THREE-DIMENSIONAL RECONSTRUCTION OF A HUMAN MAMMARY FIBROADENOMA[1]

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BECAUSE of its relatively high incidence and its complex and unique structure, the human mammary intracanalicular fibroadenoma early attracted the attention of surgeons and pathologists. Thus, many observations, as well as conjectures, about its structure and mode of development were made by the study of single or serial sections.

The present work arose from chance discovery of a minute human breast tumor having the histologic characteristics of a fibroadenoma. Because of its small size, it seemed particularly suitable for study by means of three-dimensional representations based on drawings of serial histologic sections.

The Specimen

Clinical History.

The tumor was discovered in a mass of breast tissue removed from a married white woman, 31 years old. She had visited her physician because she had missed her regular menstrual period one month before, and had had intermittent vaginal spotting since then. For a month or two, also, she had been aware of a tender lump in her right breast and a similar but non-tender mass in the opposite breast. Her physician believed her to be about five weeks pregnant and suspected a threatened abortion. The tumor was found in the tender mass which was removed from the upper outer quadrant of the right breast. The patient's vaginal spotting stopped, and without further complications she gave birth to a healthy male infant eight months later.

Gross and Microscopic Description.

The surgical specimen consisted of an irregular mass of breast tissue 3 cm. in average diameter. Its cut surface showed strands of pale gray tissue intermingled with yellow fat. No tumor was visible.

Microscopically, the breast tissue was hyperplastic. Lobules were larger and appeared more numerous than normally, and fibroadipose tissue was relatively less abundant. The acinar epithelium was low cuboidal in form and in places appeared piled up or pseudostratified. Periacinar connective tissue was lightly stained and loosely arranged.

In a section prepared from one of the tissue blocks there was a circumscribed lesion about 1.5 mm. in diameter, bounded on about two thirds of its periphery by a capsule of connective tissue. The capsule and surrounding adipose tissue contained recently extravasated blood believed to be incidental to the surgical procedure. Predominant in the lesion was the somewhat myxoid connective tissue element, which formed typical oval or rounded areas partly separated by a single or double layer of cells of the epithelial component. These cells had basophilic cytoplasm and uniform nuclei. Mitotic figures were not seen. The cells were flattened where the myxoid masses were most nearly apposed, and cuboidal elsewhere. In the angular interstices, delineated by the rounded areas of the connective tissue component, the epithelial cells sometimes lined small spaces partly filled with eosinophilic material and, at the periphery of the tumor, formed clusters of tubules similar to the lobules elsewhere in the surgical specimen.

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This report is based on a thesis submitted in partial fulfillment of requirements for the M.Sc. degree. The investigation was made while the author was a second-year student in Northwestern University Medical School. It was supported by a training grant and by research grant C-1750, both from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

The author wishes to express his appreciation to Dr. Thomas C. Laipply for providing the specimens for the present study; to Dr. Wendell J. S. Krieg, for his helpful instructions on the art work; to Dr. Jerome Head, for his permission to write about this tumor, which he excised; to Miss Mae Krivich for the preparation of the serial sections; and to Dr. Willard T. Hill for his advice.

