Virchows Arch. Abt. A Path. Anat. 349, 215—228 (1970)

A Stereomicroscopic Study of the Mastopathic Human Breast

II. Peripheral Type of Duct Evolution and its Relation to Cystic Disease

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Received August 29, 1969

Stereomikroskopische Studie der durch Mastopathie veränderten menschlichen Mamma

II. Die peripherische Form der Milchgangsevolution und ihre Beziehung zur Cystenmamma

Zusammenfassung. Die stereomikroskopische Untersuchung sog. Cystenmmamen zeigt, daß die Cysten durch Ektasie der sog. Kanälchen-Endäste entstehen. Dagegen werden die Stamm-Milchgänge einer Involution zugeführt. An der Cystenbildung beteiligen sich auch die Acini. Als morphogenetische Reize kommen hormonelle Dysregulationen in Frage. Durch die unterschiedliche Ausbildung der Kanälchenproliferation einerseits, die Involution sowie Cystenbildung andererseits resultiert ein buntes, wenig einheitliches Bild.

Summary. The stereomicroscopic study of cystic disease of the breast revealed the presence of abnormal ductules near the terminal sites of the original lactiferous ducts. This alteration was the key feature of cystic disease since the involution of abnormal ductules possibly may have induced the stricture of the original duct by increasing fibrosis around the site of duct evolution. The phenomenon could contribute to the creation of cystic dilatation of distal ducts and acini. Multiple large cysts characterizing the morphology of cystic disease may represent the end stage of distended ducts and acini. Prolonged and repeated unbalanced stimulation of hormones could produce progressive and regressive alterations in the same breast. This modifies the original alteration into more pleomorphic and complicated types.

Diffuse nodular transformation of the breast with multiple cystic changes is called cystic disease which is considered as the most advanced form of mastopathic lesion (Kuzma, 1966). Histologically, sections show pleomorphic alterations of both epithelium and stroma. Their histogenesis has not been clearly established. A stereomicroscope analysis of cystic disease revealed the presence of abnormal ductules at the periphery of original lactiferous ducts (Tanaka and Oota, 1969). Significant increase in stromal density and stricture of the duct were noted at the corresponding sites. Unlike the nodular lesion, the original structure of lactiferous ducts and lobules in cystic disease was well preserved and could be appreciated in

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This investigation was carried out at the Department of Pathology, Faculty of Medicine, Tokyo Medical and Dental University from 1958 to 1960 and was partially supported by a special research grant of the Japanese Ministry of Education.

thick preparations. Thus the alteration at the periphery of original lactiferous ducts appeared to be an important change in cystic disease. This paper provides morphological data obtained from three cases of cystic disease and discusses a possible role of abnormal duct evolution at the periphery of original ducts for the histogenesis of cystic disease.

Material and Methods

Material and methods used in this study were the same as those used in our previous publication (Tanaka and Oota, 1969). Specimens were obtained from three different cases of advanced cystic disease, and an additional five specimens diagnosed as slight mastopathy were used for reference. The punch technique was applied to foci where advanced duct lesions were apparent. Wax-reconstruction was not employed in this study because of the very complicated histology of the abnormal ducts.

Observations

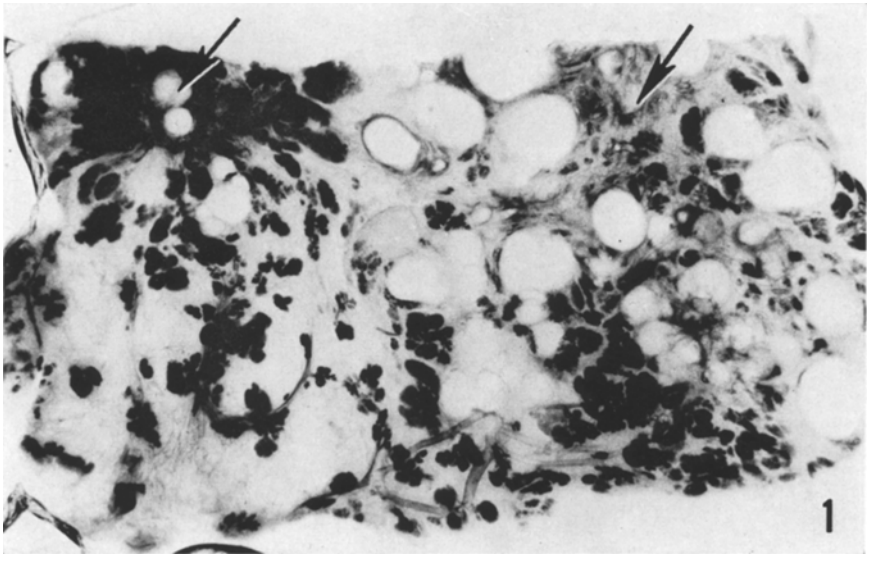
Specimens from the three cases showed the typical histology of advanced cystic disease in two cases and prominent blunt duct adenosis in one. Although histology was slightly deviant in one case, the main stereomicroscopic alterations of these three were the same being and consistent with the peripheral type of abnormal duct evolution. This alteration was not noted in the nodular lesion and in the slightly mastopathic breasts used for reference. Since details of abnormal duct evolution differed in each case, the illustrations are grouped separately according to the different cases.

