COMPARATIVE STUDIES OF CANCEROUS VERSUS NONCANCEROUS BREASTS

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I. BASIC MORPHOLOGIC CHARACTERISTICS

THE PRESENT STUDY represents an effort to determine whether fundamental structural differences exist in the breast tissue of women who do have mammary cancer and those who do not have this disease. In other words, the main objective has been to ascertain if there is any characteristic "soil" in which mammary carcinoma is apt to develop. Another interest has been to search for abnormalities in these breasts that could be referred to certain hormonal influences, and finally an attempt has been made to evaluate the relationship between so-called chronic cystic mastitis and mammary cancer. The investigation was not begun with any preconceived point of view concerning these problems, and it has been constantly borne in mind that little positive information might be secured. A study of this sort necessarily enters into debatable matters about which a vast literature has accumulated. Due to the large volume of such literature, reference can be made only to specific papers which seem most pertinent to the findings under discussion.

The material for comparative gross and microscopic analysis was secured during 1940 from operations performed on the Breast Service at the Memorial Hospital. It consisted of 300 cancer-containing breasts from radical mastectomies and 200 specimens of noncancerous breast tissue from partial mastectomies or very occasional simple mastectomies. The material was sectioned specifically for this planned study, and in every case both normal and abnormal appearing tissues were embedded. No selection of cases was made with the following exceptions: No irradiated breast was included. A few cases were excluded in which there was total or near total replacement of the breast tissue by carcinoma. In the cases of local excision, it was required that the mass of breast tissue be large enough to furnish satisfactory representative sections. Thus, it was necessary to exclude a small number of assorted noncancerous lesions excised with a margin too small for our purposes. Finally, no case was included in which the operation was undertaken for pyogenic or specific infection of the breast.

We recognize the disadvantage of comparing the findings in complete mastectomies with findings in partial mastectomies. This disproportion in tissue mass, however, is largely compensated for, since in doing a local excision, the surgeon may be expected to select the most obviously abnormal portion of the breast and is careful to remove a margin of less involved or uninvolved tissue. So, if a gross abnormality is present it appears likely that it will be removed. In order to balance microscopic findings as much as possible, compar-

able amounts of grossly unaltered tissue were embedded in both the cancer and the noncancer cases. The total mass of tissue embedded in the two groups of cases has been equal in amount exclusive of the cancer itself.

In this survey the following plan of analysis was employed: Each case was tabulated for the presence or absence of specific lesions, so that composite percentage figures for each of the two types of cases were secured. The two general groups were then subtabulated, decade by decade, to enable proper comparison, since the influence of age in the frequency of certain lesions is so great that this must be insisted upon in interpreting results. For closer analysis of certain specific lesions, it was then considered necessary to tabulate other lesions that occurred in unison with the particular one under examination. By this method it is possible to learn the sort of histologic environment in which a given lesion is apt to be found and it permits one to detect trends in occurrence that indicate fundamental interrelationships, or their lack. By no means do the figures given for the incidence of certain lesions imply that they represent absolute values. The frequency of microscopic lesions can always be elevated somewhat by embedding innumerable blocks. Terminology in breast lesions is by no means standardized. Where commonly employed terms are used, effort has been made to define our own usage of these, and where unaccustomed ones are used, special effort has been made to describe the lesions in full.

The average age of the 300 cancer cases was 49.5 years, that of the 200 noncancer cases 39 years. The distribution by decades is shown below.

TABLE I

Decade	Cancer Cases	Noncancer Cases
10–20		4
20–30	3	30
30–40	54	68
40–50	104	78
50–60	66	16*
60–70	60	3
70+	13	1
Total	300	200

* In tabular analyses that appear in succeeding sections, comparative histologic findings are given for the third, fourth, and fifth decades. Since the series of 200 noncancerous breasts contained only 16 cases in the fifth decade, 24 consecutive noncancerous breasts were added to this group, so that observations are based on the more significant number of 40 cases.

Subjects to be discussed will appear in the following order:

I. Factor of atrophy
II. Cysts
III. Duct papillomatosis
IV. Blunt duct adenosis
V. Apocrine epithelium
VI. Sclerosing adenosis
VII. Periductal mastitis
VIII. The mammary lobules
IX. Relation of so-called chronic cystic mastitis to mammary cancer
X. Histologic findings in breasts after administration of estrogenic substance

I — FACTOR OF ATROPHY

Inasmuch, as mammary cancer occurs most frequently in breasts that are beginning to undergo atrophy, or are already in varying degrees of this state, can any differences in this process be found in cancerous as opposed to noncancerous breasts? The principal feature in atrophy of the mammary gland is reduction of its parenchyma to an extent that is much more complete than in most organs. Atrophy begins at the lobular terminations of the duct system and proceeds toward the nipple so that the end-result is near, or total, loss of lobules and more or less diminution of the terminal and small ducts. Extreme variations in the degree of atrophy can be seen in individuals of the same age-group, and occasionally breasts are seen that maintain the integrity of their lobules for surprisingly long periods beyond the menopause. As an illustration, we have recently studied sections from a surgical excision done three years after the menopause. In this case the lobules were not only very numerous but they possessed abundant acini, and, here, mitoses were found in surprisingly large numbers. In the absence of various quantitative and qualitative metabolic determinations, no explanation attempted could be supported. The patient had a strong family history of mammary cancer. In atrophy of the breast other changes, such as loss of periductal myoid, duct dilatation, fatty replacement of fibrous stroma, and subsidence of certain proliferative and cystic lesions, accompany the decreasing number of mammary lobules.

An estimate of the number or frequency of the mammary lobules is the most convenient index for estimating atrophy. No very exact method of estimating the number of lobules seems required, nor is it reasonably possible, and we have merely listed cases as having "numerous," "average" or "few" lobules. Table II shows the frequency of lobules in the cancer and noncancer cases as separate whole groups and also shows a comparison by decades.

TABLE II

	Number of Lobules		
	Numerous	Average	Few
200 noncancer cases	13%	61%	25%
300 cancer cases	8%	36%	56%
Noncancer cases, age 30–40	10%	60%	30%
Cancer cases, age 30–40	10%	51%	39%
Noncancer cases, age 40–50	12%	55%	33%
Cancer cases, age 40–50	10%	57%	33%
Noncancer cases, age 50–60	3%	25%	72%
Cancer cases, age 50–60	3%	27%	70%

The only significant discrepancy shown is in the lobule frequency of the two types of cases when compared as whole groups. This is at once referable to the greater average age of the cancer-containing breasts, since, in equivalent decades, there is close uniformity. It appears justifiable to state the obvious conclusion that mammary lobules are not more or less numerous in cancerous than noncancerous breasts in the same age-group.

It may be inquired if any of the common proliferative lesions of the breast

tend to persist in cancerous breasts and disappear from noncancerous breasts, presumably supplying a possible source for the development of cancer. This is given a negative answer in other sections of this paper where these lesions are shown to regress sharply in the 50- to 60-year decade.

The question of the relation of mammary atrophy to mammary carcinoma is of very considerable speculative interest. It is of interest from at least two viewpoints: Certain it is that atrophy is a precursor of cancerization in certain tissues, although causal relationship of such atrophy to cancer is not clear. Our observations as regards mammary atrophy fail to indicate that such atrophy is significantly more frequent in the cancerous breast when compared to the noncancerous breast of similar age. The second point of interest concerns the question of hormone etiology of mammary cancer. Where those hormones which presumably are concerned with mammary lobule growth or persistence concerned in a major way with mammary cancer development, one might at least expect some difference in lobular status in the cancerous versus the noncancerous breast; that is, one might anticipate the finding of greater lobule abnormality outside the actual cancerous area in the cancerous breast than in the "normal" for the age-group. This matter will be discussed in some detail in a later section pertaining specifically to lobule structural patterns.

II — CYSTS

Included in these tabulations are only those cysts visible to the naked eye, and, hence, those cysts measuring from about one millimeter upwards in diameter are represented. It is our belief that if one reports on microscopic cysts, serial sections are required to prove complete isolation and loss of communication with adjacent ducts or lobules. If microscopic lesions that appear cystic are included, it is inevitable to confuse, in some measure, blunt end ducts, dilated ducts or distended lobule components. No lesion was included as a cyst unless it was an isolated structure distended with fluid and totally separate from duct and lobule system. The figures will not separate cases with solitary cysts from those with multiple ones, since in both types of material the solitary cysts, whether large or small, were so few as to be insignificant.

In the 200 noncancerous breasts, cysts as qualified in the preceding statements were found in 106, or 53 per cent. Of the 300 cancer breasts, 82, or 27 per cent, contained cysts. The average age of the benign cases with cysts was 41.1 years and in the cancer cases with cyst, the average age was 48.4 years. When the occurrence of cysts is studied by decades, the following is seen (Table III).

TABLE III

Decade	Comparative Frequency of Cysts in Noncancerous Cases	Cancer Cases
30–40	52%	34%
40–50	65%	18%
50–60	30%	25%

Accordingly, it is obvious enough that cysts are distinctly more characteristic of noncancerous than cancerous breasts. Indeed, in the decade 40–50,

which is the most common ten-year period for the appearance of mammary cancer, they are less than one-third as frequent in cancer-bearing breasts as in breasts free from cancer. Cysts, like many other lesions of the breast, may appear at a relatively early age, but are often transient structures and they become decreasingly numerous as old age is reached. Observations extended beyond the age of 60 (in material additional to that studied here) show that between 60–70 years of age, the incidence of cysts in both cancerous and noncancerous breasts falls sharply. Statistically, cysts seem to play a negative rôle in mammary cancer. The lower incidence of cysts in cancer-bearing breasts cannot be explained by the supposition that the cysts are replaced by the cancers, for morphologic evidence is directly opposed. In tracing the genesis of mammary cancer, one finds true intracystic carcinoma to be one of the rarest morphologic types. Terminology in breast pathology is so loose that the term "intracystic" is often employed when the proper designation is "intraductal." This common practice has led to much confusion as to the frequency of intracystic cancers as well as intracystic papillomas. If one studies the walls of cysts he finds with extreme rarity any evidence of atypical or other epithelial proliferation. It is actually much more common to find no epithelial lining at all. In the 300 cases of mammary cancer under consideration here, only two could be shown convincingly to have arisen in a cyst.

The question may be raised as to what other lesions are apt to be found in breasts that contain cysts and if the same lesions appear regardless of whether the breast is or is not cancer-containing. For making these determinations, all of the cyst-bearing breasts were tabulated for the presence or absence of 14 definite histologic characters. In Table IV are also shown figures for the frequency of these lesions as they occurred in the entire group of 200 cases without cancer and the 300 cases with cancer.

TABLE IV

	Frequency of Various Lesions in			
	106 Noncancer, with Cysts	200 Consecutive Cancers	82 Cancers, with Cysts	300 Consecutive Cancers
1. Hyperplasia of duct epithelium	52%	39%	80%	57%
2. Duct papillomatosis	42%	29%	50%	36%
3. Intracystic papilloma	2%	2%	1%	1%
4. Blunt duct adenosis	40%	26%	40%	26%
5. Apocrine epithelium	67%	42%	57%	39%
6. Sclerosing adenosis:				
A. Diffuse	1%	1.5%	2%	0.3%
B. Focal	18%	11%	13%	7%
7. Fibro-adenoma	9%	19%	10%	7%
8. Tendency to fibro-adenoma	5%	3%	8%	6%
9. Stasis and distention of ducts	41%	36%	62%	42%
10. Duct metaplasia	42%	34%	62%	45%
11. Periductal mastitis	23%	22%	20%	14%
12. Fat necrosis	1%	2%	2%	1.3%
13. Lobule frequency:				
Numerous	14%	13%	10%	10%
Average	62%	61%	41%	35%
Frequent	24%	26%	49%	55%
14. Periductal myoid atrophy	31%	27%	56%	42%

From Table IV a general summary may be drawn that no obvious qualitative divergence is detectable when comparing the noncancerous elements of cancer-containing breasts with breast tissue removed surgically from noncancerous breasts when the common denominator of each group is the presence of one or more cysts. True enough, there are certain quantitative differences of lesser degree which are substantially diluted when the factor of age is considered. Cysts may be regarded as relatively passive structures representing essentially the end-phase of a pathologic process. Characteristically, they are accompanied by a group of what may be termed proliferative processes somewhat more numerous than the proliferative processes seen in a general average of breasts when these proliferative processes are enumerated with disregard of the presence of cysts.