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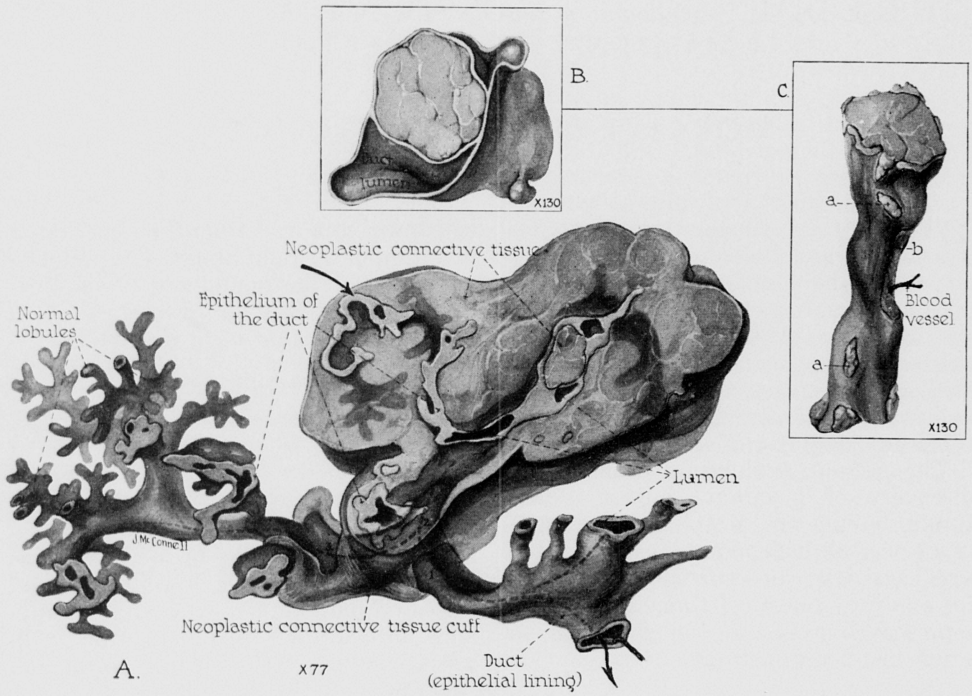


Fig. 1. A. The artist's drawing of the multilayered reconstruction shown in Figure 2. Arrow points to an epithelial band which represents the fused epithelium of two opposite walls of a duct. Part of the lumen is still patent.

B and C. Two single paper three-dimensional reconstruction drawings. B, By tracing the serial sections (fig. 7) it was found that the two lumina are parts of the same lumen which is here partly outlined and divided into two by the invaginated mass of connective tissue. C, This represents a duct which, for illustrative purposes, is stripped of its periductal connective tissue. It is filled up by the invagination which started in the area b. *The blood vessel marks the entrance to the invagination,* a, *Openings in the epithelium which represent the pressure atrophy effect of neoplastic connective tissue compressing the epithelium of the wall of the duct. (Figure is 1/3 of original magnification shown above.)*

Preparation of Serial Sections.

The tumor remaining in the tissue block was cut in 84 serial sections 15 micra thick. Hematoxylin and eosin stain was used for all except 14 sections which were specially stained to show elastic fibers.

Techniques of Study.

To make the drawings, a microscope was arranged to project the image of the tumor on a drawing board at magnifications of 53, 77, or 130 times. Both a single paper three-dimensional drawing and a multiple, transparent cellophane sheet reconstruction were made.

1. Single sheet representation of three dimensions: this technique was a modification of that described by Krieg (7).

Each of these drawings was made upon the same piece of paper. Every other or every third or fourth section was drawn. In order to represent depth accurately, the distance between successive outlines in the drawing was calculated by multiplying the actual distance between sections by the magnification. For example, the thickness of each section was 15 micra, and if every other section were drawn under magnification of 130, the distance would be 30 by 130, or 3900 micra, which is about 4 mm.

When an object, drawn according to the calculated distance, was either too low or too elongated for one to appreciate its architecture, the distance between successive sections was arbitrarily either increased or decreased by a constant fraction in order to bring out the desired

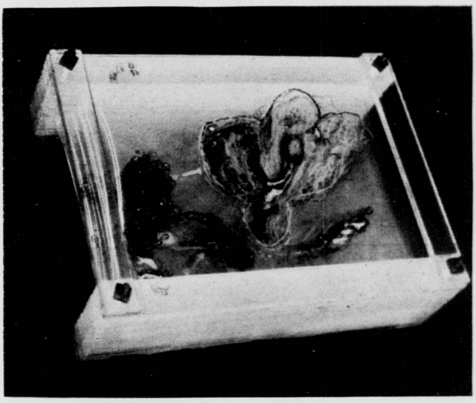


Fig. 2. Photograph of the multilayered three-dimensional cellophane model of the fibroadenoma.

feature of the reconstruction. To superimpose drawings correctly, straight structures cut in cross section in several successive sections were used as guides. When the desired number of sections (10 to 20) had been drawn, the successive outlines were connected by short lines and then appropriately shaded to give the drawing three-dimensional form. The outlines of the original reconstruction were traced on a second sheet of paper with the aid of a glass-drawing surface illuminated from below, and, thus, a more finished but equally accurate copy was made (fig. 1, B and C). In this way, all of the tumor found in the tissue block, as well as selected parts of it, were drawn.