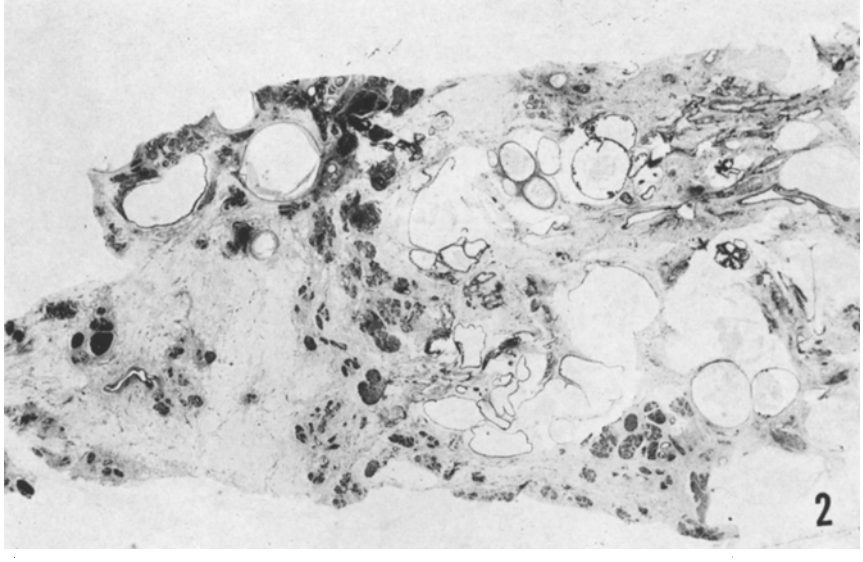
1. R-39717 (Figs. 1—8)

A macroscopic specimen showed typical feature of cystic disease, i. e. increase in general consistency and the presence of cysts of various sizes. There were zones of patchy yellowish coloration with significant increase in stromal consistency. Stereomicroscopic specimens from the adjacent tissue revealed the presence of normal-looking ducts and lobules (Figs. 1, 2) except where stromal consistency was increased. Here the arrangement of lobules was distorted (Figs. 1—4). Large ducts near the centers of the affected areas were stained deeply by hematoxylin possibly due to the presence of intraductal epithelial proliferation. Atypical ductules were noted around the large ducts (Figs. 5—8). Abnormal ductules resembling a bouquet (Tanaka and Oota, 1969) were seen on occasion (Fig. 6). Small foci of sclerosing adenosis were seen histologically corresponding to these areas. The relationship between above two structures was directly confirmed by histologic examination of punch specimens as illustrated in Figs. 7 and 8. Dilated ducts with atrophic lobules were noted commonly in fibrotic regions (Figs. 1, 2). Generally, the lobules noted in uninvolved areas were hyperplastic and appeared large. A majority of cysts appeared unstained in hematoxylin (Figs. 1, 2), but the presence of tall epithelium on the cyst wall was recognized easily by stereomicroscopy. Apocrine metaplasia of these epithelial cells was seen histologically. No connection between cysts and nearby large ducts was clearly discerned.

2. R-42621 (Figs. 9—13)

The general appearance of macroscopic specimens was similar to that observed in the previous case. Although the original structure of lactiferous ducts and lobules was distorted significantly in some places, there remained foci which





Figs. 1—8 from R-39717

Fig. 1. A thick preparation showing many normal-looking lobules scattered throughout the specimen except in foci (arrows) where abnormal arrangement of ducts and lobules is seen. (H) × 3.7

Fig. 2. Histology of adjacent tissue showing typical morphology of cystic disease. (HE) × 3.6

included ducts of normal appearance. Evolution of ductules took place from terminal branchings at multiple locations (Fig. 9). Histologic sections showed the presence of severe ductal proliferation around the smaller ducts, cysts of various sizes, intraductal papillomatosis and stromal fibrosis (Fig. 10). Proliferation of

