroadenoma. Insert within a semicircle shows punch specimen. (H) ×4.5. A high-power view of the insert showing typical fibroadenoma histology in Fig. 30 (indicated by arrow in Fig. 29). (HE) ×80

Figs. 31 and 32. A stereomicroscopic view of a microfibroadenomatous lesion in Fig. 31. (H) ×100. Note the similarity between abnormal ductules of this photograph and typical intracanalicular fibroadenoma illustrated in the previous figures. Histology of this lesion is shown in Fig. 32. (HE) ×100







Figs. 33—35. Fibroadenoma, pericanalicular type

Fig. 33. A thick preparation showing well organized pattern of ductules without differentiated lobules. (C) ×6.0

Fig. 34. A high-power view of the duct terminal resembling immature lobules (indicated by arrow in Fig. 33). (C) ×70

Fig. 35. Histology of the adjacent specimen shows blunt ducts and increased stromal elements. This histology may not be representative for the pericanalicular type of fibroadenoma but the stereomicroscopic appearance is hardly distinguishable from the two preceding illustrations. (HE) ×40

appearance was hardly distinguishable from that of certain types of blunt duct adenosis as in gynecomastia.

The structure of abnormal ducts and ductules was more or less distorted in specimens with advanced fibrosis. The ducts were irregularly distended and the periphery of the ductules dilated to give a cystic appearance. These structures were interpreted as cysts by ordinary microscopy (Ingleby, 1942). It was quite rare to find the typical "bundles of noodles" in nodular lesions with advanced fibrosis even though the presence of sclerosing adenosis was reported histologically. The ductal epithelium of such specimens showed various signs of regressive alterations such as smaller cellular size and pyknotic nuclei. Various other histologic alterations such as apocrine metaplasia, cystic dilatation of ducts with or without secretions and intraductal papillomatosis may be associated with abnormal ductules. These changes were considered to be secondary.

Discussion

Stereomicroscopically, the most significant feature of human mastopathy was the evolution of abnormal ducts (or ductules) which failed to form typical lobules and organized dichotomous divisions (Oota and Tanaka, 1959, 1961). Alterations caused by the ductal evolution corresponded to adenotic changes seen histologically as confirmed by the punch technique. From our present data, one can distinguish two types of abnormal ducts by their original sites of evolution, i. e. peripheral or proximal. Both types were probably induced by the same mechanism, but led to different clinical and pathological manifestations. The proximal type was characterized by the evolution of large ducts which formed a tumorous lesion called nodular adenosis or fibroadenoma. The peripheral type involved lactiferous ducts near their terminal branchings. The abnormal ductules were of terminal nature and the change is considered to be the key alterations of cystic disease (Tanaka and Oota, 1969). The three-dimensional structures of these ducts differed considerably from normal; however, abnormal ducts of adenosis are qualitatively normal since they are known to react to physiological humoral stimulations. Disappearance of mastopathic lesion during and after the pregnancy would support such conclusions.

The advantage of the stereomicroscopic method for the study of physiological mammary glands has been confirmed and the method appeared to be useful for the study of mastopathic breasts. Several authors have attempted to apply the stereomicroscopic method to human mastopathic breasts but failed to reveal details of abnormal ducts. Ingleby (1942) classified simple and secretion cystic disease. Later Ingleby and Gershon-Cohen (1954) classified adenosis in four groups: type A, well formed lobules with hyperplasia of epithelial and myoepithelial cells; type B, lobules consisting of dilated ductules with hyperplasia of myoepithelium; type C, similar to type B but with scanty or absent myoepithelium; type D, sclerosing adenosis. None of the first three types fits our present classification and no "bundles of noodles" were found in the type D lesion. Goldschmidt and Hueck (1953) simply illustrated various features of abnormal ducts in mastopathy and fibroadenoma. No specific analyses were made of morphogenesis and histologic type. The peculiar ducts described as Brusthel or Faecher in intracanalicular fibroadenoma by the previous authors were also noted in our investigation.

Studies on mastopathic breasts using the reconstruction method have been attempted on simpler lesions. Loeschcke (1930) demonstrated a connection between apocrine cysts and ducts. Fraenkel (1934) and Demetrakopoulos (1958) reconstructed foci of fibroadenoma and concluded that the lesion was not blastomatous as judged by the well organized pattern of the abnormal ducts. In general, the wax-reconstruction method is a time-consuming technique and extensive analysis covering wide areas is hardly possible. Therefore, it is practically impossible to analyze large and complicated lesions common in mastopathic breasts by this method alone.

The effects of hormones may be considered. This subject has been discussed extensively by Geschickter (1947) in his monograph. In short, ductal development in longitudinal direction is induced by estrogen and the formation of lobules or acini is regulated by a balanced stimulation between estrogen and progesterone. The pituitary and placental hormones induce lactation only. In conditioned animals, these phenomena were reproduced (Nandi, 1958). In the adult female, these two hormones control the development of mammary ducts and abnormal growth of both ducts and acini may be induced by an abnormal balance of two regulators. Estrogen stimulation beyond the physiological level does not result in extension of the duct system but in an abnormal and stunted gland (Geschickter, 1947). Inbalance between two ovarial hormones results in irregular epithelial buds at the ends of the mammary tubules (Geschickter, 1947). Severe intraductal epithelial hyperplasia could be produced by the administration of progesterone *in vitro* (Prop, 1966). These data suggest that the evolution and growth of abnormal ductules in mastopathic breasts were highly influenced by two ovarial hormones. It is likely that the excess axial growth noted in both sclerosing and blunt duct adenosis is induced by hyperestrogenism. Significant epithelial proliferation noted in intraductal papillomatosis or irregular budding within a lobule may be produced by progesterone excess. Pleomorphism of the ductal figures in a given mastopathic breast suggests that ductal susceptibility to hormonal stimulation is variable or that the distribution of hormones is not uniform within the same breast. Repeated episodes of inbalanced hormonal stimulations would tend to complicate the histological pattern.

Our present observation that the key alteration in mastopathic breast is the evolution of abnormal ducts provides a unitarian interpretation of its pleomorphic histology. By stereomicroscopy the unique arrangement of ductules is successfully demonstrated in sclerosing and blunt duct adenosis. However, it should be stressed that the method here described is only suitable for the analysis of epithelial alteration and is unfavorable for the study of lesions with significant stromal alteration. Thus conclusions regarding small fibroadenoma cannot be extended to larger lesions like those of fibroadenoma phyllodes.

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