It is of interest to compare the lesions in noncystic breasts with the findings just recorded for cystic breasts of both benign and cancerous breasts.

TABLE V

	Frequency of Various Lesions in			
	106 Noncancer, with Cysts	94 Noncancer, without Cysts	82 Cancers, with Cysts	218 Cancers, without Cysts
1. Hyperplasia of duct epithelium	52%	23%	80%	48%
2. Duct papillomatosis	42%	14%	50%	31%
3. Intracystic papilloma	2%	2%	1%	1.5%
4. Blunt duct adenosis	40%	9%	40%	20%
5. Apocrine epithelium	67%	14%	57%	32%
6. Sclerosing adenosis:				
A. Diffuse	1%	1%	2%	0%
B. Focal	18%	6%	13%	4%
7. Fibro-adenoma	9%	30%	10%	6%
8. Tendency to fibro-adenoma	5%	5%	8%	5%
9. Stasis and distention of ducts	41%	28%	62%	34%
10. Duct metaplasia	42%	25%	62%	39%
11. Periductal mastitis	23%	19%	20%	12%
12. Fat necrosis	1%	3%	2%	1%
13. Lobule frequency:				
Numerous	14%	12%	10%	11%
Average	62%	52%	41%	35%
Frequent	24%	36%	49%	64%
14. Periductal myoid atrophy	31%	22%	55%	36%

Table V emphasizes in greater contrast than the preceding one the tendency of certain lesions to occur in cyst-containing breasts irrespective of the presence of cancer. These lesions include hyperplasia of duct epithelium, duct papillomatosis, blunt duct adenosis, apocrine epithelium and sclerosing adenosis. All of these can be regarded as proliferative or hyperplastic in nature. It should be noted that fibro-adenoma fails to follow this tendency and in the benign group is actually reversed. Fibro-adenoma must be regarded as a proliferative lesion, but it seems to be of a different order from other mammary proliferations. Also to be noted is the greater frequency in cyst-containing breasts of lesions designated as "stasis and distention," "duct metaplasia," "periductal myoid atrophy" and "periductal mastitis." That these are secondary phenomena dependent upon pressure and obstructive factors will be explained in a section to follow.

III — DUCT PAPILLOMATOSIS

Under this designation are included all stalked papillary adenomas. These are usually found in the large- or medium-sized ducts and are usually macroscopic. Also, included here are cases with partial or complete epithelial plugging of the smaller stems of the duct system. These lesions are often seen with no vascular stalk, and it is admitted that they are not papillary adenomas in the strictest sense of the word. They are, however, papillary in a modified sense and of distinctly greater magnitude than lesions spoken of here as simple hyperplasia of duct epithelium. In a large part they are microscopic and almost invariably multiple. They are present in many more cases than are the macroscopic stalked papillomas, but in nearly every case where a stalked papilloma is present these lesions can be found in some other portion of the breast tissue. No universally accepted standard exists for the lower level of epithelial hyperplasia where one ceases to use the term papillomatosis, and any division must be more or less arbitrary. Undoubtedly, writers on breast pathology do not uniformly conform in terminology. It is our belief, that in the material here, a relatively strict interpretation is made, and that in many other hands the figures for the papillary lesions might be considerably higher. In any event, the same level of inclusion or exclusion is adhered to when enumerating these papillary lesions in the two types of material under examination here. The stress is always to compare the same kinds of lesions. Emphasis is again made that in this section we are considering papillary lesions that are intraductal in location, and the statement is repeated that true "intracystic papillomas" are of very uncommon occurrence. It would be necessary to have several thousand consecutive cases of cancerous and noncancerous breasts to yield a sufficiently large number of true intracystic papillomas before adequate comparisons could be made.

In the series of 200 breasts without cancer, duct papillomatosis was found in 58, or 29 per cent. In the 300 breasts containing cancer, this finding was made in 108, or 36 per cent. It should be noted that the figures quoted would be appreciably elevated if papillary hyperplasias of pink-staining apocrine epithelium were included. Foci of apocrine epithelium are sometimes found in a papilloma, to be sure, but no case was included in which the papillary element was solely apocrine. The mammary apocrine element is discussed in a separate section. Although repetitive, the statement is emphasized that the lesions recorded here as constituting papilloma or papillomatosis are not minimal in nature, and would certainly be regarded by any reasonable observer as meriting the dignity of the term.

The occurrence of papillomas by decades in recorded in Table VI.

TABLE VI

Decade	Frequency of Duct Papillomatosis in Noncancerous Cases	Cancer Cases
30–40	18%	24%
40–50	40%	40%
50–60	23%	28%

Table VI indicates no very great difference in the frequency of duct papillomatosis in the two types of material under analysis when equivalent age-groups are considered. The somewhat higher figure, 36 per cent for duct papillomatosis in the entire series of 300 cancerous breasts against the figure 29 per cent for 200 noncancerous breasts is, likewise, not of sufficient degree to indicate more than a trend.

If no impressive difference in frequency, then, is there a difference in the kind of papillomatosis? This may be ascertained from the following comparisons:

1. Are macroscopic papillomas more common to one group than the other? Analysis shows that of the 58 benign breasts with papillomas, 14, or 26 per cent, were greater than 1 mm. in diameter. Of these 14 cases of macroscopic papillomas, six showed additional foci of microscopic papillomatosis. Of the 108 cancerous breasts with papillomas only eight, or 7 per cent, were macroscopic, and in each of these eight cases additional foci of microscopic papillomatosis were found. These findings are not startling, and can be summarized by stating that macroscopic papillomas are more characteristic of benign than cancerous breasts, and that "solitary" macroscopic papillomas are decidedly accented in this group. In passing, it can be said that the bulk of the macroscopic papillomas falls between the ages 50–60, but extremes below 30 and beyond 60 occur.

2. Is there a difference in the "degree" of the papillomatosis of cancerous and noncancerous breasts? The term "degree" is used here to designate the multiplicity of the lesions and is qualified by the relative terms marked, moderate and slight.

TABLE VII

DEGREE OF PAPILLOMATOSIS

	Slight	Moderate	Marked
Noncancer group (58).....	31, or 53%	16, or 27%	11, or 20%
Cancer group (108).....	69, or 64%	27, or 25%	12, or 11%

Again, nothing very impressive is seen in the comparative figures. The above grouping by "degree" does not take into special account the minute histology of the single cells.

3. Are the papillary lesions of one group more or less apt to be atypical, histologically, than in the other? The term "atypical" here indicates a disturbance in cell uniformity and includes the usual traits such as altered stainability, variation in size and/or shape, and loss of polarity. All of these characters are subject to much variation ranging from trivial alteration to a stage where they merge imperceptibly with the histology of cancer. When a case is called "atypical" it signifies that it is at least of a certain substantial level of atypism. No effort is made to classify beyond this arbitrary line. In the 58 cases of papillomatosis from noncancerous breasts only five were considered atypical while in the 108 cancer-containing breasts, the papillomatosis was considered atypical in 45. It is emphasized that the lesions

were not part of a cancer. The far higher incidence of atypical papillomatosis in cancerous breasts is one of the few outstanding differences recorded in this comparative study. It is a qualitative difference about five times more common in cancer-containing breasts. The contrast is made more obvious by recalling that orderly papillomatosis is almost as common in one type of material as the other.

Table VIII shows the lesions that occur in unison with papillomatosis. For purposes of comparison the table includes the absolute frequency of the same lesions as they occurred in the two groups as a whole.

TABLE VIII

LESIONS ACCOMPANYING DUCT PAPILLOMATOSIS

	58 Noncancer Cases, with Duct Papillomatosis	200 Consecutive Noncancer Cases	108 Cancer Cases, with Duct Papillomatosis	300 Consecutive Cancer Cases
1. Hyperplasia of duct epithelium	90%	39%	95%	57%
2. Intracystic papilloma	4%	2%	1%	1%
3. Blunt duct adenosis	62%	26%	49%	26%
4. Apocrine epithelium	63%	42%	50%	39%
5. Sclerosing adenosis:				
A. Diffuse	2%	1.5%	1%	0.3%
B. Focal	16%	11%	13%	7%
6. Fibro-adenoma	8%	19%	4%	7%
7. Tendency to fibro-adenoma	10%	3%	4%	6%
8. Cysts	74%	53%	32%	27%
9. Stasis and distension of ducts	56%	34%	53%	42%
10. Duct metaplasia	48%	34%	64%	45%
11. Periductal mastitis	36%	22%	16%	14%
12. Fat necrosis	0	2%	1%	1.3%
13. Lobule frequency:				
Numerous	12%	13%	10%	10%
Average	62%	61%	40%	35%
Few	26%	26%	50%	55%
14. Periductal myoid atrophy	54%	27%	52%	42%

The percentage differences are nowhere great enough to show any fundamental difference in the lesions that accompany papillomatosis in cancerous as opposed to noncancerous breasts—at least no difference that is not manifest in these two groups taken as a whole. It is of distinct interest to note again the tendency of certain cystic and proliferative lesions to occur in unison—cysts, hyperplasia of duct epithelium, duct papillomatosis, blunt duct adenosis, apocrine epithelium and sclerosing adenosis. Each of these lesions has been, or will, be discussed from the point of view of what morphologic part they seem to play in mammary carcinogenesis. Attention is called, again, to the failure of fibro-adenoma, another proliferative lesion, to be found concomitantly with the other lesions just mentioned, further suggesting that fibro-adenoma is a different proliferative manifestation. In the section on cysts, factors influencing the frequency of periductal mastitis and associated lesions have been mentioned, and no further comment will be made until this group is separately dealt with.

A further means of comparing the cancerous and noncancerous series is afforded by tabulating the preceding group of 14 lesions as they occur in the absence of duct papillomatosis.

TABLE IX

COMPARATIVE FINDINGS IN BREASTS WITH AND WITHOUT DUCT PAPILLOMATOSIS

	58 Noncancer Cases, with Duct Papillomatosis	142 Noncancer Cases, without Duct Papillomatosis	108 Cancer Cases, with Duct Papillomatosis	192 Cancer Cases, without Duct Papillomatosis
1. Hyperplasia of duct epithelium	90%	23%	95%	35%
2. Intracystic papilloma	4%	1%	1%	1.5%
3. Blunt duct adenosis	62%	14%	49%	13%
4. Apocrine epithelium	63%	35%	50%	33%
5. Sclerosing adenosis:				
A. Diffuse	2%	1%	1%	0.5%
B. Focal	16%	11%	13%	3%
6. Fibro-adenoma	8%	23%	4%	9%
7. Tendency to fibro-adenoma	10%	3%	4%	7%
8. Cysts	74%	44%	32%	25%
9. Stasis and distention of ducts	56%	27%	53%	36%
10. Duct metaplasia	48%	28%	64%	34%
11. Periductal mastitis	36%	17%	16%	13%
12. Fat necrosis	0	3%	1%	1.5%
13. Lobule frequency:				
Numerous	12%	13%	10%	10%
Average	62%	67%	40%	33%
Few	26%	27%	50%	57%
14. Periductal myoid atrophy	54%	17%	52%	36%

In Table IX the same trends as formerly noted are repeated in sharper contrast. Regardless of whether breasts do or do not contain a cancer, they tend to maintain similar structure when cross-examined on the basis of possessing a common histologic factor such as presence or absence of duct papillomatosis. As the noncancerous proliferative lesions of cancerous breasts are analyzed, it begins to be apparent that the pattern of the breast tissue is more influenced by the presence or absence of these noncancerous lesions than by the presence of the cancer itself.