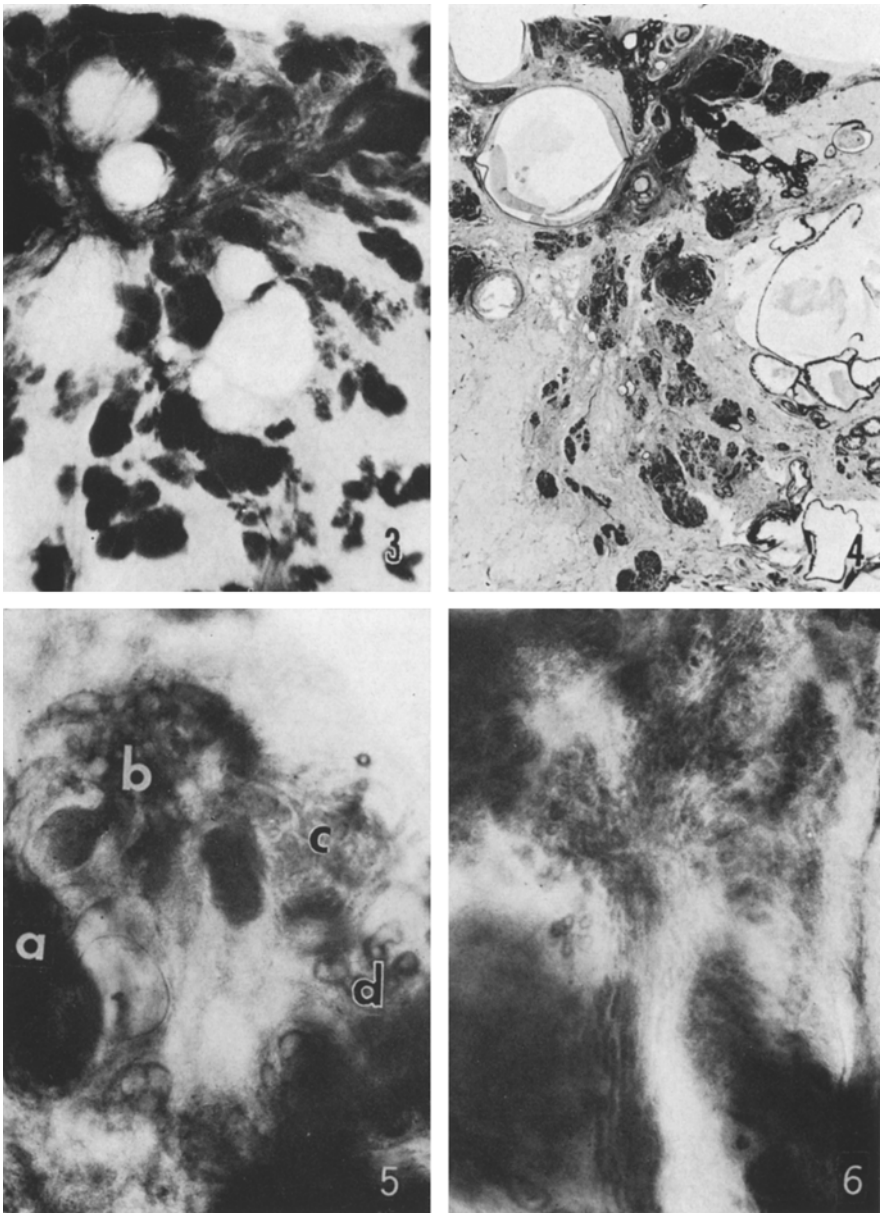
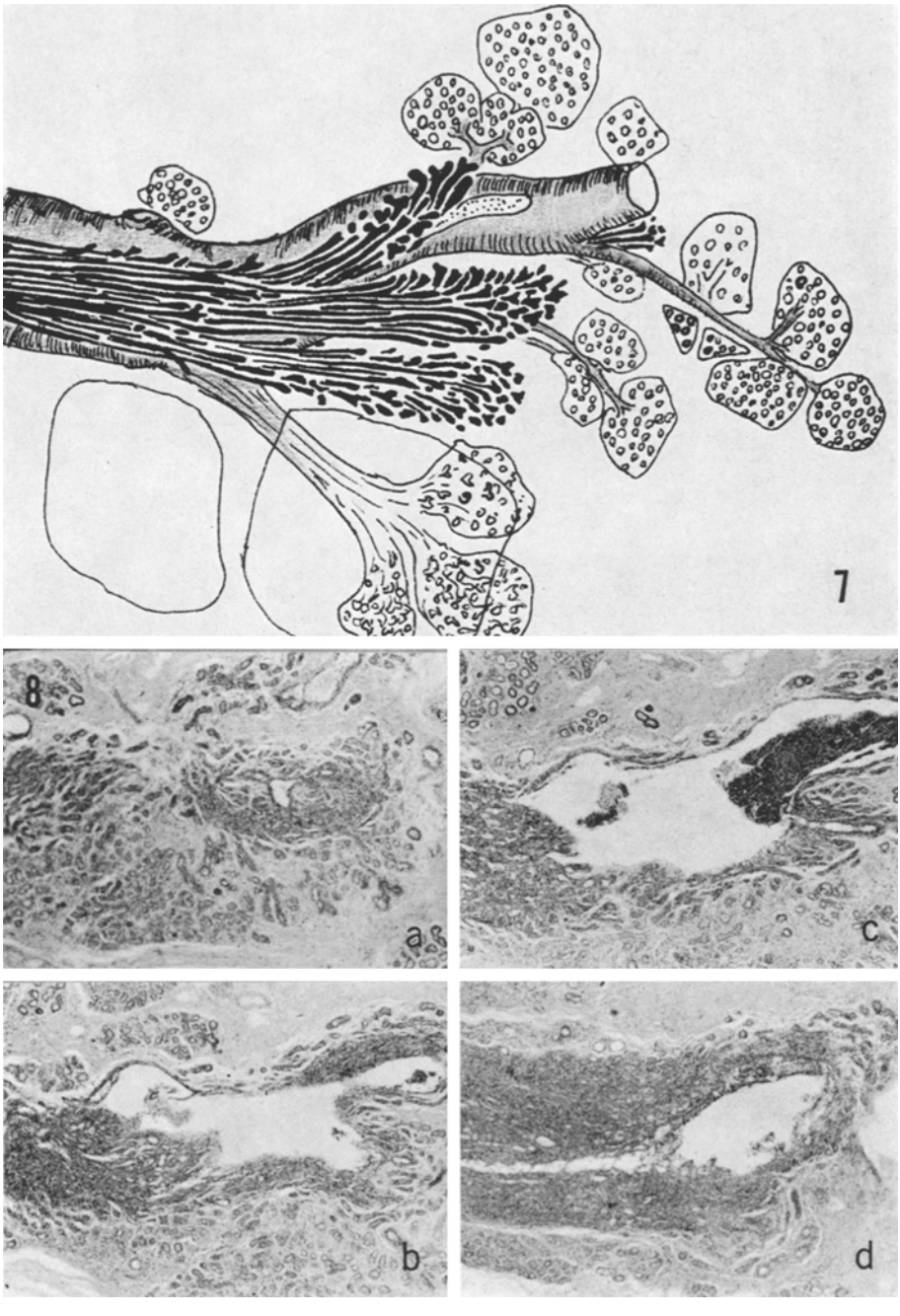


Fig. 3. A low-power view of one of the marked places in Fig. 1 representing distorted arrangement of ductules and lobules. Several cysts are present. (H) × 8.3

