LOBULAR CARCINOMA IN SITU *

A Rare Form of Mammary Cancer

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With increasing emphasis on the early diagnosis of cancer it is obvious that the pathologist will observe increasingly early histologic manifestations of this disease. In recent years it has become apparent to us that various forms of carcinoma *in situ* were being encountered in ever greater frequency and in locations where such phenomena were hitherto but rarely discovered. Examples of entirely noninfiltrative lesions of a definitely cancerous cytology have been accumulated for almost every mucosa-lined structure.

Carcinoma *in situ* in the breast is a disease which has been recognized for many years. The term, however, has not been employed and for the usual form of the disease the designation "noninfiltrative comedo-carcinoma" has served. Nevertheless, comedo-carcinoma constitutes an example *par excellence* of carcinoma *in situ* of a glandular organ. This form, however, is a disease mainly of the larger duct system. One is much less apt to think of carcinoma *in situ* as a disease of small lobular ducts and lobules. The latter process is relatively rare. One of us (F. W. S.) had occasion several months ago to conduct a clinical-pathological symposium † on tumors of the breast at which a lesion of this type was presented. It was found that the malignant character of the process was not recognized by a number of pathologists. For this reason it is felt desirable to review certain features of such tumors.

An impression of the incidence of this type may be gained through a survey of the mammary cancers observed during the past year at the Memorial Hospital. There were two typical examples of strict carcinoma *in situ* of lobules and terminal lobular ducts in approximately 300 primary, operable, mammary cancers. Additional examples of the lesion have been seen during

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this period in material submitted from other institutions for consultation. The latter fact testifies to nonrecognition of the fundamental potentialities of the pattern.

It is apparent, however, that this type of mammary cancer, *i.e.*, cancer originating in lobules and terminal ducts, is more common than this incidence would appear to indicate, for, when the tumor infiltrates, it is apt to do so in a peculiar fashion which permits one, after some experience, to recognize the high probability of such origin even though it is impossible actually to trace it. Moreover, in the fully infiltrative form it is often possible to detect outlying areas where lobular carcinomatosis ***in situ*** is still very apparent. Thus, in these same 300 cases there were 5 in which the pattern was very marked, 2 in which it was moderately developed, and 5 in which it was noted definitely but was scanty in amount.

When this pattern of carcinogenesis is present it is not necessarily the only mode of origin. This may be true, but in some instances a lobular type is combined with different modes of development. Thus there are patterns of combined lobular carcinoma and infiltrating duct cancer beginning in multiple papillary adenomatosis, lobular cancer combined with quite dissimilar large cell comedo-carcinoma both infiltrating and ***in situ,*** and lobular carcinoma plus tubular adenocarcinoma—again quite dissimilar histologically. Hence it is wholly improbable that this lobular carcinoma ***in situ,*** or "totilobular carcinoma," as we have occasionally designated it to emphasize its origin in terminal ducts and all constituents of the lobule, constitutes a separate entity other than in the clinical sense and when in its noninfiltrative phase. At that stage involvement of lymph nodes has never been seen.

There is no way in which a clinical diagnosis of lobular carcinoma ***in situ*** can be made. Patients with cancers of this variety, or with the later infiltrative phase, are in the same age group as are those bearing other mammary cancers. In the noninfiltrative phase the breast reveals none of the classic clinical signs of cancer. The nipple is erect. Retraction is absent. Skin dimpling and fixation are absent. Discharge or bleeding from the nipple has not been noted. The mass is movable and diagnosis is usually "chronic cystic mastitis" or fibro-adenoma. In fact, in our most

marked case the surgeon encountered a gush of fluid on exploration of the mass, a number of small cysts were noted grossly, and cancer remained wholly unsuspected until sections were made. There is no way by which it *can* be recognized grossly. The pathologist sees only congeries of what look like large lobules, if indeed he recognizes anything at all abnormal. Since there is little piling up of epithelium in terminal ducts, necrosis does not occur and hence the chalky streaks so characteristic of many cancers are lacking. Of course, with the development of infiltration the gross morphology becomes that of any mammary cancer. The existence of unrecognizable lesions of this totilobular structure is disquieting to one who trusts his gross diagnosis and suggests the necessity of frozen section in any lesion where disproportion in the size of lobules is evident.