The direct part played by duct papillomatosis in the morphogenesis of cancer of the breast cannot be stated in very exact terms. In contrast to cysts and other common lesions, however, there is ample evidence of a far more direct relationship. In the 300 mammary carcinomas studied here, there were 45 examples of atypical papillary hyperplasia with various degrees of change bordering on the histology of cancer. In over one-half of the 300 cancers, there was evidence of duct origin represented by papillary or stratified intraductal foci of tumor. In the remainder of these mammary carcinomas the duct origin could not be satisfactorily traced, but by far the greatest number had the histologic traits usually seen in infiltrating duct carcinoma. In a small number of cases, lobule origin was apparent (about one in 25), and in still another small group simultaneous duct and lobule participation seemed present. The traceability of mammary cancer to any structure but the mammary ducts is uncommon, so that any theory of carcinogenesis in the human female breast must necessarily concern itself principally with lesions of the duct system. The commonest abnormality of the duct epithelium is papillary or near-papillary hyperplasia, and every conceivable transition can be noted to *in situ* or infiltrating cancer. Since the

usual mammary carcinoma is fully developed and advanced when it comes under observation no one can say what percentage of these cancers develops on a basis of papillomatosis, but it can be said that this basis does exist for some of the cases, and it is rare to find any early duct cancer of the breast in the absence of atypical papillomatosis.

The fact previously noted that atypical papillomatosis is seldom seen in noncancerous breasts is the only impressive difference shown so far. The actual number of papillary lesions that eventually become mammary cancers must necessarily be a very minute fraction, and we know of no way at the present to prognosticate the probable course of any given histologic type. It is certain that most of these lesions disappear from the breast, and in the material studied here there are many examples of the retrograde phases of these lesions, namely, varying degrees of abortive fibrosis with gradual obliteration of epithelial component. Now and then, however, one will find an area of papillomatosis in which the hyalinosis is apparently interrupted by a new surge of epithelial hyperplasia which may or may not show histologic atypism. This observation prompted the query as to whether or not a characteristic of cancerous breasts was persistence of papillary lesions. This is answered in the negative by noting that both noncancerous and cancerous breasts between ages 40–50 have papillary lesions in the same frequency—40 per cent; and the corresponding figures for the ages 50–60 are 23 per cent for noncancerous and 28 per cent for cancerous breasts. In the noncancer group the 58 cases of papilloma included five that were histologically atypical. This number is entirely too few to ascertain if age influences atypicalness, and no conclusion can be drawn from their occurrence at ages 48, 43, 55, 41 and 46. In the cancer cases with atypical papillomatosis, the age curve is practically identical with the age curve of the cancer cases with nonatypical papillomatosis, and in addition the same age curve is followed by the nonatypical papillomatosis of the noncancer series of cases.

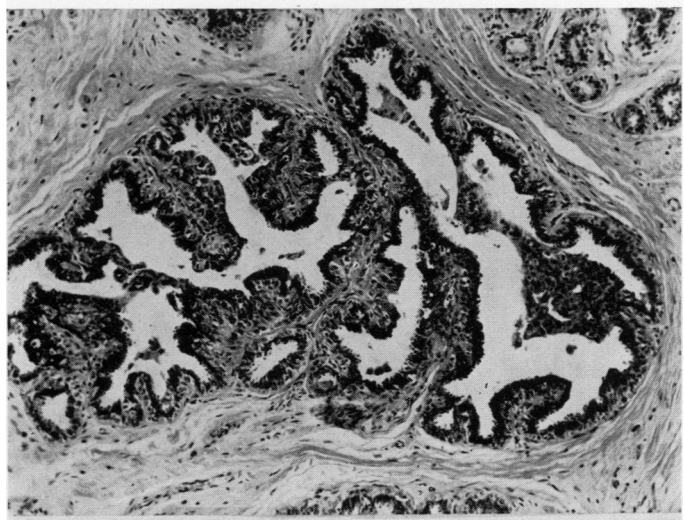
To illustrate transitions from orderly duct papillomatosis to mammary carcinoma is not difficult if samples are selected from several cases, but the entire gamut of alteration occurs only in the exceptional single case. Such a case with step-like histologic sequences is shown in Figures 1 through 8.

IV — BLUNT DUCT ADENOSIS

Blunt duct adenosis is a term we have used to designate one of the common proliferative lesions of the breast. Although it is undesirable to invent new terms, nevertheless, this designation expresses the principal characteristic of these structures, namely, that they are ducts which end abruptly and do not terminate in lobules. The origin, course and termination of these blunt end ducts can be traced easily in serial sections. It was after this sort of study that it became obvious that one cannot rely upon a single microscopic section in deciding whether a given structure is a minute cyst or not; hence the limiting of tabulation of cysts in this paper to cysts of

macroscopic proportion. Blunt end ducts usually originate at the distal or near distal extremities of the duct system, and since they begin at a point where periductal myoid tissue is absent or markedly attenuated, they typically lack this myoid investment and have a relatively poorly developed

FIG. 1



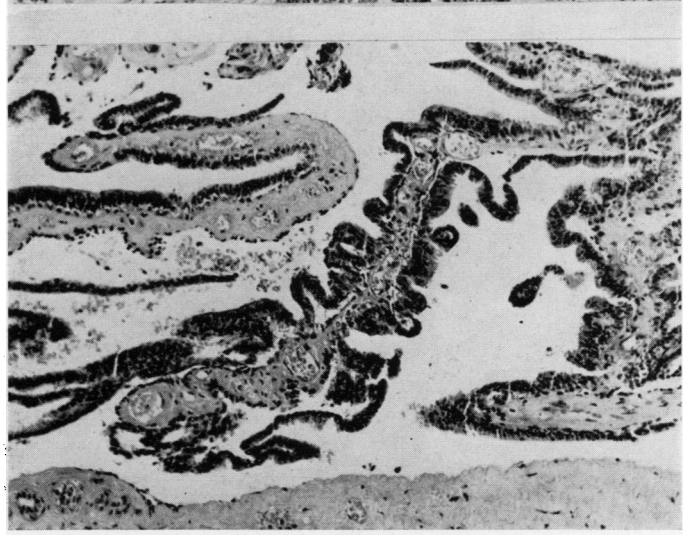


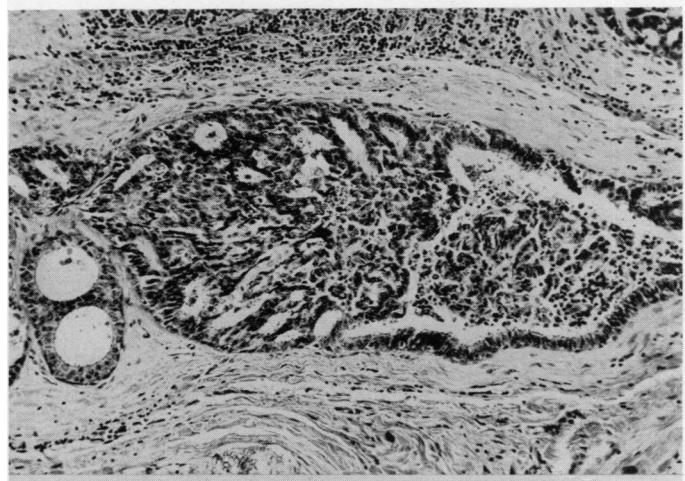
FIG. 2

FIG. 1.—Orderly vascularized papillomatosis of medium-sized mammary ducts. (Figures 1 through 8 are taken from a single breast)
FIG. 2.—Portion of a 1.5-cm. papilloma in a large duct. Orderly structure.

wall. On occasions this myoid element is seen at or near the main stem of a "parent" blunt duct, but it invariably disappears within a space of a millimeter. The elastica in the walls of these ducts is quite variable in amount, but commonly one sees in the breast tissue adjacent, an apparent

condensation of extraductal elastica. The initial branch of a blunt end duct may not divide, but ordinarily one and often many subdivisions are encountered in serial sections. They are apt to end in a cluster of closely but irregularly spaced blind channels but with no resemblance to usual lobule formation. It is to be noted that these structures have long since lost their

FIG. 3



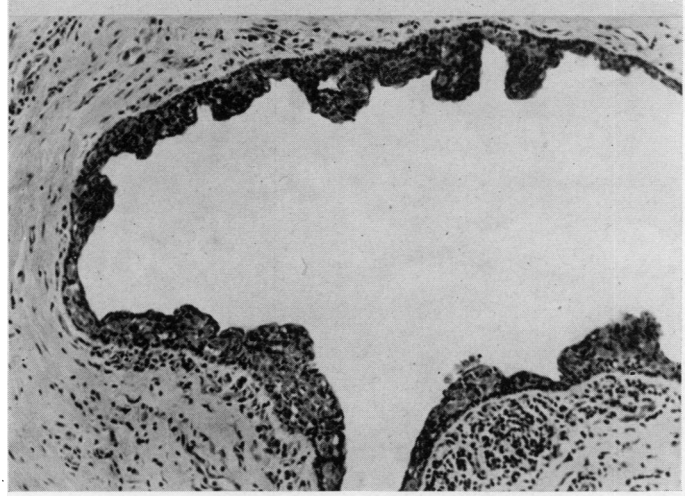


FIG. 4

FIG. 3.—Less orderly papillary and partly solid hyperplasia. Not vascularized.
FIG. 4.—Nonvascular stratification and papillary piling-up. Cytology atypical.

myoid envelope, whereas in the mammary lobules it is common for the terminal duct to retain its myoid layer until or even after it enters the lobule. The blunt end ducts furthermore often have relatively wide lumina which are actually wider by far than the mammary ducts from which they sprouted. The epithelial lining of these ducts is by no means uniform and

is apt to vary from point to point in any given duct or its divisions. Sometimes there is a two-layered epithelial lining with a low or flat basal row and an outer row that varies from low to quite tall cylindrical. Often the inner row of cells extrudes from its distal border a pink, homogeneous "cytoplasmic prolongation" identical with what is often seen protruding from

FIG. 5

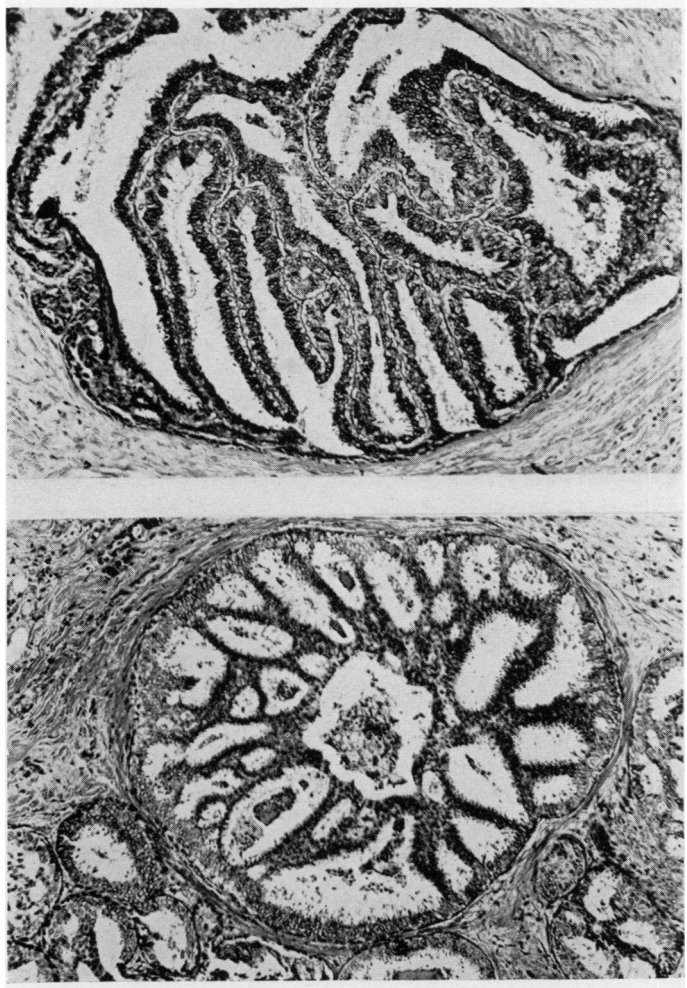


FIG. 6

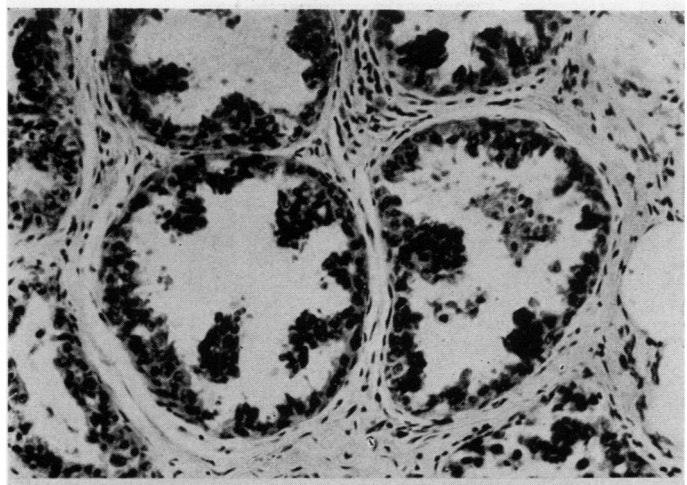
FIG. 5.—Intraductal papilloma cytologically rather uniform except at left lower corner. Over-all pattern atypical in spite of dominant maintenance of polarity.