2. Multiple sheet representation: for this reconstruction, India ink drawings of the individual sections were made on separate sheets of transparent cellophane and colored with china-marking pencils.

A mounting for each series of drawings was devised from strips of rigid transparent plastic (Lucite or Plexiglas), laid along the edges of and between successive sheets, and fastened together with bolts passed through the ends (fig. 2). The thickness of the strips was equal to the product of the magnification times the distance (in micra) between the surfaces of the successive sections drawn.

Glass panels are ordinarily used to interpose between drawings of cellophane, but the use of plastic strips yielded a construction that was lighter and more rigid, and capable of holding more drawings because of its greater transparency.

Structure of the Tumor.

Figures 1 and 2 are photographs of the single-sheet and multiple-sheet reconstructions of the lesion and of adjacent tissue. They show parts of two systems of ducts, each drained by a terminal duct. The terminal ducts join to form a secondary excretory duct into which terminal ducts also empty from other duct systems not shown in the reconstructions.

One of the duct systems branches widely and forms slightly hyperplastic but otherwise normal lobules consistent with five weeks' pregnancy. The other system forms a few normal lobules (bottom fig. 6), but for the most part it is greatly, often almost unrecognizably, distorted, and constitutes the epithelial part of the fibroadenoma.

Despite the distortion, the epithelium of the second duct system can be traced in continuity from the terminal duct through the substance of the tumor to the normal lobules at its periphery. Within the tumor, the epithelium forms channels which, in some places, are dilated and form small cysts, but in other places are greatly narrowed or completely obliterated. Where a lumen is no longer present, the epithelium forms solid bands or thin sheets of varying curvature. Both in the walls of the channels and in the epithelial sheets, ovoid or elongated defects frequently occur. The thickness of the epithelial component of the walls of the channels varies in different portions of the tumor, as shown in greater detail in photomicrographs (figs. 3 and 6 to 9).

The major portion of the tumor is composed of myxoid connective tissue. It occurs chiefly as partly fused nodular masses in the tumor, but it also invests the terminal duct as a tapering cuff. At the junction with the duct from the neighboring normal duct system, the myxoid connective tissue merges gradually with the normal periductal tissue. Figures 4 and 5 show details of this transition.

The characteristic feature of the connective tissue in the tumor, as revealed by the reconstructions, is its frequent invagination of the walls of the epithelial channels. In some of these instances, a