Microscopically the process shows the following characters: There is a sudden and abrupt alteration in lobular cytology (Fig. 1). A group of normal-appearing lobules is interrupted by the presence of a lobule or group of lobules in which, although these lobules may be within normal limits in size or even smaller than normal, the cells are large (Fig. 2). They are perhaps twice the size of those of the normal lobules and their nuclei are in proportion. The nuclei tend to be rather clear; they show no hyperchromatism. The cytoplasm is apt to be opaque, somewhat acidophilic, and occasionally vacuolated. The compact, orderly arrangement of the epithelium of the normal lobule gives place to a decided looseness, a loss of cohesion. Layers do not multiply as layers but cells are progressively displaced toward the lumina in a disorderly fashion, eventually obliterating the space. Slight degenerative changes may result in the formation of central mucoid globules. Mitoses are rare. It is usually necessary to survey a section of two or three entire lobules to find a single mitosis. The cells lose polarity, varying in shape while maintaining surprisingly uniform size. They occasionally assume what looks like a loose reticular structure.

The type of lobule which undergoes this transformation varies. Large lobules, small lobules, lobules with mucoid stroma, metaplastic lobules, and hyalinized lobules, may all assume this pattern. Occasionally only part of a lobule is involved and a sharp line of division between normal epithelium and carcinoma *in situ*

is seen. No constant perilobular inflammatory infiltration accompanies the change.

The earliest manifestation of lobular carcinoma *in situ* may be found in isolated cells or groups of cells in the lobule or in the terminal lobular duct (Fig. 3). Presumably multiple isolated cells are the first sign but that stage is soon past. Such cells recall certain features of Paget's disease and we have designated them "pagetoid" cells. The clinical entity, Paget's disease, has not been encountered in this group of cases. In some areas there is a suggestion of general lobular epithelial hypertrophy prior to the stage which one might designate as neoplastic, a graded progressive increase in cell size so gradual that demarcation is impossible. In the earliest phase, the occurrence of pagetoid cells is limited to those cells near the limiting membrane.

It should be emphasized that this lesion occurs in multiple lobules. It has been forcibly impressed upon us that a breast in which this process occurs in the slightest degree constitutes an extreme hazard. Whereas it is not clinical cancer until infiltration occurs, it is always a disease of multiple foci. Hence it is never safe to leave the breast with local excision only, even if the entire palpable lesion has been removed. Whenever the process has been found by local excision, subsequent simple mastectomy has shown additional foci of disease. In our first case, local excision revealed this process and we were unfortunately not aware of its significance. Within the space of a few months the patient had infiltrating cancer with axillary metastases and now has skeletal dissemination. It is our feeling that simple mastectomy is essential, with further procedure dependent on finding the least evidence of infiltration.

The mode of infiltration of these lobular cancers is peculiar and somewhat obscure. One often sees evidence of a sudden, almost explosive liberation of cells from their natural boundaries. The term "explosive" is used with full realization that temporal elements are not known. Nevertheless the resultant picture is often that of a terminal duct, possibly showing the noninfiltrative phase of the tumor, but surrounded by large numbers of isolated, loose cells of rather uniform size but of varying shape (Fig. 4). They are not especially hyperchromatic. In some fields they might readily be confused with large mast cells. In others

they suggest the morphology of the periductal myoid cells. They are, however, liberated cancer cells and when they metastasize to nodes their form and distribution are such that they might be confused with cells of reticulum cell sarcoma. Their wide infiltration within the breast itself may lead to the invasion of residual lobular connective tissue in lobules which themselves have not given rise to neoplasm. Thus they replace lobules which undergo atrophy. Why atrophy occurs is not know to us. Pressure in this case does not satisfactorily account for it although it may very well do so in the case of expanding mammary cancers of more solid type. The isolated cells may evoke considerable desmoplastic response on the part of the connective tissues.