FIG. 6.—Distinctly more advanced alteration of same general pattern as Figure 5. Low-grade intraductal papillary carcinoma.

the cells of normal mammary ducts. In addition to the relatively orderly epithelial lining just mentioned all degrees of stratification continuing to papillomatosis appear, and are by no means uncommon. It is not very unusual to find apocrine metaplasia of the epithelial lining of blunt end ducts. Finally,

blunt end ducts may have a single low or flat row of epithelium. The variable structure of blunt end ducts seems in all likelihood referable to whether the process is seen in an early or late phase. The early lesions have relatively narrow lumina with taller lining cells while the later lesions show broader lumina and shorter lining cells. Mitoses are uncommon but far more apt

FIG. 7



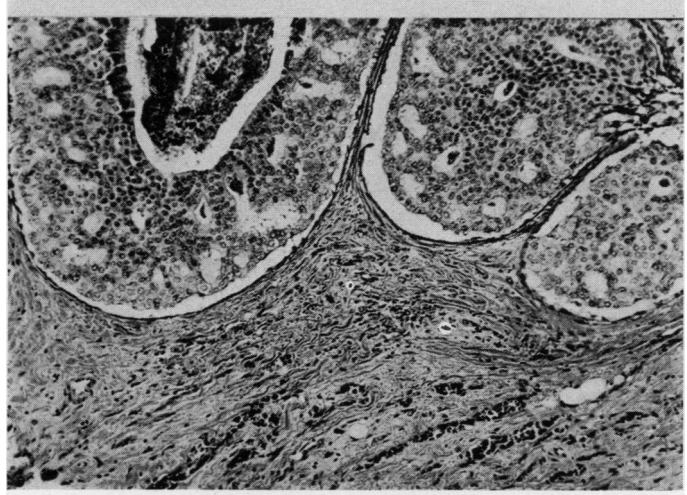


FIG. 8

FIG. 7.—Papillary intraductal carcinoma.
FIG. 8.—Fully developed intraductal and infiltrating carcinoma.

to occur in the earlier proliferative phases. In a single breast, blunt end ducts of every phase may be found, as if the organ had responded to multiple periods of stimulation alternating with periods of quiescence. The very late phases of great dilatation and flattening of epithelium practically never show any sign of proliferation. The degree of blunt duct adenosis ranges

from an occasional focus to a level where almost all of a several centimeter mass of breast tissue may be made up principally of these structures. In such a marked case, two findings stand out. There are practically no lobules, and small- (1–2 Mm.) and medium- (1 cm.) sized cysts are very numerous. This supports the idea of an origin of blunt end ducts from terminal ducts, with subsequent lobule obliteration as the dilatation progressively involves the preexisting lobules. It further suggests that cyst formation may be an end-result of blunt duct adenosis. Finally, the smallest cysts one sees invariably fail to have a circumferential layer of myoid.

In the 200 noncancerous breasts blunt duct adenosis was seen in 52, or 26 per cent, and in the 300 cases of mammary cancer, the figures are 78, or 26 per cent. By decades the occurrence is as shown in Table X.

TABLE X

OCCURRENCE OF BLUNT DUCT ADENOSIS

Decade	Noncancer Cases	Cancer Cases
30–40	36%	28%
40–50	28%	45%
50–60	20%	13%

The divergence in the frequency of blunt duct adenosis in the decade 40–50 is the greatest shown. A possible explanation for this is presented in the following: It has been previously shown in the decade 40–50 that cysts occurred in 65 per cent of noncancerous breasts and in only 18 per cent of cancerous breasts. It also seems, on the basis of preceding morphologic observation, that blunt duct adenosis is apt to eventuate in cyst formation. Hence, one may suggest that for the decade 40–50 the tendency in the benign cases is toward cyst formation with partial obliteration of the structures from which they arose. Consequently, there is a relative diminution of these antecedent structures in the age-period when cysts are most common. Similarly, in the decade 40–50 the tendency in the cancer cases is away from cyst formation, and this results in a greater relative frequency of the antecedent structures in the age-period when cysts are relatively fewest. It is, likewise, apparent that these blunt end ducts become less frequent with advancing age, hence sharing in the general tendency toward atrophy of the mammary system.

Table XI enumerates the lesions that accompany blunt duct adenosis. As in preceding tables, the frequency of these lesions as they occur in the cancer and noncancer groups as a whole is represented.

Quantitative differences again are shown and particularly noticeable is the marked tendency for the previously designated cystic and proliferative lesions to occur simultaneously, namely, cysts, hyperplasia of duct epithelium, duct papillomatosis, blunt duct adenosis, apocrine epithelium and sclerosing adenosis. Emphatically presented, again, is the failure of fibro-adenoma to be accented with this group. No differential feature between cancerous and noncancerous breasts appears that is not explainable by the preliminary comparisons of these types of breasts in various age groups.

TABLE XI

LESIONS ACCOMPANYING BLUNT DUCT ADENOSIS

	52 Noncancer Cases, with Blunt Duct Adenosis	200 Consecutive Noncancer Cases	78 Cancer Cases, with Blunt Duct Adenosis	300 Consecutive Cancer Cases
1. Hyperplasia of duct epithelium	77%	39%	84%	57%
2. Duct papillomatosis	60%	29%	61%	36%
3. Intracystic papilloma	Not charted	2%	Not charted	1%
4. Apocrine epithelium	63%	42%	53%	39%
5. Sclerosing adenosis:				
A. Diffuse	2%	1.5%	1%	0.3%
B. Focal	27%	11%	14%	7%
6. Fibro-adenoma	14%	19%	6.5%	7%
7. Tendency to fibro-adenoma	13%	3%	6.5%	6%
8. Cysts	87%	53%	44%	27%
9. Stasis and distention of ducts	40%	36%	53%	42%
10. Duct metaplasia	50%	34%	74%	45%
11. Periductal mastitis	30%	22%	15%	14%
12. Fat necrosis	0	2%	0	1.3%
13. Lobule frequency:				
Numerous	11%	13%	14%	10%
Average	68%	61%	41%	35%
Few	21%	26%	45%	55%
14. Periductal myoid atrophy	37%	27%	50%	42%

A further means of cross-analysis is afforded by comparing the cancer and noncancer breasts that show blunt duct adenosis with those that do not.

TABLE XII

COMPARATIVE FINDINGS IN BREASTS WITH AND WITHOUT BLUNT DUCT ADENOSIS

	52 Noncancer Cases, with Blunt Duct Adenosis	148 Noncancer Cases, without Blunt Duct Adenosis	78 Cancer Cases, with Blunt Duct Adenosis	222 Cancer Cases, without Blunt Duct Adenosis
1. Hyperplasia of duct epithelium	77%	25%	84%	47%
2. Duct papillomatosis	60%	18%	61%	28%
3. Intracystic papilloma	Not charted		Not charted	
4. Apocrine epithelium	63%	34%	53%	34%
5. Sclerosing adenosis:				
A. Diffuse	2%	1.5%	1%	0.5%
B. Focal	27%	7%	14%	4%
6. Fibro-adenoma	14%	21%	6.5%	9%
7. Tendency to fibro-adenoma	13%	2%	6.5%	5%
8. Cysts	87%	41%	44%	21%
9. Stasis and distention of ducts	40%	33%	53%	40%
10. Duct metaplasia	50%	30%	74%	36%
11. Periductal mastitis	30%	18%	15%	14%
12. Fat necrosis	0	3%	0	2%
13. Lobule frequency:				
Numerous	11%	13%	14%	9%
Average	68%	57%	41%	33%
Few	21%	30%	45%	58%
14. Atrophy of periductal myoid	37%	24%	50%	39%

The same trends seen in Table XII are repeated in sharper contrast with the accent still on the simultaneous occurrence of the lesions already designated.

Blunt duct adenosis cannot be associated with pregnancy or nursing, inasmuch, as these states were equally common in the cases with or without this lesion and, further, blunt duct adenosis is seen in individuals who have

never been pregnant. Finally, these structures show no relation to the phasic changes of the menstrual cycle. They are, undoubtedly, proliferative manifestations and they apparently can exist for considerable periods, eventuate in cyst formation, or undergo involution and atrophy.

FIG. 9

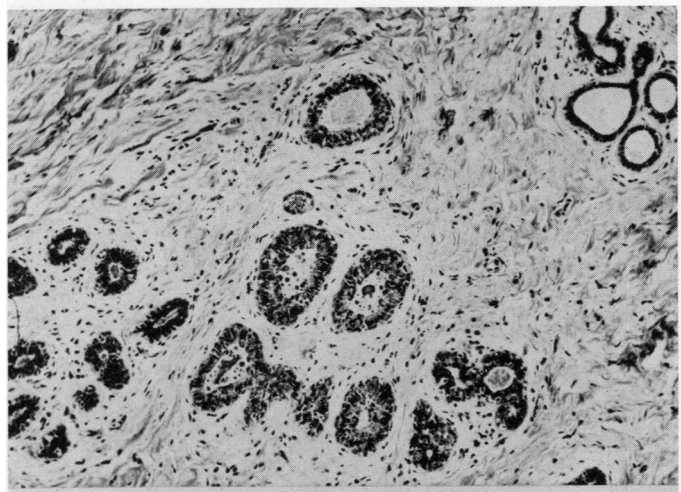


FIG. 10

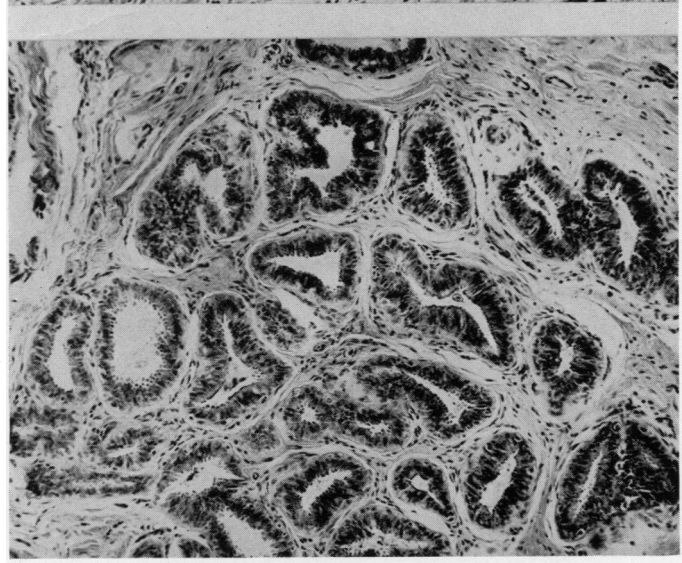


FIG. 9.—Relatively early phase of blunt duct adenosis. Failure of normal lobule formation.
FIG. 10.—Process of blunt duct adenosis more fully developed.