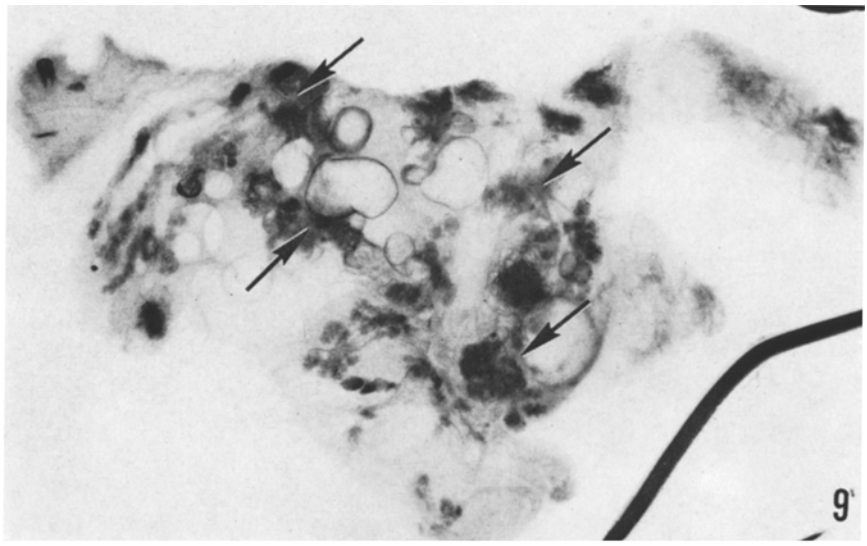
Fig. 4. Histology of the same area in an adjacent section. Note the presence of abnormal ducts and ductules in distorted pattern. (HE) × 6.3

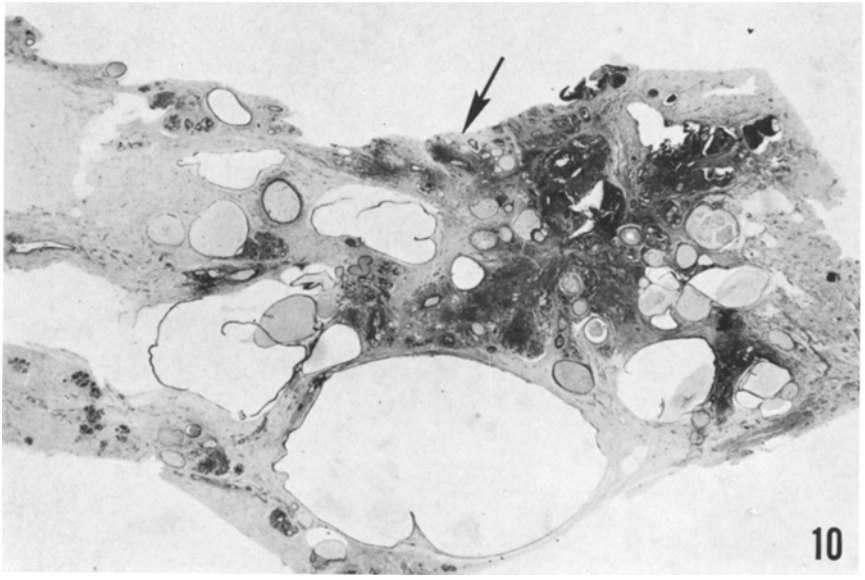
Fig. 5a—d. A high-power view of abnormal ductules noted in a distorted area. Four different types of abnormal ductules are seen in this photograph. a dense structure probably represents either an aggregate of ductules or a duct with intraductal papillomatosis, b atypical ductules noted frequently in blunt duct adenosis, c ductules forming a conglomerate, d ductules with club-shaped endings. (H) × 75

Fig. 6. A high-power view of abnormal ductules in parallel array representing sclerosing adenosis. (H) × 75



Figs. 7 and 8. A sketch of ductules developed along a medium size duct in Fig. 7. This alteration resembles those in Fig. 6. Fig. 8 consists of photographs taken from serial sections of the punch specimen which included the lesion illustrated in Fig. 7. Note the presence of many ductules around the stem duct in the middle. The photographic sequence a to d corresponds to the top to the bottom of the specimen under observation. (HE) × 60



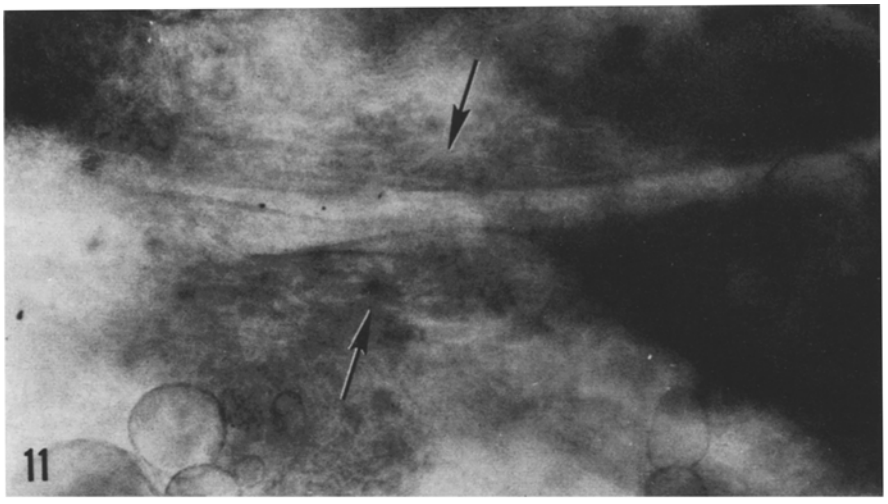


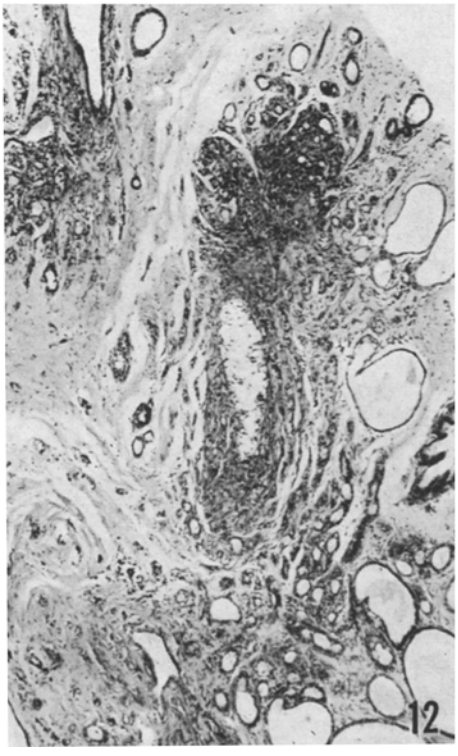
Figs. 9—13 from R-42621

Fig. 9. A thick preparation showing greatly distorted arrangement of both ducts and lobules. Several cysts of smaller sizes are seen. Very dense foci (arrows) indicate the sites of abnormal duct evolution. (C) × 5.0