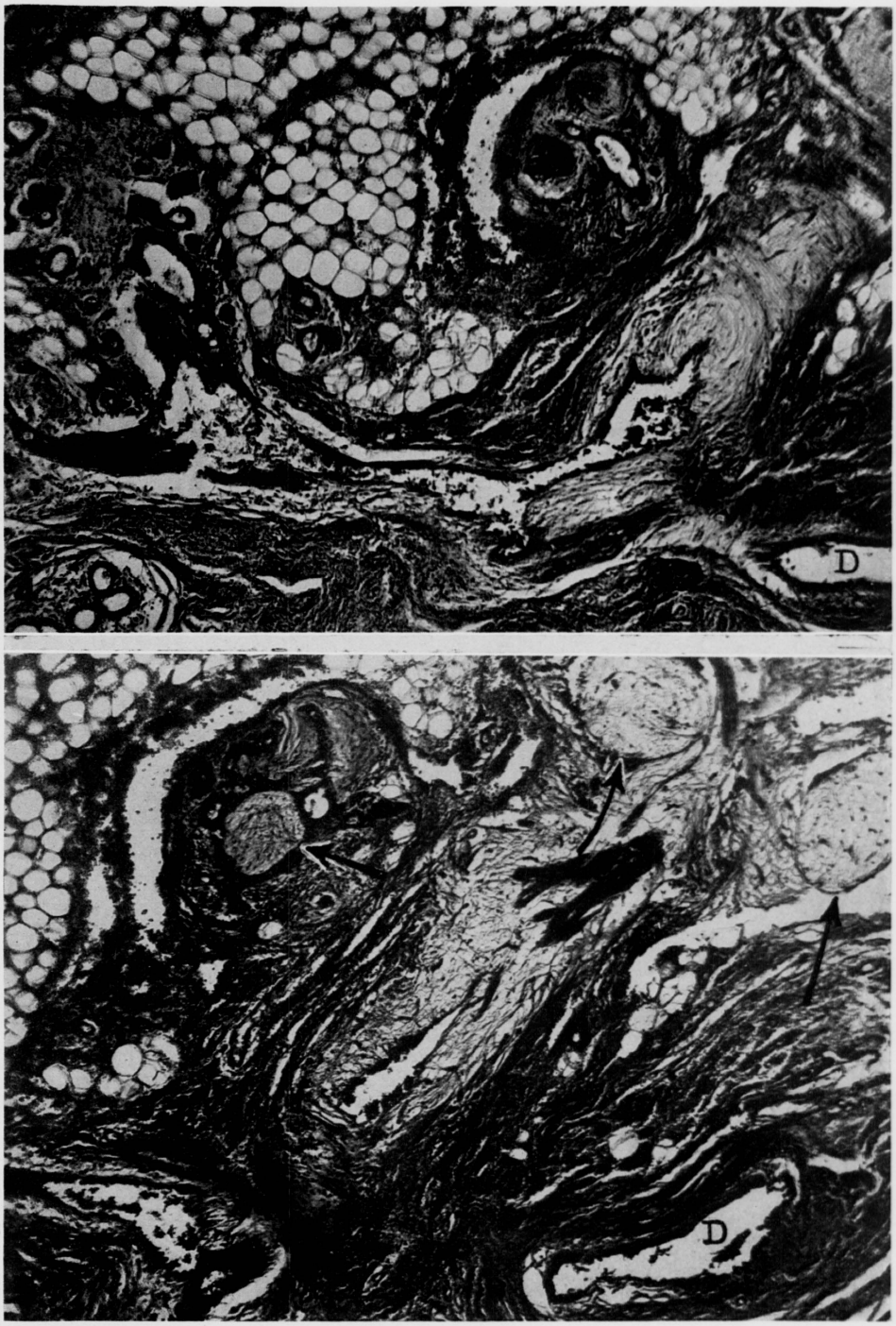
Fig. 3. The intracanalicular fibroadenoma. Arrows point to the attenuated epithelium between two adjacent connective tissue masses (see also fig. 8, arrow) (X80).

rounded nodule of connective tissue simply compresses one wall of the channel against the opposite side, thus partly or wholly occluding the lumen. In other instances, the connective tissue, still covered with epithelium, extends in a tongue-like projection in either direction within the lumen of the channel. The reconstructions in Figure 1, B and C illustrate the nature and extent of these invaginations, and further details can be seen in the photomicrographs of Figures 6 and 9.

Discussion and Review of Literature

Sir Astley Cooper (14) early recognized this benign tumor, and called it "Chronic mammary tumor." Five years later, in 1850, Birkett (12) described the tumor as "lobular imperfect hypertrophy" and made a few drawings from microscopic slides. Deaver and McFarland (15) first suggested that the fibroadenoma is primarily a lobule of breast tissue directly connected with the normal mammary ducts. Nicholson (9, 10) and Cheatle and Cutler (13) reached a similar conclusion from study of serial sections. Their view is confirmed in the present study, which showed that the epithelial component of a fibroadenoma and of normal lobules at its periphery was part of a single duct system. This system drained through a terminal segment into a normal excretory duct which also received the terminal ducts of adjacent groups of normal lobules.