Since distension of the lobule does not assume marked proportions prior to infiltration, some other factor must be invoked to explain the mass eruption of tumor cells. We suspect some lytic action of the tumor cells, naturally not to be detected by anatomic study.

The question has arisen as to whether tumors of this type deserve the designation of "acinar" carcinoma. We have not as yet observed a mammary cancer which in our opinion might properly be considered acinar cancer. It is largely a question of terminology. We do not feel that we can draw sharp lines between terminal ducts and acini. We prefer to regard the acinus as a structure which develops during lactation and which thus constitutes a physiologic phase rather than an anatomic entity. It is to avoid confusion that we employ the term "lobular carcinosis *in situ*."

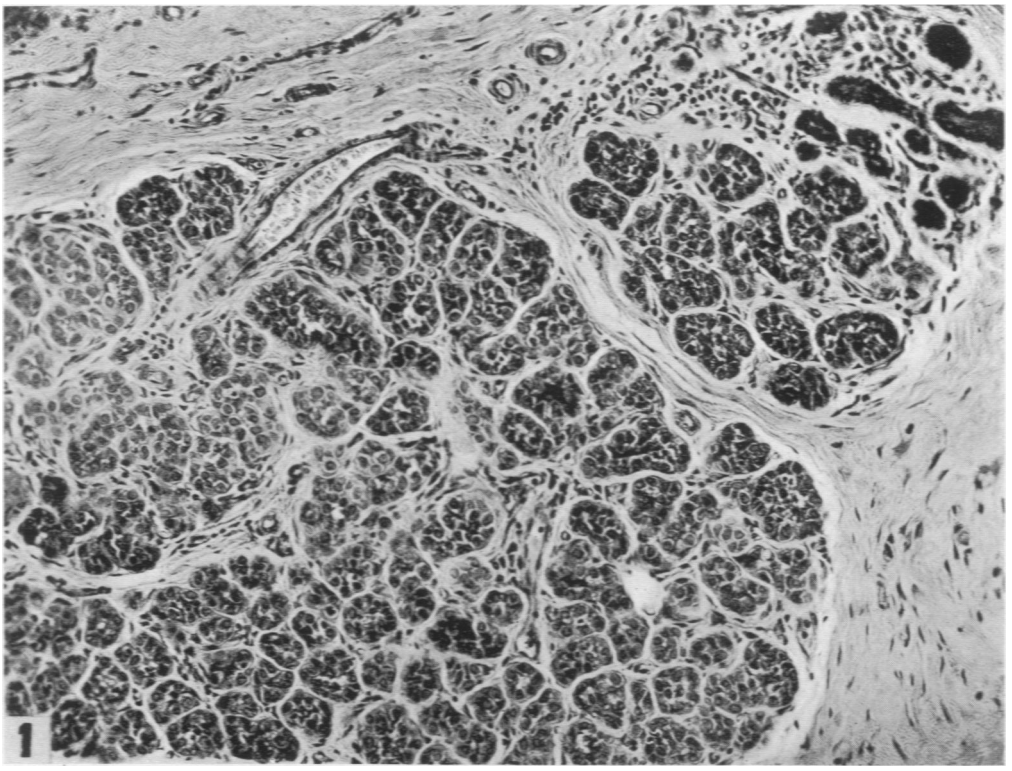
Naturally, the existence of lobular carcinoma *in situ* presupposes that lobules are present. The breast may not be atrophic. Nevertheless there exists a type of carcinoma which apparently takes origin in smaller ducts and which begins in cells of pagetoid type, identical with those seen in lobular carcinoma *in situ*, and this type of cancer may occur in the non-lobule-containing atrophic breast.

DESCRIPTION OF PLATES

PLATE 93

FIG. 1. Lobular carcinoma *in situ*. At the upper right there is shown a portion of a normal lobule for comparison. × 170.