Fig. 10. Histology of an adjacent section demonstrates cysts, striking duct proliferation around small stem ducts, intraductal papillomatosis and stromal fibrosis. (HE) × 5.6

abnormal ductules near the terminals of the original ducts were seen in thick preparations (Fig. 11). Some of these features were already shown in our previous publication (Tanaka and Oota, 1969). These ductules were more slender than those





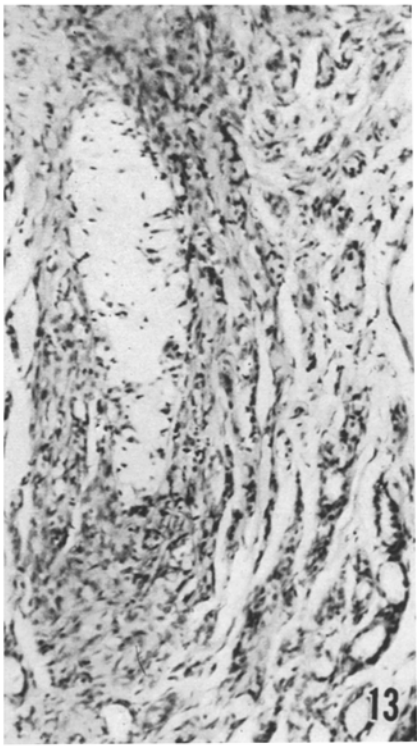
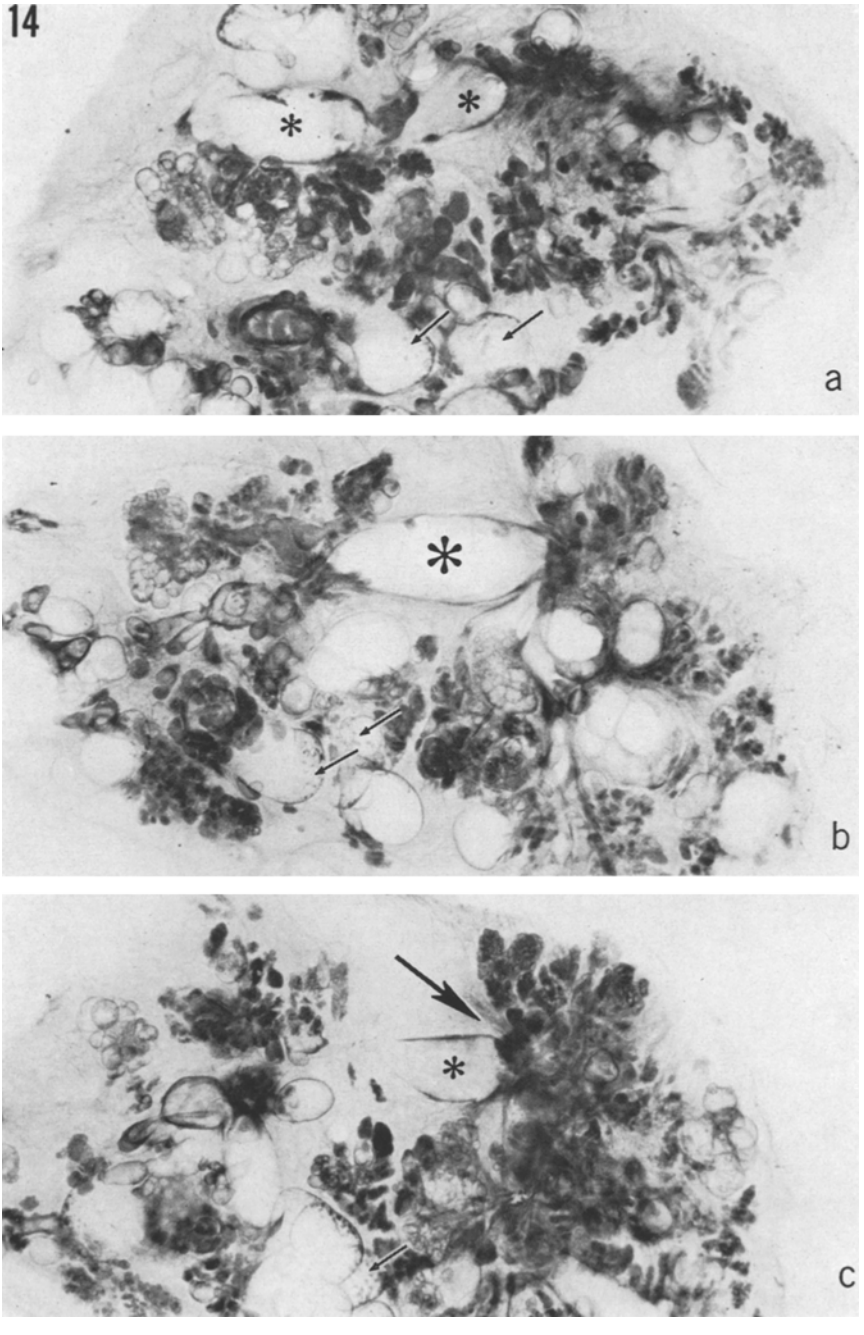