It is difficult to be sure of the part blunt end ducts play in the morphogenesis of mammary carcinoma. Papillomatosis occurs in blunt end ducts but it is not as common as in the permanent duct system and is far less liable to show histologic atypism. Any duct that is the site of papillomatosis is very

likely to show atrophy of its periductal myoid layer and, since absence of myoid is a prime characteristic of blunt end ducts, there are many occasions when one is uncertain whether to call a papilloma-containing duct a permanent duct or a newly formed blunt end duct. We were able to trace cancer to

FIG. 11

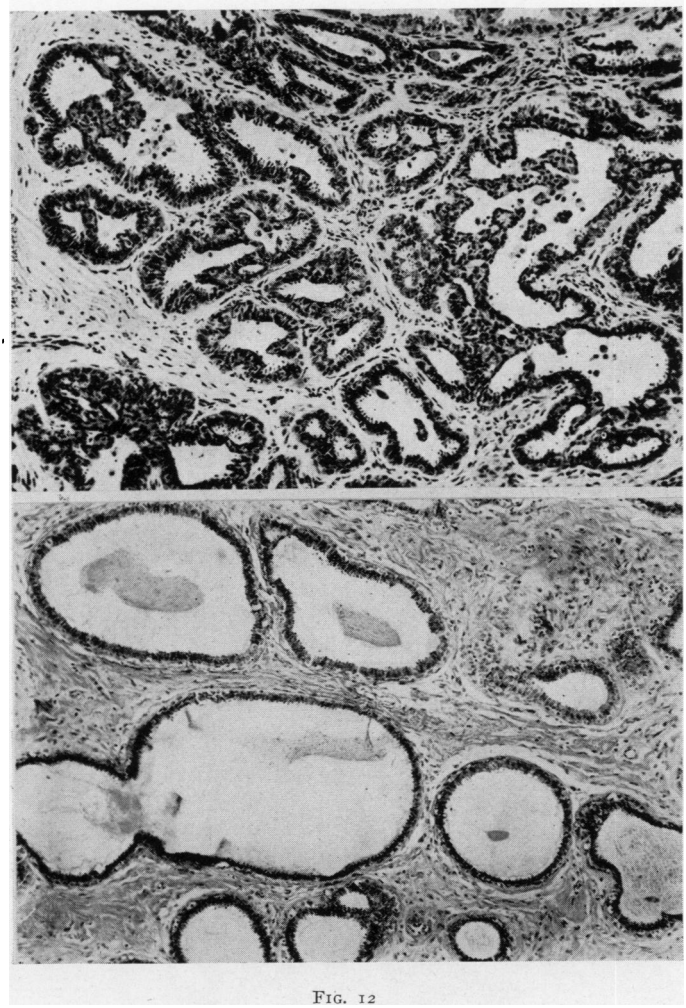


FIG. 12

FIG. 11.—Papillomatosis in a group of blunt end ducts.
FIG. 12.—Intermediate phase of blunt duct adenosis. Subsidence of proliferative impulse, widening of lumina.

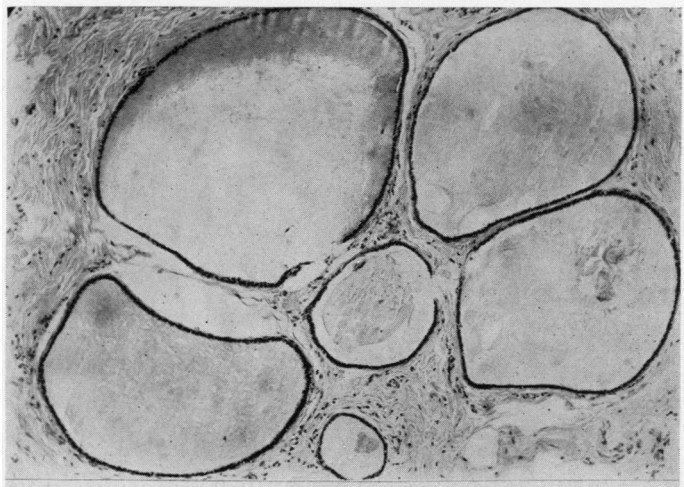
this source with reasonable certainty in only four out of 300 cases, which is in all probability a somewhat low figure. Some of the principal structural traits of blunt duct adenosis are represented in Figures 9 through 13.

V. APOCRINE EPITHELIUM

This term refers to epithelium consisting of the very characteristic large, usually tall, cylindrical cells that have relatively small nuclei and abundant,

clear, bright, eosinophilic cytoplasm. Aggregates of this kind of epithelium can commonly be seen in the gross as discrete yellowish-brown, slightly elevated, glistening areas, usually 1–2 Mm. in diameter but occasionally of much larger dimension. The larger aggregates are almost invariably partly cystic

FIG. 13



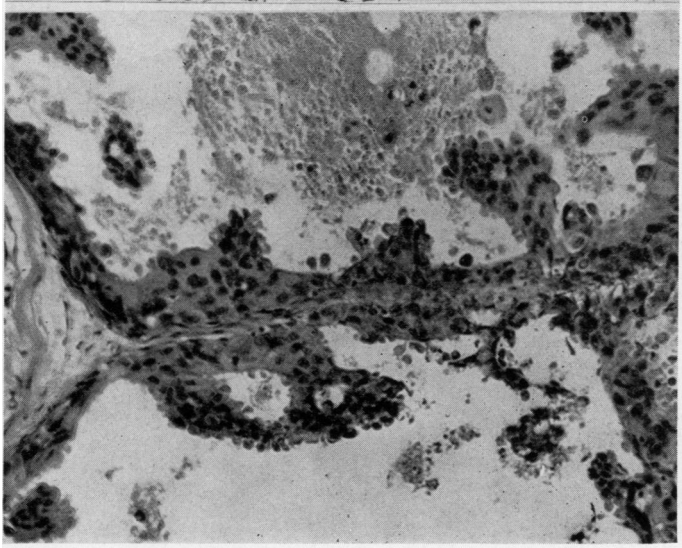


FIG. 14

FIG. 13.—Late phase of blunt duct adenosis.
FIG. 14.—Apocrine epithelium in papillary form. Cytology not atypical.
(Figures 14 through 17 were taken from a single breast)

and/or adenomatoid. Microscopically, in single sections, apocrine epithelial islands may be seen as apparently isolated glandular or cystic structures or, less often, they are seen in direct continuity with a mammary duct that is lined elsewhere by conventional epithelium. When examined in serial

sections, it is surprising how often a connection with ducts or lobules is demonstrated, and it becomes evident that this is the usual structural relationship. Complete isolation from the duct system is shown on occasion and, when this is true, cystic distention is the rule. Papillary hyperplasia of slight or moderate degree is rather common, appearing in about a third of apocrine epithelial foci of both cancerous and noncancerous breasts.

Some form of apocrine epithelium was seen in 42 per cent of breasts free from cancer, and in 39 per cent of breasts containing cancer. Most of these findings are based on microscopic study and, hence, are largely chance observations. The frequency would of course be greater if very numerous blocks were made, and we can only regard the figures given here as comparative and not absolute. Table XIII shows the incidence by decades.

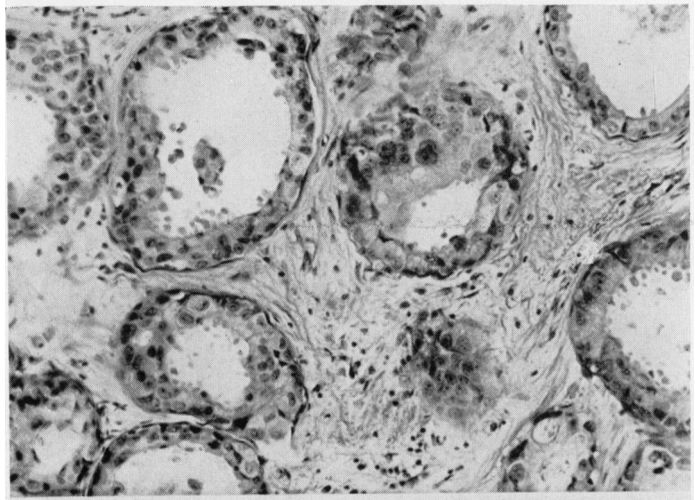
TABLE XIII

OCCURRENCE OF APOCRINE EPITHELIUM

Decade	Noncancer Cases	Cancer Cases
30–40	33%	25%
40–50	47%	44%
50–60	40%	31%

Thus, no wide divergence can be demonstrated between cancer and noncancer cases. It is worth noting, however, that these structures are most frequent during the decade 40–50, when the breast shows its highest level of noncancerous proliferative lesions. Without the series of noncancerous breasts as a control group, the common occurrence of this kind of epithelium in cancer cases might be interpreted as being important in mammary cancerigenesis, especially by those who claim that a high proportion of breast cancers are of sweat gland origin, which viewpoint we emphatically reject. The same is equally true of other lesions, but it is our desire to show that mere statistical association needs the support of demonstrable morphologic relationship before any given lesion can be ascribed a place of importance in the actual histogenesis of cancer. Pursuing this course as regards apocrine epithelium, it was possible to designate only three mammary cancers in 300 as showing histologic characters that would prove or suggest origin from this source. Furthermore, it is difficult to find in either cancerous or noncancerous breasts any foci of apocrine epithelium that show histologic atypism. In the 500 cases studied here, only two examples of this change were found. Both of these atypical foci were papillary and in each case the breast contained a cancer. One of these was an infiltrating duct carcinoma of usual type and the other a carcinoma with quite large cylindrical cells having relatively small nuclei and abundant clear, eosinophilic cytoplasm. In a large series of mammary cancers about 3 per cent are composed of cells resembling the apocrine type. There is then no way of ascribing a major morphologic rôle to these cells in mammary carcinogenesis. It is not possible to detect transitions from mammary apocrine epithelium to mammary cancer in any but the very exceptional case. Such a sequence is shown in Figures

FIG. 15



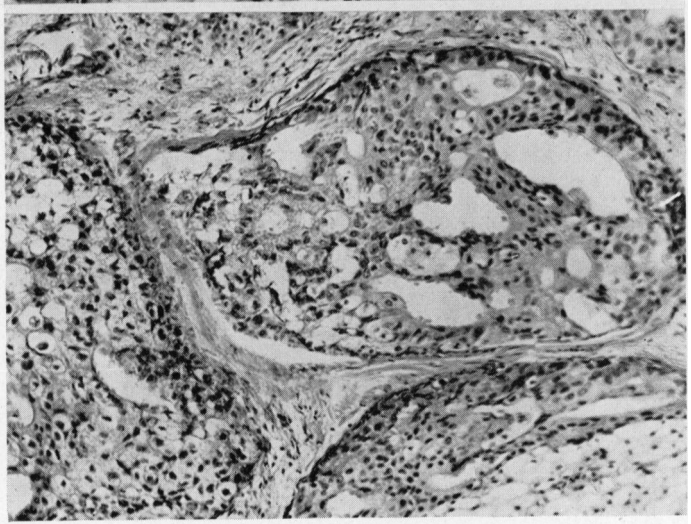
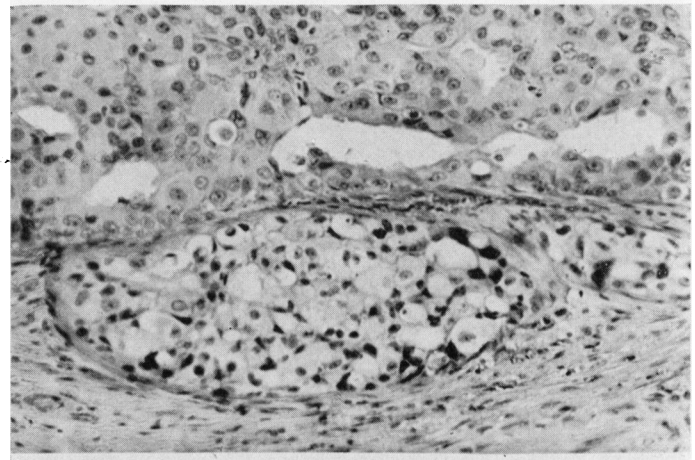


FIG. 16

FIG. 15.—Ducts lined by apocrine epithelium, portions of which are of atypical structure.