FIG. 2. Higher magnification of involved lobules in the same area as Figure 1. × 450.



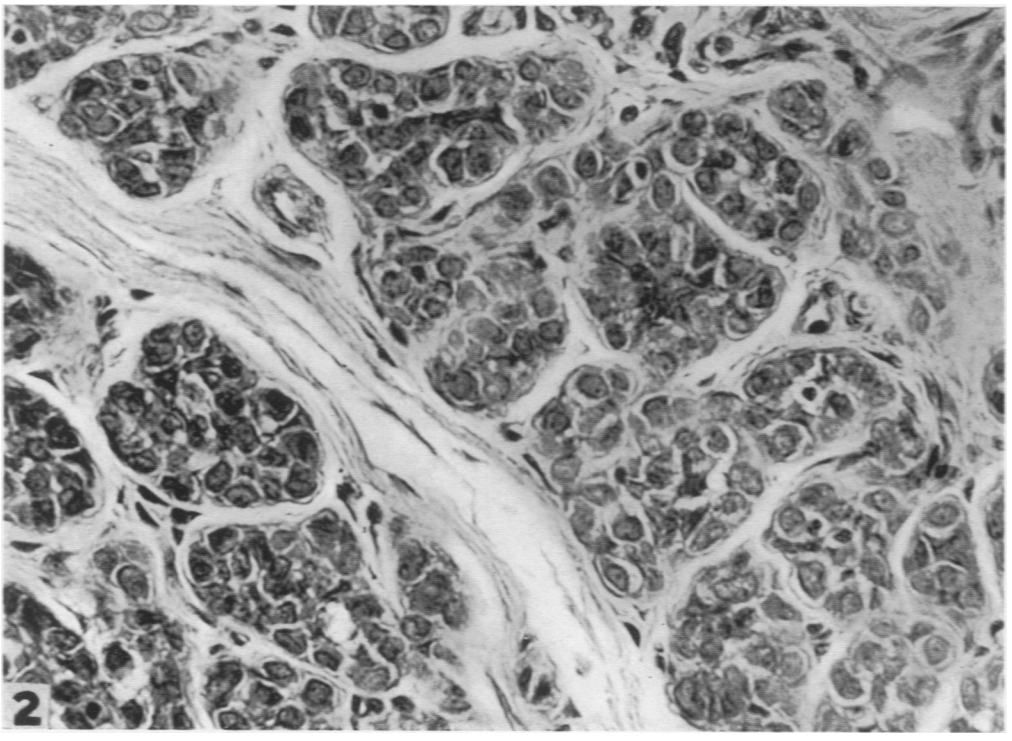


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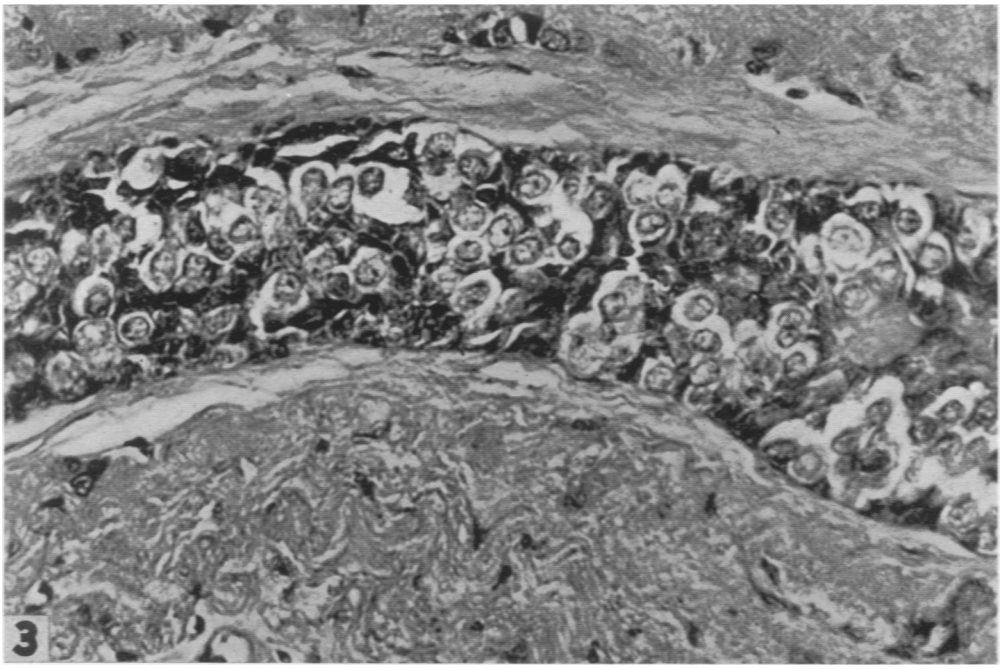
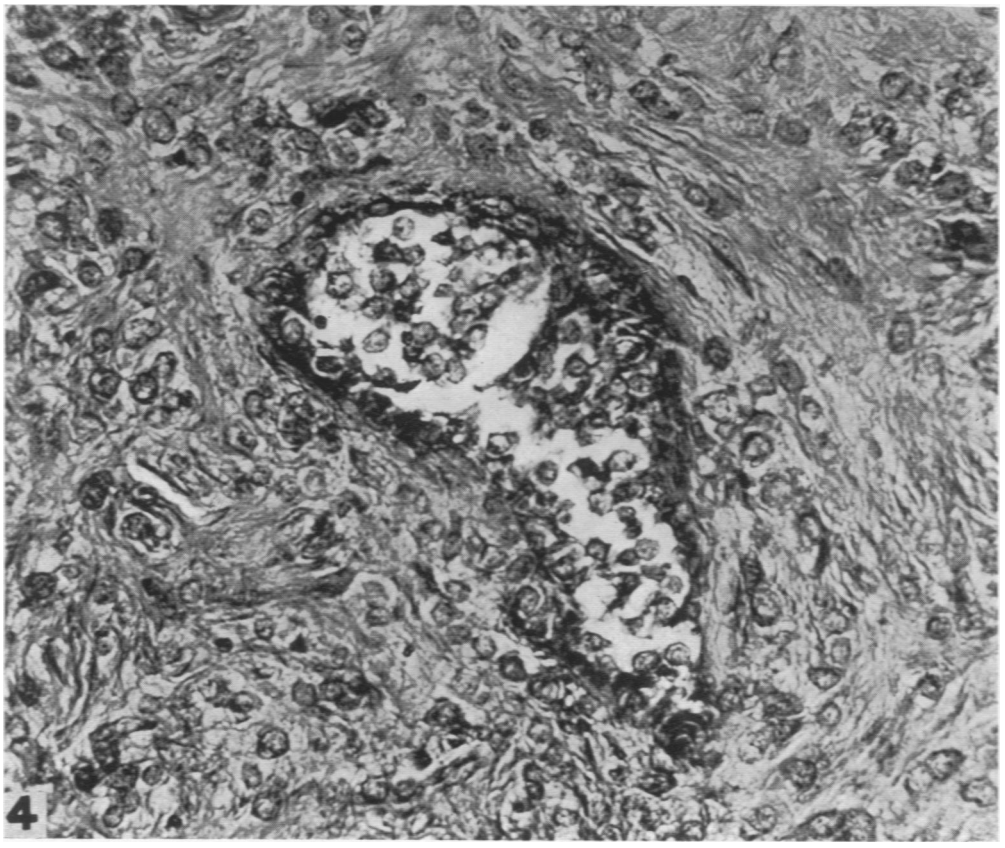
PLATE 94

FIG. 3. Terminal duct with "pagetoid" cells. × 450.

FIG. 4. Invasive phase developing from lobular carcinoma *in situ*. A terminal duct with "pagetoid" cells is shown, with surrounding infiltrative cancer cells. Despite the infiltration the periphery of the lobule (not shown) still showed connective tissue encapsulation. × 450.





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