Fig. 11. A high-power view of proliferating ductules (arrows) in a thick preparation. A stem duct is seen as a clear band in the middle. (C) × 170

Figs. 12 and 13. Histological appearance of a medium-sized duct with abnormal ductules in Fig. 10 (arrow). (HE) × 100. The detail is enlarged in Fig. 13. Note the presence of many atrophic ductules around a medium sized duct. (HE) × 250



Figs. 14—16 from R-45953

Fig. 14a—c. Views of three adjacent thick preparations. (H) × 7.0. A duct marked by a large asterisk in b connected with ducts marked by small asterisks in a and c. Photograph a from the bottom and photograph c from the top of the specimen. Note an organized development of the duct with impaired lobules. Cysts with tall epithelium (small arrows) are seen

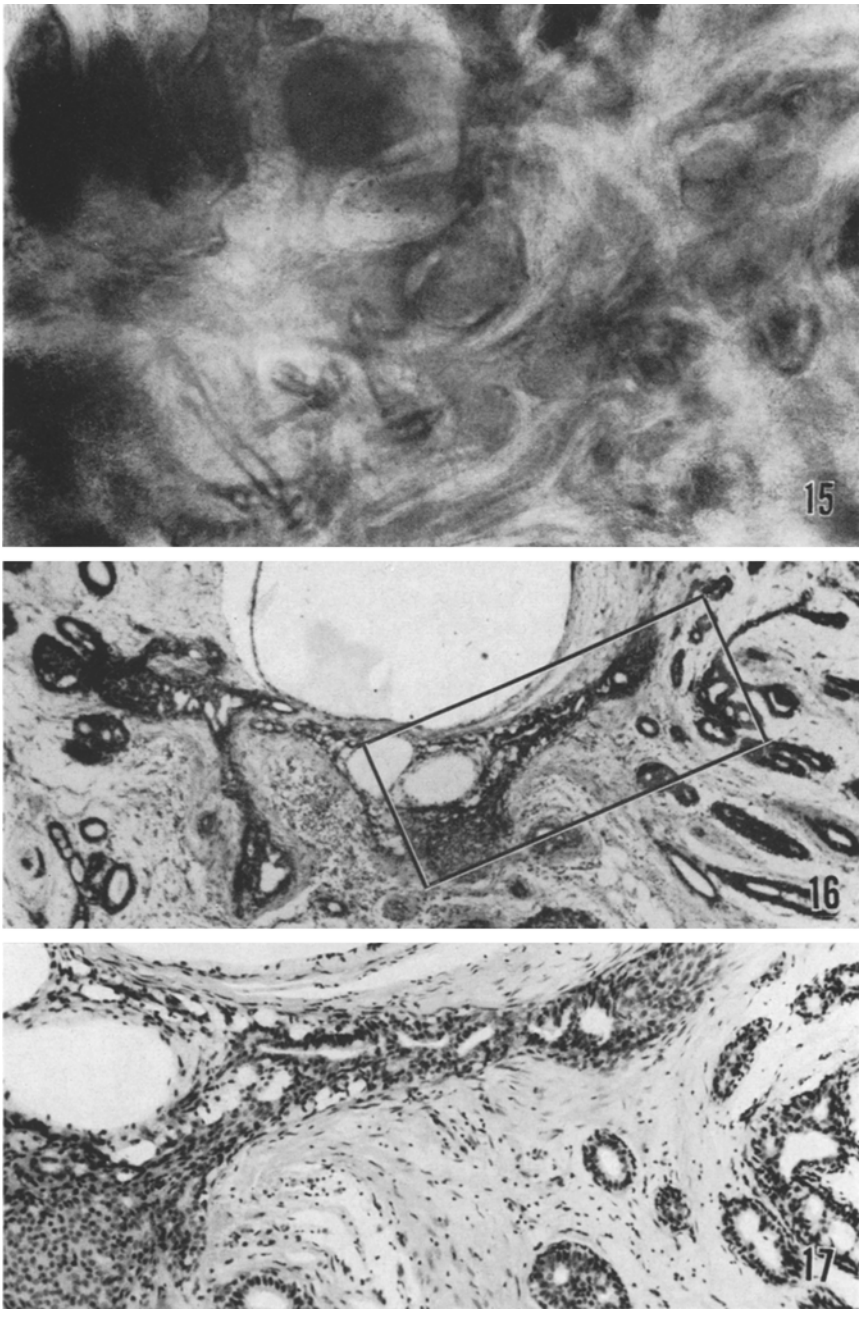


Fig. 15. A high-power view of atypical ductules in the region indicated by a large arrow in Fig. 14c. Evolution of ductules at this area is atypical. Proliferated ductules are of blunt duct type and stained strongly possibly due to the presence of intraductal papillomatosis. (HE) × 100

Fig. 16. Histology of a punch specimen from an affected site. Cysts, blunt duct proliferation and stromal fibrosis with round cell infiltration are seen. (HE) × 100

Fig. 17. A high-power view of an abnormal ductule marked in Fig. 16. (HE) × 250

of the previous case and in an unique bouquet arrangement (Tanaka and Oota, 1969) was also recognized. This alteration was confirmed as a minute focus of sclerosing adenosis by the punch technique. The new ductules extended distally along their stem ducts. Ductules growing both perpendicularly to the axis of the stem duct and proximally were noted occasionally. These abnormal ductules often were dilated. Thus the cysts observed in this case could be the end stage of acinar dilatation. The walls of the ducts of the affected site were highly refractile suggesting increase in stromal density. These abnormal ductules showed signs of involution such as low epithelium, pyknotic nuclei, desquamation of epithelium with foamy appearance, increase in stromal fibrosis and extremely narrow lumina (Figs. 12, 13).