FIG. 16.—Noninfiltrating carcinoma composed of apocrine epithelium.

FIG. 17



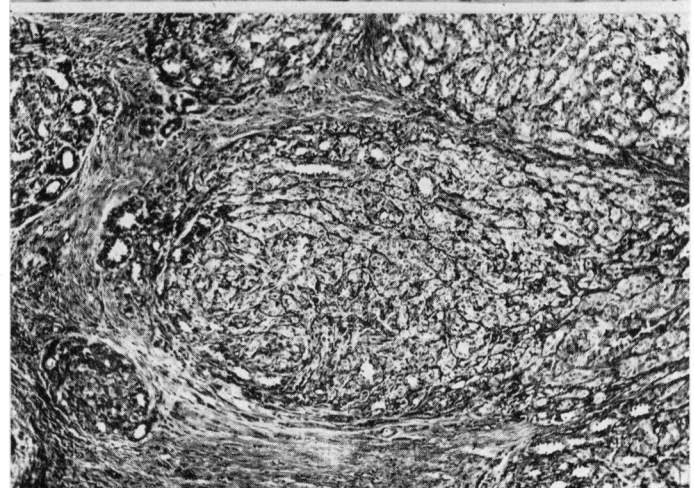


FIG. 18

FIG. 17.—Intraductal and infiltrating carcinoma made up of apocrine cells.

FIG. 18.—Highly cellular, florid phase of sclerosing adenosis. Single field of type commonly confused with mammary carcinoma. Section from a discrete 2.5 cm. mass.

14 through 17, the illustrations being taken from a single breast. All the epithelium shown had the characteristic eosinophilic tinctorial quality. Axillary nodes were involved in this case.

Table XIV is designed to show what lesions are apt to occur in cancerous and noncancerous breasts when the common factor is the presence of apocrine epithelium. As usual, the occurrence of these lesions in the 200 benign breasts and 300 cancerous breasts, as a whole, is included.

TABLE XIV

LESIONS ACCOMPANYING APOCRINE EPITHELIUM

	84 Noncancer Cases, with Apocrine Epithelium	200 Noncancer Cases	117 Cancer Cases, with Apocrine Epithelium	300 Cancer Cases
1. Hyperplasia of duct epithelium	65%	39%	70%	57%
2. Duct papillomatosis	45%	29%	45%	36%
3. Intracystic papilloma	0	2%	1%	1%
4. Blunt duct adenosis	56%	26%	47%	26%
5. Sclerosing adenosis:				
A. Diffuse	1%	1.5%	0	0:3%
B. Focal	23%	11%	14%	7%
6. Fibro-adenoma	8%	19%	6%	7%
7. Tendency to fibro-adenoma	4%	3%	8%	6%
8. Cysts	83%	53%	40%	27%
9. Stasis and distention of ducts	50%	36%	62%	42%
10. Duct metaplasia	52%	34%	71%	45%
11. Periductal mastitis	30%	22%	20%	14%
12. Fat necrosis	0	2%	2%	1.3%
13. Lobule frequency:				
Numerous	10%	13%	7%	10%
Average	59%	61%	39%	35%
Few	31%	26%	54%	55%
14. Periductal myoid atrophy	37%	27%	45%	42%

TABLE XV

COMPARATIVE FINDINGS IN BREASTS WITH AND WITHOUT APOCRINE EPITHELIUM

	84 Noncancer Cases, with Apocrine Epithelium	116 Noncancer Cases, without Apocrine Epithelium	117 Cancer Cases, with Apocrine Epithelium	183 Cancer Cases, without Apocrine Epithelium
1. Hyperplasia of duct epithelium	65%	19%	70%	42%
2. Duct papillomatosis	45%	24%	45%	30%
3. Intracystic papilloma	0	3%	1%	2%
4. Blunt duct adenosis	56%	4%	47%	12%
5. Sclerosing adenosis:				
A. Diffuse	1%	2%	0	2%
B. Focal	23%	5%	14%	2%
6. Fibro-adenoma	8%	27%	6%	8%
7. Tendency to fibro-adenoma	4%	6%	8%	4%
8. Cysts	83%	31%	40%	19%
9. Stasis and distention of ducts	50%	25%	62%	30%
10. Duct metaplasia	52%	22%	71%	30%
11. Periductal mastitis	30%	16%	20%	11%
12. Fat necrosis	0	3%	2%	1%
13. Lobule frequency:				
Numerous	10%	14%	7%	13%
Average	59%	59%	39%	32%
Few	31%	27%	54%	55%
14. Periductal myoid atrophy	37%	20%	45%	39%

The trends shown in previous tables are repeated in Table XIV, and in Table XV a further comparison is shown by charting the lesions occurring in breasts that do and do not contain apocrine epithelium.

Study of the preceding tables justifies the statement that apocrine epithelium is most apt to be found in a breast containing certain noncancerous proliferative lesions. This is further supported by the following: Rather commonly in cases of papillomatosis, isolated foci of apocrine cells or glands are seen in that part of the papilloma which protrudes into the duct lumen. These foci are often multiple and are entirely separated from one another, so that it seems reasonable under these circumstances to regard them as metaplastic in nature, newly formed, and, therefore, proliferative. It can also be shown that apocrine elements take part in sclerosing adenosis and blunt duct adenosis, the component parts of which are certainly newly formed structures. Occasional mitoses may be found in areas of epithelium of apocrine pattern, indicating that these are in some instances at least proliferative rather than static structures. We believe that all "pink epithelium" in the breast arises on a basis of hyperplasia and metaplasia. Absolute determination of this would depend on studying material from breasts of gradually decreasing age-groups until the earliest manifestations are encountered. We have seen apocrine elements in a breast of an infant a few months old. This was, however, in an actively proliferative adenomatoid lesion of papillary character.

In summary, an analysis of cancerous and noncancerous breasts, using the presence or absence of apocrine epithelium as the means of comparison, shows no essential difference.

VI. SCLEROSING ADENOSIS

The terms "fibrosing adenomatosis," "sclerosing adenomatosis" and "sclerosing adenosis" have long been used interchangeably in this Hospital to identify a specific lesion quite commonly misinterpreted and erroneously diagnosed as mammary carcinoma. The interchangeable terms above are incompletely descriptive since they designate only one phase of the process to be described here, namely, that of sclerosis. These lesions have been also termed "myo-epithelial" tumors.[1] The phase of fibrous sclerosis, however, is the one usually seen, it is quite characteristic, and hence it seems permissible to stress this feature in selecting a term applicable to the lesion. The stage of fibrous sclerosis is, of course, a late one and it is not usual to see the earlier or "florid" phase of pure epithelial efflorescence. So far, we have seen only a single case in which the microscopic structure was purely "florid." It is rare to find "floridness" the chief feature in any case, but over a period of some years all conceivable intermixtures of florid areas and sclerosing areas have been observed.

Sclerosing adenosis occurs in two forms. In the first of these a palpable tumor mass is present. In the second, minute focal areas are seen only on microscopic examination and the lesions are but incidental findings. The

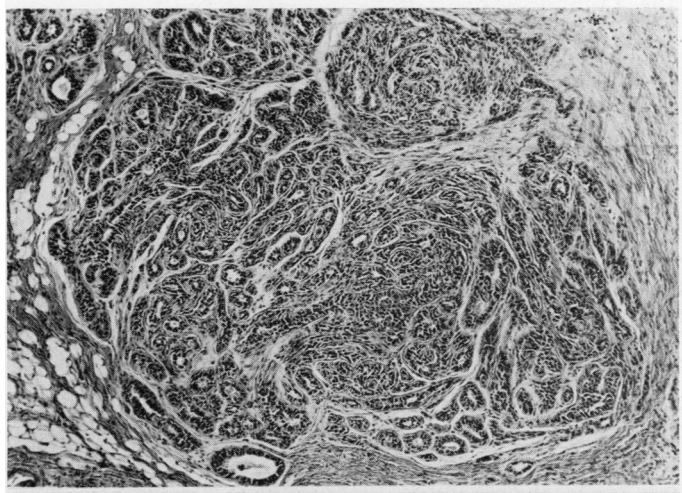
focal microscopic lesions are 20 to 30 times as frequent as the discrete tumors, and present no clinical problem.

When sclerosing adenosis presents as a palpable lump the true identity of the process can be established by the following characters: The lump is freely movable in the breast and there are no secondary skin changes. The patients are usually in the twenties or thirties. We have seen no case below puberty and only a few in the teens. Now and then the lesion occurs after forty and in isolated instances in the fifties and sixties. The tumors are customarily seen by the pathologist when a specimen is locally excised and submitted for frozen-section, the clinical diagnosis having been fibro-adenoma or cyst. The consistency is ordinarily less rubbery than in fibro-adenoma and less firm than in mammary carcinoma. However, both extremes are possible. The tumors lack the smooth globoid or elliptical shape of a fibro-adenoma and instead show nodularity of varying coarseness. They are discrete but are apt to be indefinitely encapsulated. On section, resistance to cutting is variable, depending on elasticity or firmness. The cut surface is grayish-white as a rule but may be partly or chiefly faint, pinkish-yellow. Usually, the chalky streaks so common in mammary cancer are absent but in several instances they have been observed. The most important gross observation is the detection of usually definite lobulation that may vary from a millimeter to over a centimeter. The lobulations are chiefly in direct contiguity but they may merge imperceptibly or sometimes be separated by an interval of a few millimeters. There is often a certain minor degree of translucence. The lobulated surfaces customarily project slightly. The periphery of the tumor is characteristically noninfiltrating in appearance but some specimens may be confusing in this respect. Given a case in which there is distinct lobulation, neat circumscription and an absence of chalk streaks, a gross diagnosis of cancer is unlikely. But there are a few cases in which lobulation and circumscription are not clear and if chalk streaks and undue firmness are added, one is very apt to get a gross impression of mammary cancer. Fortunately, this combination of characters is rare. If the gross impression of cancer is carried over to the frozen or paraffin section, danger is increased since further microscopic confusion is possible.