Delbet (2) believed that the first step in the development of fibroadenoma is epithelial proliferation and the formation of cysts and that subsequent overgrowth of connective tissue and invagination of cysts result in the characteristic pattern. Observations made in the present work support a contrary view: that the connective tissue alone largely accounts for the pattern of the tumor. Cysts were formed wherever it seemed that invaginations of connective tissue had blocked the lumen of a duct. Such cysts could be differentiated from involutional cystic changes occurring in long standing fibroadenomas by the presence of epithelium lining the cystic duct and by the absence of degenerative and necrotic material in the lumen (16). Wherever



Figs. 4 and 5. The duct at center of Figure 4 is the result of the union (1) of the terminal duct at the center of both figures and (2) of the normal terminal duct at the lower left of Figure 5. The normal duct, D, *is the excretory duct to which both terminal ducts drain. The arrows in Figure 5 point to three seemingly separate fibroadenomatous islands which were found, in subsequent sections, to be continuous with the duct system of the tumor. The normal lobules at the left of both figures are consistent with 5 weeks' pregnancy and drain into the duct shown to their right (X66).*

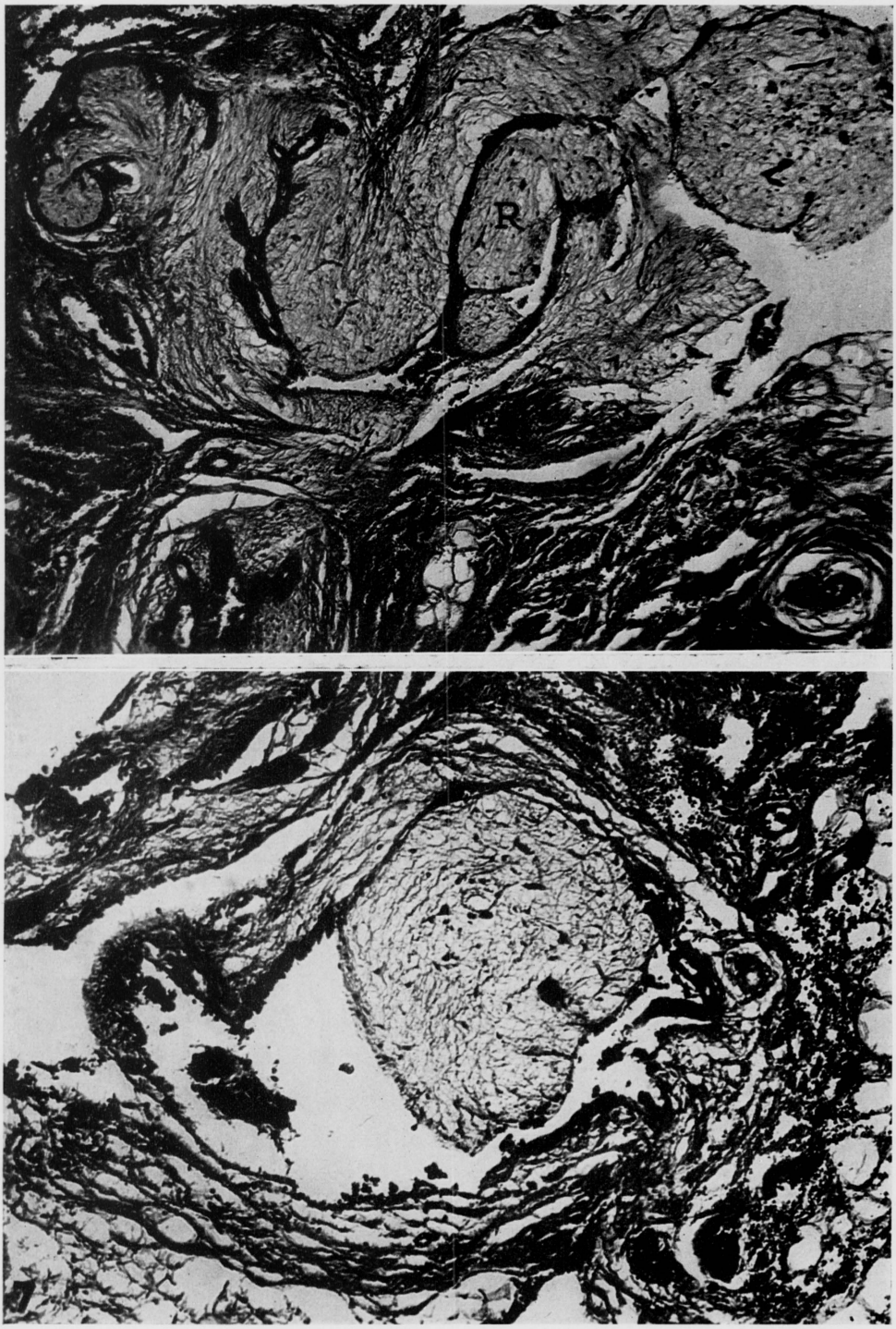
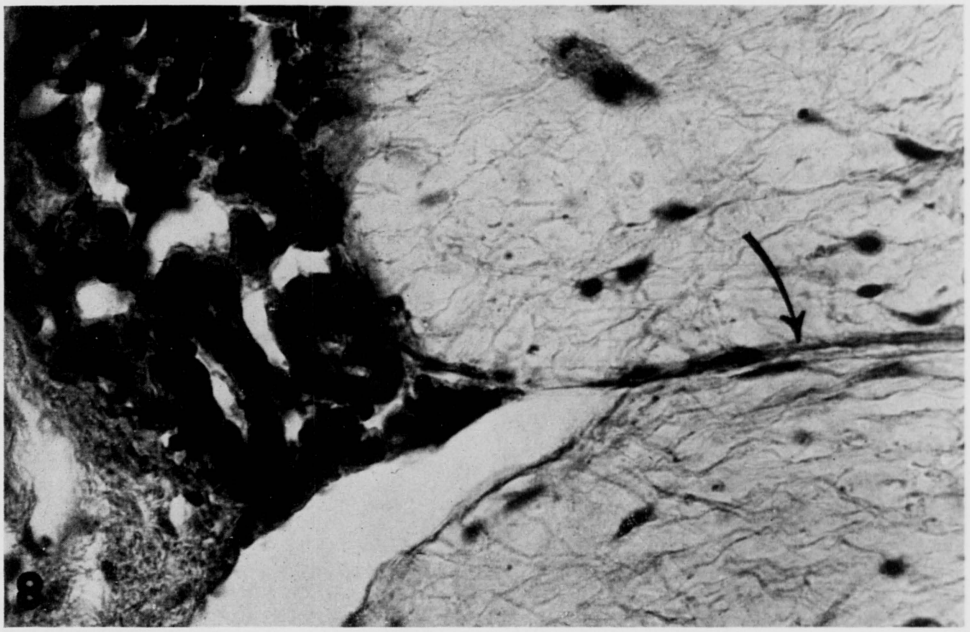


Fig. 6. The normal lobule at the lower part of figure drains into the neoplastic terminal duct at center of Figure 5. The part marked by R *was reconstructed in Figure 1C. (X70)*

Fig. 7. This is a section through the reconstruction in Figure 1B. The cyst-like expansion of the duct at the center is toward the point of least resistance, i.e., the soft fatty tissue at the lower left. The material inside the cyst-like space is multilayered epithelium artefactually detached from the walls of this space. (X136)