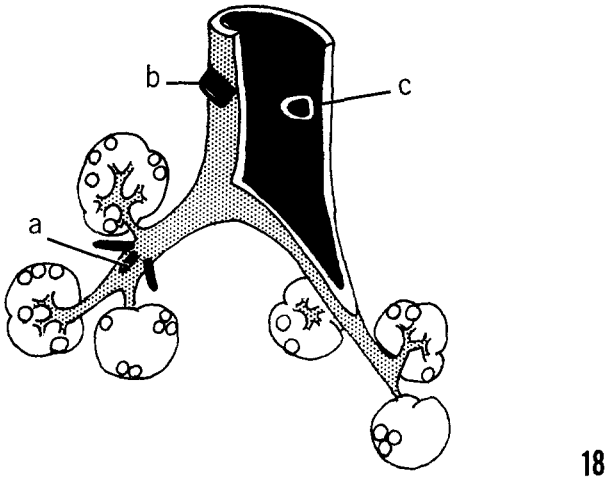
3. R-45953 (Figs. 14—17)

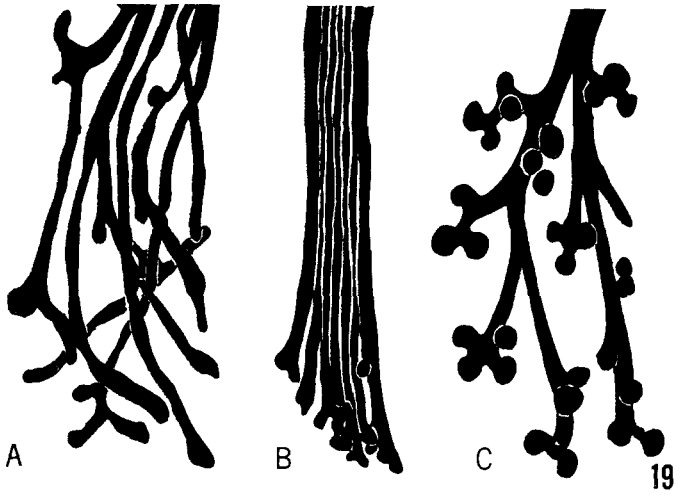
The specimen was of about thumb-tip size and included many small cysts which contained a cheesy substance. Histological examination revealed the presence of prominent blunt duct adenosis, cysts of various sizes and stromal fibrosis with round cell infiltration. The general alteration was less pleomorphic than that of two previous cases. In thick preparations stained with hematoxylin, a lactiferous duct of medium size was noted in the middle of the specimen (Fig. 14). This duct formed incomplete lobules with organized dichotomous divisions (Fig. 14). All larger ducts were moderately dilated and the duct wall appeared refractile suggesting the presence of fibrosis. The dilated ducts were interpreted as cysts in macroscopic specimens. Near the branchings of the duct, proliferation of atypical ductules was noted. Advanced duct stricture was noted near these areas. One example is demonstrated in Figs. 14c and 15. Abnormal ductules were larger and fewer than those of the previous two cases. They ended bluntly and no appearances suggesting "bundles of noodles" were noted. Punch technique applied to the sites of abnormal duct evolution revealed the presence of blunt duct adenosis (Figs. 16, 17). Cystic dilatation of duct periphery and lobules was frequently noted in this specimen (Fig. 14).

Because of the presence of many cysts microscopically, this case was included with cystic disease, and three-dimensional study revealed the presence of the peripheral type of duct evolution. It was evident that, at least in this case, many cysts were connected with the large ducts. Abnormal ductules near the branchings were possibly responsible for the induction of duct stricture in this case.

Discussion

Our present investigation on advanced cystic disease showed that the most significant alteration was noted near or at the terminal branchings of the original ducts. The ducts and lobules of uninvolved areas remained well preserved. Evolution of abnormal ductules was noted corresponding to such areas and could be interpreted as the primary alteration of cystic disease. This change was classified previously as the peripheral type of abnormal duct evolution (Tanaka and Oota, 1969). Many cysts which characterize the disease were possibly formed by the stricture of larger ducts in association with persistent secretion of related acini and ducts. The duct stricture could be the consequence of the involution of abnormal ductules. A significant role of myoepithelial elements for the induction





Figs. 18—21. Schemata illustrating morphogenesis of mastopathy in human breast

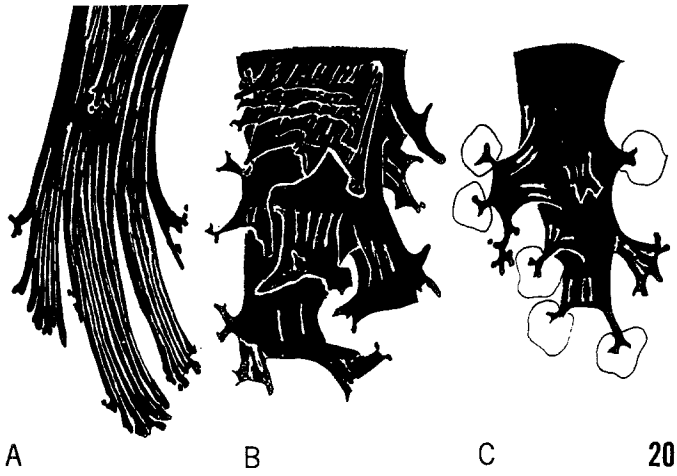
Fig. 18. The schema represents a lactiferous duct with two branchings and six lobules. Black ductules, a, b and c represent abnormal ductules. a Shows evolution of ductules near the terminal branching. b Shows evolution of a single duct at the proximal position. c Represents intracanalicular evolution

Fig. 19 A—C. Schemata of three different patterns of duct proliferation. A demonstrates an irregular pattern noted in blunt duct adenosis. B is a parallel arrangement in sclerosing adenosis. C is an organized, dichotomous division with impaired lobules characteristic of pericanalicular type of fibroadenoma

of stromal fibrosis in mastopathic breasts has been proposed (Murad and Haam, 1968). Since the peripheral type of duct evolution involves multiple sites in the breast, the lesion in cystic disease is always diffuse without forming any nodular lesion, which is common in the proximal type of duct evolution (Tanaka and Oota, 1969).