The chief pitfall in microscopic diagnosis, particularly in frozen sections, is seeing what superficially appears to be infiltration. When properly analyzed, it becomes evident that this picture is the result of abortive fibrosis or hyalinosis. It is the stage of sclerosis where epithelium has lost the initiative and is "choked" by fibrous or hyaline matrix. This connective tissue dominance produces irregular patterns where thin epithelial columns are haphazardly isolated. Due to constrictive pressure the shape of the epithelial cells is apt to be variable, and the sum total yields an impression of pleomorphism plus invasiveness. It is important to note that, at this phase of the process, nuclear staining is regular and mitoses are absent. Looked at with a low power lens one is often able to detect lobulation even when it is

grossly inconspicuous, and it is usual to find that the greatest degree of sclerosis occurs at the periphery of the lobulated portions. Eventually the entire area of lobulation will become hyalinized, but this is a change that may require many years. In almost any case certain microscopic fields can be found which, if viewed alone, would certainly pass for cancer, and

FIG. 19



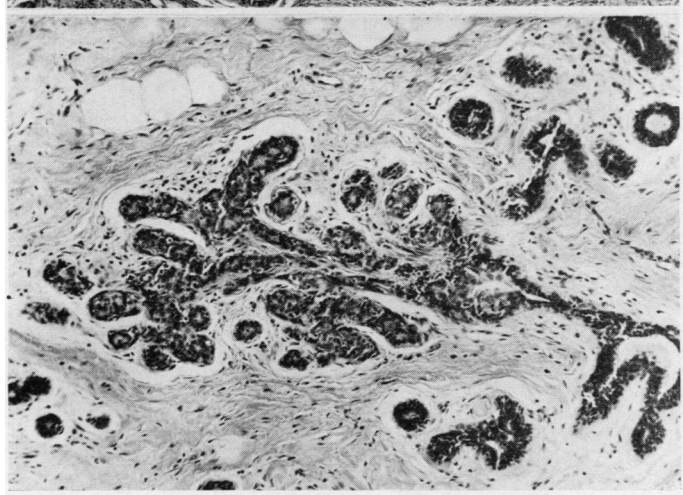


FIG. 20

FIG. 19.—Section from a palpable mass. Intermediate phase with moderate sclerosis.
FIG. 20.—Focal lobular area of sclerosing adenosis. No palpable mass. Beginning sclerosis.

it is necessary that the lesion be examined as a whole and the various changes reconstructed, to insure proper interpretation. The occurrence of cellular areas in these tumors is a further source of microscopic confusion. It has been stated before that florid and sclerosing areas may be present in the same tumor.

During the florid phase moderate cellular variability may be seen and mitoses are not infrequent. These findings must also be discounted and the decision as to diagnosis made on estimating all of the features present. During the florid phase there is extensive multiplication of duct-like structures. Both extra- and intralobular members of the mammary paren-

FIG. 21

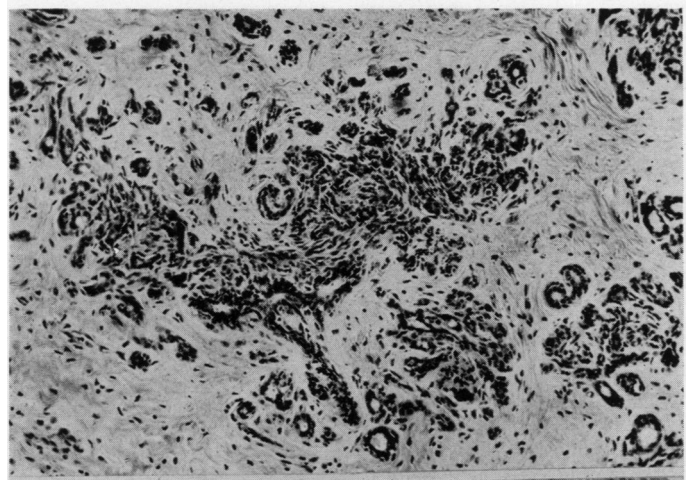


FIG. 22

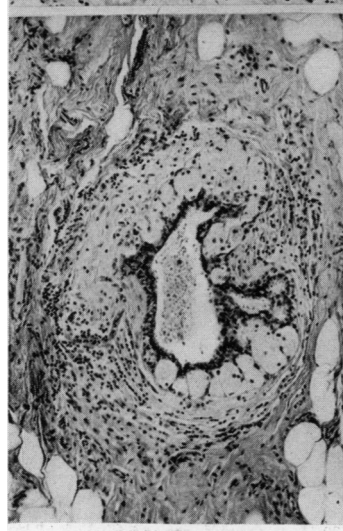


FIG. 23

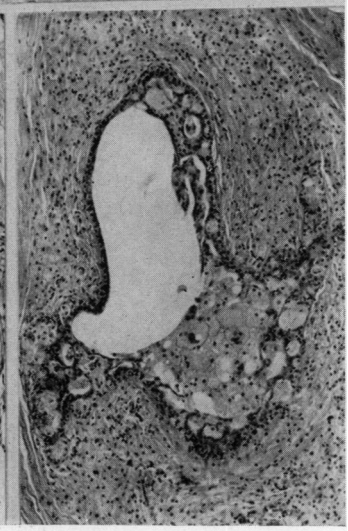


FIG. 21.—Advanced stage of sclerosing adenosis with obliteration of lumina. No palpable mass.

FIG. 22.—Dilated mammary duct containing stasis material. Periductal inflammation with infiltrate of lymphocytes and large fat-filled phagocytes.

FIG. 23.—Same process as in Figure 22, but somewhat more advanced.

chyma are seen to participate and the newly formed ducts often show papillary and solid epithelial plugging. Sometimes the proliferation is so diffuse that solid epithelial islands, small and large, are formed in which lumina are not visible, and again single microscopic fields can be found

that would be individually indistinguishable from cancer. In purely florid areas connective tissue does not participate. Even in the florid phase of sclerosing adenosis there is a tendency to lobulation. A generalization may be made that in either phase, the lesion is "put together" in a different fashion than is mammary cancer. Some of the microscopic qualities of sclerosing adenosis are reproduced in Figures 18 through 21.

It seems clear enough that sclerosing adenosis can begin in an intralobular position or commence in near-terminal or terminal ducts that fail to form normal mammary lobules. This view of origin is supported by the fact that the newly formed tubular structures practically never have a circumferential myoid investment. When sclerosing adenosis presents as a palpable mass, lobule participation in the tumor proper may not be visible but in outlying breast tissue it is commonly observed. In the focal microscopic form of sclerosing adenosis lobular origin is by far the more common, and often the lesions are of such small proportion that normal lobule size may be maintained, and in some lobules all of the lobule constituents do not necessarily participate. Both florid and sclerosing phases can be seen in the focal microscopic form of sclerosing adenosis, and the only real difference between this form and the tumorous form is that one occurs in miniature.

It may be well to repeat that sclerosing adenosis infrequently produces a palpable tumor. This infrequence is undoubtedly the chief reason that it is so apt to be mistaken for cancer. On a Surgical Service that does over a thousand breast operations yearly, the annual occurrence of the palpable or clinical form of the disease ranges from six to twelve cases.

In the 200 noncancerous cases studied here, three discrete tumors due to sclerosing adenosis were seen, while in the 300 cancer cases, there was only one example, in addition of course, to the cancer. In the statistics to follow, these few instances of discrete tumor cases have been merged with the focal microscopic type. Thus, in 200 breasts without cancer, sclerosing adenosis was found in 12.5 per cent and in 300 breasts containing cancer, in 7 per cent. The number of cases in either group is insufficient to give reliable percentage figures by decades, but this is nevertheless shown in Table XVI.

TABLE XVI

INCIDENCE OF SCLEROSING ADENOSIS

Decade	Number of Noncancer Cases, with Sclerosing Adenosis	Number of Cancer Cases, with Sclerosing Adenosis
20–30	5	0
30–40	4	2
40–50	16	9
50–60	0	3
60–70	0	6

The only impressions that can be gained from Table XVI are that sclerosing adenosis (in essence, the focal microscopic form) is most common in the decade 40–50, and that the lesion, as such, can endure in the breast far beyond the menopause.

Table XVII shows the lesions that occur together with sclerosing adenosis.

TABLE XVII

LESIONS ACCOMPANYING SCLEROSING ADENOSIS

	26 Noncancer Cases, with Sclerosing Adenosis	200 Noncancer Cases	20 Cancer Cases, with Sclerosing Adenosis	300 Cancer Cases
1. Hyperplasia of duct epithelium	60%	39%	85%	57%
2. Duct papillomatosis	56%	29%	75%	36%
3. Intracystic papilloma	0%	2%	0%	1%
4. Blunt duct adenosis	60%	26%	60%	26%
5. Apocrine epithelium	52%	42%	70%	39%
6. Fibro-adenoma	16%	19%	5%	6%
7. Tendency to fibro-adenoma	4%	3%	5%	6%
8. Cysts	64%	53%	60%	27%
9. Stasis and distention of ducts	32%	36%	65%	42%
10. Duct metaplasia	44%	34%	75%	45%
11. Periductal mastitis	26%	22%	20%	14%
12. Fat necrosis	0%	2%	0%	1.3%
13. Lobule frequency:				
Numerous	28%	13%	10%	10%
Average	52%	61%	45%	35%
Few	20%	26%	45%	55%
14. Periductal myoid atrophy	36%	27%	55%	42%

From the foregoing it is clear that other cystic and proliferative lesions of types previously mentioned, tend to occur along with sclerosing adenosis; and, moreover, they occur with greater than usual frequency. One proliferative lesion, fibro-adenoma, does not follow this trend nor has it done so in former analyses.

It does not seem possible to show a fundamental difference between cancerous and noncancerous breasts on the basis of sclerosing adenosis. That this lesion has little or no part to play in mammary cancerigenesis we now feel reasonably certain. We have never seen any crucial morphologic evidence in any case that a mammary carcinoma was arising on a basis of sclerosing adenosis. The very occasional case in which cancer and sclerosing adenosis merge in the same microscopic field has always shown more convincing evidence of origin from other sources or simultaneously in sclerosing adenosis and other sources, so that satisfactory traceability to sclerosing adenosis as a precancerous entity has been lacking and the coexistence attributed to chance. For years, conservative local surgery has been recommended in cases of sclerosing adenosis, and no incident yet has occurred to alter this point of view.

The etiology of this lesion is unknown. The microscopic appearance does not change with phases of the menstrual cycle. Menstrual histories of the patients reveal nothing characteristic. In one case the patient, age 24, presented a 1.5-cm. lump in her breast that had been present and unchanged for six months. A 20 mg. pellet of estradiol was implanted adjacent to the lump. During 12 weeks of observation the lump in her breast changed not at all in character. At the end of this period the pellet and the breast tumor with adjacent breast tissue were excised. At the time of removal

the pellet weighed 14 mg. The 1.5-cm. mass was a fibro-adenoma, with focal areas of sclerosing adenosis. In the adjacent breast tissue were additional foci of sclerosing adenosis. All areas of sclerosing adenosis were similar in structure and in the phase of fibrous sclerosis. None of the usual features of the florid phase was seen. This case was of interest because of the apparent negative response of the sclerosing adenosis (and for that matter the surrounding breast tissue) to estradiol administration.

Highly florid focal sclerosing adenosis has been observed in the breast of one pregnant patient. However, comparison with florid lesions in breasts of nonpregnant individuals renders it impossible to state that the concomitant pregnancy increased the floridity of the lesion, since equal degrees of floridity occur quite apart from pregnancy. Every phase of the process has been seen in individuals who have never been pregnant, from which it is obvious that pregnancy is not a necessary initiating growth factor, and it is not a postlactational involutional phenomenon. Material studied to date has given no clue to what initiates the early or florid phase. It can be said that this pattern is much more common in the third and fourth decades, but on occasion unusually florid cases are seen in older women, an extreme example being in a patient age 62. The period during which a lesion may remain in a florid phase is also indeterminate but this character was seen in one tumor whose presence had been known for 12 years. In another florid case, the lump was first noted shortly after injections of unstated amounts of theelin. In still another case the lump was observed prior to theelin therapy, and after administration of 100,000 units, the symptoms of lump were said to have been partially relieved. In the section, however, the histology was anything but that of a lesion presumably "relieved," the florid characters being extremely prominent. These chance observations cannot, of course, answer questions on etiology, but they tend to emphasize the unpredictability of hormonal influences.