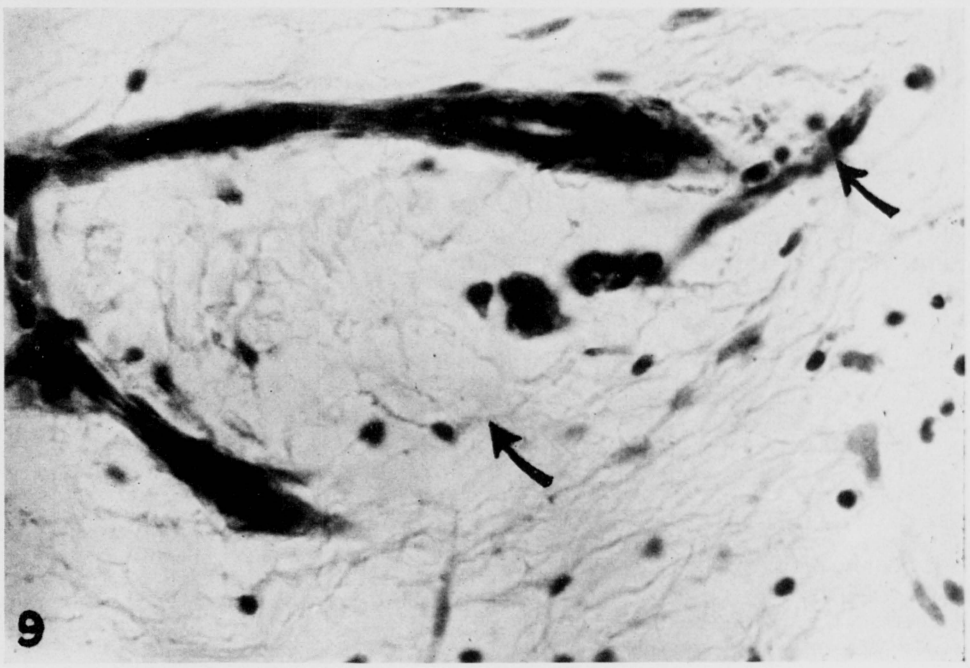


Fig. 8. Myxoid connective tissue and some epithelial tubules at the periphery of the tumor. Arrow points to the atrophied epithelium. (X700)

Fig. 9. This is the part reconstructed in Figure 1C. Connective tissue fibrils, and a blood capillary (arrow), mark the entrance of the periductal connective tissue into the tongue-like invagination of the duct whose lumen is almost completely obliterated and whose opposite epithelial walls are fused. (X700)

the connective tissue growth was abundant, the epithelium was compressed or atrophic or had disappeared between two masses of connective tissue. On the other hand, in places in which there seemed to be room for the epithelium to grow, as in the walls of cysts, or near the periphery of the tumor, it was as abundant as in normal lobules.

In single sections, Cheatle and Cutler (13) observed apparently separate tumor nodules about fibroadenomas and referred to them as "satellite" tumors. Nicholson (9, 10), however, showed that such nodules were actually parts of the same tumor. Similar continuity was observed in the present study.

The question of whether or not both the connective tissue and the epithelium of fibroadenomas are necessarily neoplastic remains unsettled despite many expressions of opinion (1, 2, 5, 8, 11, 17). In the fibroadenoma studied in the present work, it seems possible to account satisfactorily for its structure by assuming that there was hyperplasia of epithelium, but that only the connective tissue was neoplastic.

Since 1845, when Sir Astley Cooper wrote that "the tendency of the disease is found in the uterine excitement" (14), growth of fibroadenomas during pregnancy and in other periods of hormonal stimulation has been reported frequently both in women and in experimental animals (3, 4, 5, 6, 16). The present tumor was found in a woman five weeks pregnant. The correlation between its minute size and the short period of pregnancy is consistent with the view that the fibroadenoma developed as a result of hormonal stimulation.

Summary

1. A minute mammary fibroadenoma, discovered in a pregnant woman, was studied in three-dimensional reconstructions based on serial sections.

2. The tumor contained an epithelial duct system which entered the normal excretory system of the breast.

3. The reconstructions showed compression and invagination of the duct system by connective tissue, and associated obstruction, cyst formation, and atrophy of the ducts.

4. The pattern of the fibroadenoma could be accounted for by the assumption that only its connective tissue component was neoplastic.

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