A stereomicroscopic study of cystic disease has been attempted by a few workers. Ingleby (1942) distinguished two types of cystic disease and concluded that cysts were formed by a process of hypersecretion. No explanation was presented in the report prepared by Goldschmidt and Hueck (1953) for the morphogenesis of cystic disease.

From our present investigations, the process involved in the formation of mastopathy in human breast may be postulated as follows (Figs. 18—21). 1. Evolution of abnormal ducts or ductules occurs at various sites of the original lactiferous duct (Fig. 18). The changes can be classified into two major forms according to the site of abnormal duct evolution, peripheral and proximal. The peripheral type implies that the duct evolution occurs near the end branchings of the original duct and that the abnormal ductules are of terminal nature. In the proximal type, the duct evolution occurs at the proximal end of the original duct. The duct originating from this site may have more growth potential than those of the peripheral origin. These differences in sites of origin lead to different features of mastopathy. The peripheral type of duct evolution is the most important change responsible for cystic disease. The proximal type is responsible for the creation of nodular adenosis and fibroadenomas. 2. Single or multiple budding of abnormal ducts and ductules may occur at one site (Fig. 18). The evolution of the abnormal ducts occurs at multiple locations in the peripheral type; however, the evolution of a single duct may occur in the proximal type. 3. The budding from extracanalicular position and duct evolution from an intracanalicular site may be expected in a larger duct (Fig. 18). 4. Abnormal duct and ductules develop forming abnormal structures in the breast. The early change may be interpreted as adenosis. Development of abnormal ducts and ductules may be controlled by the type of dyshormonal stimulations. The axial growth is mainly controlled by estrogenic stimulation whereas the formation of lobules is dependent on progesterone-estrogen balance. 5. Various growth patterns may be distinguished in abnormal ducts and ductules. An irregular arrangement of ductules is manifested as blunt duct adenosis (Fig. 19A). A parallel array of ductules in a pattern ("bundles of noodles") represents a three-dimensional feature of sclerosing adenosis (Fig. 19B). The organized growth pattern of a duct with impaired lobules is recognized in pericanalicular type of fibroadenoma and certain types of blunt duct adenosis including gynecomastia (Fig. 19C). 6. In larger lesions, severe adenosis consists of abnormal ductules with prominent longitudinal growth (Fig. 20A) and typical sclerosing adenosis is common in this lesion. A nodular lesion consisted of many flattened ducts with significant infoldings of duct wall is intracanalicular type of fibroadenoma (Fig. 20B). There are certain ducts that resemble an intracanalicular type of fibroadenoma but show many undifferentiated lobules (Fig. 20C). 7. Changes in acini may be noted but they are less significant than those of the duct. On occasion, there are hypertrophic lobules comprised of numerous acinal endings. 8. Abnormal ducts once formed (Fig. 21B) may become atrophic without leaving any alteration in the breast (Fig. 21C). Abnormal involution may occur more frequently. Most cystic disease is believed to be formed during this period in the peripheral type of duct evolution (Fig. 21A). The stromal fibrosis at the site of ductal evolution may lead to the stricture of the original duct and play an important role in the formation of cysts



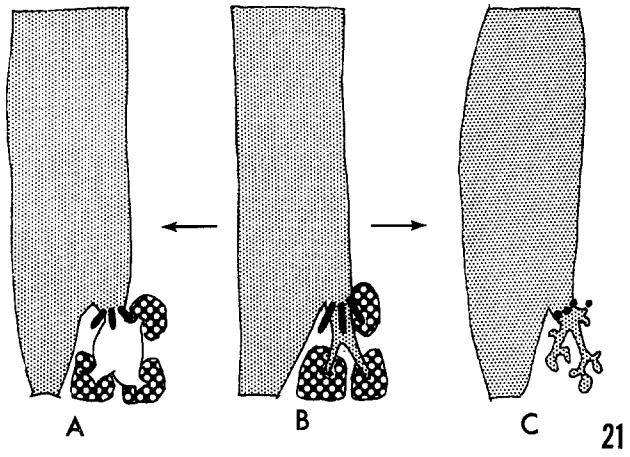


Fig. 20 A—C. Three-dimensional features of abnormal ducts in nodular lesions. A represents a duct with excess axial growth noted in florid adenosis which includes sclerosing adenosis and blunt duct adenosis. B shows a duct with multiple flattened ducts characteristic of intracanalicular type of fibroadenoma. No typical lobules are formed in this lesion. C represents a duct with poor lobules but general appearance resembles that of B. This form could be an intermediate between intracanalicular fibroadenoma and normal lactiferous duct

Fig. 21 A—C. Schemata to illustrate a possible role of the peripheral type of duct evolution in cystic disease. Evolution of abnormal ductules is shown in B. Complete involution of abnormal ductules may occur (C). More frequently, involution of abnormal ductules induces the stricture of the stem duct near the site of abnormal evolution (A). This alteration may lead to the cystic dilatation of the affected duct periphery

or cystic dilatation of the duct terminals. 9. Under prolonged and repeated stimulation, progressive and regressive alterations could be in progress in the same breast. This factor makes histology of cystic disease more complicated and pleomorphic.

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