VII — PERIDUCTAL MASTITIS

The most common histologic feature of periductal mastitis is more or less inflammatory cell infiltrate about the mammary ducts, the predominant cells usually being lymphocytes. The appearance of inflammatory cells, however, is in nearly every case preceded by other changes, namely, stasis of amorphous acellular and cellular duct content, dilatation of the duct wall and varying degrees of atrophy of periductal myoid tissue. A common accompaniment of the process is flattening of the lining epithelium of the duct, usually slight, but in severe cases quite marked so that true squamous metaplasia results. Also, commonly observed are fat-laden phagocytes within the duct lumen, scattered or clustered among the lining epithelial cells and/or dispersed about the duct wall in varying numbers where they mingle with other cells, usually lymphocytes. If the lining epithelium and wall of a duct are eroded, it is not uncommon to find old or fresh blood in the lumen or adjacent periductal tissue, and this is responsible for some cases that

present clinically with bleeding nipple as the chief symptom. Every conceivable combination and degree of these changes are observed, but over-all the most constant finding is stasis of duct content. The cause of stasis is not apparent, but it is reasonably certain that anatomic obstruction to ducts is not essential. No doubt obstruction due to duct papillomas, pressure from cysts or tumors or senile atrophy with duct dilatation facilitate the process, but on close analysis these factors do not explain many of the cases. When these lesions seem concerned the periductal mastitis occurs distally. Such lesions seldom account for the most marked or extensive cases. In noncancerous papillomatosis of multiple small ducts, there is seldom associated periductal mastitis when the papillary lesions are early and small. A solitary macroscopic papilloma is far more apt to produce this lesion and the changes appear to depend on the production of stasis of duct content. Furthermore, in comedocarcinoma, where the ducts are lined by cancer cells and there is much central necrosis, somewhat analogous to ordinary duct stasis, periductal mastitis is common and apt to be severe.

One of the consequences of duct stasis is erosion of the epithelial lining. This commonly occurs with relatively little inflammatory reaction. When, however, the duct wall is weakened or penetrated the contents of the duct gain access to adjacent tissue and further changes ensue. If the duct is surrounded by dense fibrous tissue, the reaction produced is relatively mild and not extensive. But if the adjacent tissue is fatty, the outpouring of duct content is followed by a more severe and more complicated inflammatory reaction characterized by fat necrosis in which the break-down products of the fat tissue play an aggravating rôle. The end-result is the production of foreign body type of inflammation. Cholesterol, its esters, and fatty acids are found in these areas of inflammation and are easily identified as crystals or by special staining. The process can be extremely chronic, lasting for months and years. In fully developed form, a palpable mass may be produced and the breast present brawny induration. Secondary changes in the overlying skin sometimes occur, and it is readily understandable why on occasion a clinical diagnosis of cancer is made. This clinical condition has been described by Lee and Adair[2] under the designation "traumatic fat necrosis." It is notable, however, that many cases do not give a history of trauma, and when this is lacking the term "inflammatory necrosis" is a better one. Trauma is not an essential by any means to mammary fat necrosis, but one might postulate that trauma to a breast already the seat of stasis, distention and periductal mastitis augments the chances of that breast developing clinical fat necrosis. In summary, we regard periductal mastitis as representing only a part of a pathologic complex, usually preceded by duct stasis and impairment of the duct wall and followed in some instances by varying degrees of mammary fat necrosis. In this connection see Figures 22 through 25.

Periductal mastitis was found in 44, or 22 per cent, of the 200 noncancerous breasts and in 44, or 15 per cent, of the 300 cancerous breasts.

In the 44 noncancerous breasts with periductal mastitis, the average age of the patients was 41.7 years, while in the 44 cases of cancer with periductal mastitis the average age was 49.7. The occurrence by decades is shown in Table XVIII. On account of the morphologic relationship between

FIG. 24

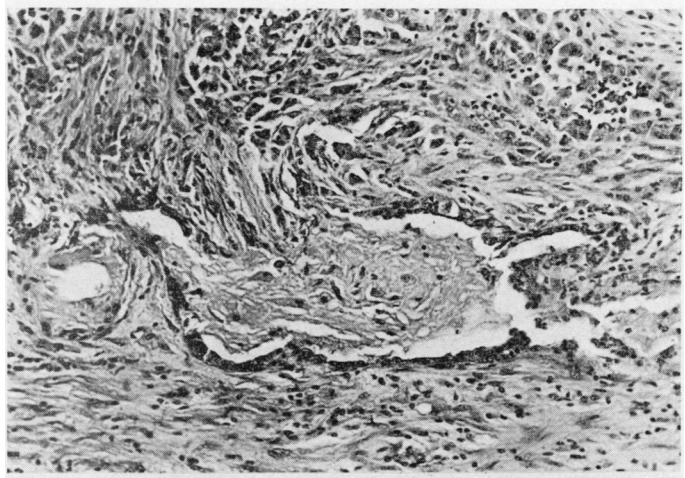


FIG. 25

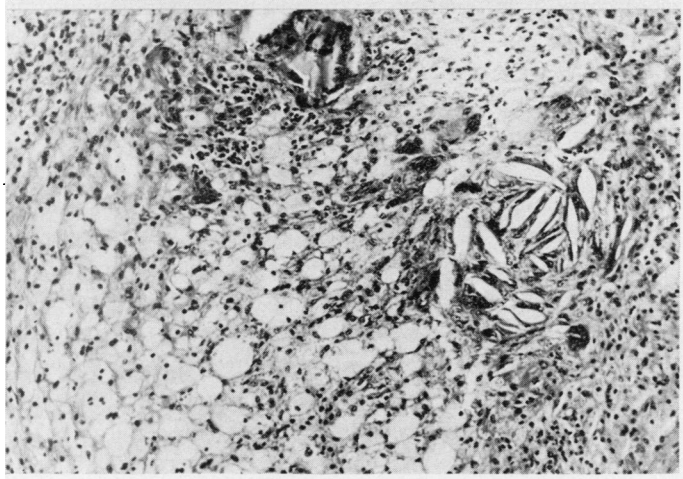


FIG. 24.—Erosion of lining epithelium and duct wall. Escape of duct content and productive inflammatory response with foreign body characters.
FIG. 25.—Sequela of leakage of duct content; fully developed inflammatory fat necrosis. Spindle-shaped spaces mark former sites of crystalline material removed by solvent chemicals. Many foreign body giant cells.

periductal mastitis and combined stasis and distention of mammary ducts, figures for the latter are included.

The greater frequency of periductal mastitis in breasts without cancer is correlated in each age-group by a correspondingly greater frequency of stasis of duct content and duct dilatation. This statistical interrelationship would not be given so much weight if it were not for the fact that it is

TABLE XVIII

OCCURRENCE OF PERIDUCTAL MASTITIS, STASIS OF DUCT CONTENT AND DUCT DISTENTION

	Noncancerous Cases		Cancer Cases	
Decade	Periductal Mastitis	Combined Stasis and Distention	Periductal Mastitis	Combined Stasis and Distention
30–40	30%	40%	10%	28%
40–50	15%	48%	8%	30%
50–60	48%	70%	18%	48%

supported by morphologic relationship, the simultaneous occurrence of the lesions in the same microscopic or larger areas. Again, it is repeated as in former sections that statistical relations are insufficient for conclusions unless given meaning by concomitant anatomic correlation.

On close examination of periductal mastitis in both groups of cases, it is evident in each that most of these lesions are of slight extent, so that only 22 per cent of the noncancerous breasts with periductal mastitis and 18 per cent of the cancerous breasts with periductal mastitis show the lesion to marked degree. It is of interest that in the entire group of noncancerous cases with periductal mastitis, fat necrosis occurred six times and in every instance the periductal mastitis, stasis and distention were marked. (Note that three of these cases of fat necrosis were from the additional cases added to the 50- to 60-year decade, and, hence, the total of six exceeds the number of cases of fat necrosis in the series of 200 noncancerous breasts). The same was noted in the cancer cases with periductal mastitis. In this group fat necrosis was found four times, always with marked degree of periductal mastitis, stasis and distention, and these cases constituted all examples of fat necrosis in the 300 cases of the cancer series.

Periductal mastitis in both the cancer and noncancer series, as previously mentioned, occurs chiefly with no demonstrable basis except stasis of duct content and dilatation. In the older age-groups this is apt to be rather diffuse (this seems related to the changes of senile atrophy) but may be predominantly focal. In younger women there is a greater tendency to focal distribution. In many cases the periductal mastitis is dependent upon local lesions such as duct papilloma and pressure from cyst or tumor. Thus we regard periductal mastitis in some cases as nonobstructive or "primary" and in some cases as obstructive or "secondary."

The cause for excessive stasis in the primary cases is not clear. The material apparently is composed of desquamative epithelial débris and it may be added to by products of secretion from or through lobular and duct epithelium. Perhaps these changes are due to excessive desquamation or secretion which exceeds the physiologic capacity of the mechanism normally disposing of duct content. Some of the marked cases do give a history of nipple discharge, but in most cases this does not occur. Periductal mastitis in minor form is no more apt to appear in breasts that have lactated than in those that have not, and multiple lactations do not play a part. We do not have enough data to state whether or not this is true of the most marked cases that present in a clinical form with segmental localization.

The presence of periductal mastitis in either cancerous or noncancerous breasts does not materially influence the occurrence of lesions other than those already mentioned as being fundamentally concerned in the process. When other lesions such as cysts and noncancerous proliferative processes are present, they never appear to begin as a result of periductal mastitis, stasis and distention of ducts or fat necrosis.

Any differences in cancerous and noncancerous breasts that show periductal mastitis are unimportant ones and depend almost exclusively on age distribution of cases. In none of the 300 cases of cancer could we trace the source of mammary carcinoma to periductal mastitis and its related lesions. The tracing of cancer to this source would, in our opinion, depend upon the demonstration of histologic transitions in the epithelium at such foci. Previously, it has been stated that the most common alteration in epithelial cells at such sites is metaplasia, usually of minor degree, and in some instances the production of true squamous characters. Another epithelial change fairly common at areas of periductal mastitis and stasis and distention is slight epithelial piling-up and loosening. This change is a minor one, usually seen in medium and larger ducts, and seems to be little more than trivial hyperplasia that desquamates rapidly. The stasis and distention as well as the periductal mastitis are usually slight in such areas, and it is almost invariable to find flattening and atrophy at sites of marked distention and periductal mastitis. It is not implied that an atrophic epithelium is unlikely to give rise to cancer. It can be said, however, that in the material studied here, no significant histologic atypism could be found in either atrophic or hyperplastic epithelium lining areas of stasis, distention and periductal mastitis. In the earliest mammary cancers seen by us in this and other material where the ducts were lined by typical cancer cells, periductal mastitis does not play the rôle of precursor.

VIII — THE MAMMARY LOBULES

The comparative examination of the character of the mammary lobules in cancerous *versus* noncancerous breasts has offered more difficulties than any other aspect of this morphologic analysis. That this has been the experience of other authors is indicated by the relative absence of detailed accounts of lobule abnormality. Perhaps these writers have felt the same major obstructing factor as we ourselves, namely, the problem posed by the question, what constitutes the normal lobule pattern of the human female breast and what changing aspects, if any, are imposed by the cyclic phases of menstruation? Insofar as we have been able to ascertain, there has been no morphologic survey of mammary lobules which has been based upon the examination of ideal material. Reports on breast tissue taken from autopsies have the disadvantage that they deal with specimens from chronic or acute diseases that may in themselves have been in part responsible for alterations in the lobule structure presented. Actually, the study of such breasts is a specific problem in itself, and should logically be prosecuted after a fundamental

normal has been established by study of "screened" material. The other source from which observations have been made is from surgical breasts, and these as a whole are *prima facie* abnormal organs. Even so, when one studies a large amount of such material and compares his findings with those of others, there seems no doubt that certain lobule patterns are more characteristic of one phase of the cycle than another. We have been able to study a limited amount of selected autopsy material and, in addition, over 300 surgical breasts from patients in whom menstrual dates were known. Our findings are in more or less agreement with the descriptions furnished by Rosenburg,[3] Dieckmann,[4] Polano,[5] and Geschickter,[6] and divergencies will not be elaborated here in histologic detail. Structural features that we consider indicative of various phases of the menstrual cycle are presented with explanatory notes in Figures 26 through 33.

After the study of material of the type mentioned above, much remains that is unsatisfactory. A vast majority of these breasts present a distinct variation in lobular structure, and it is the unusual gland that possesses even a moderately homogeneous picture. Certain of the lobule patterns when charted in relation to certain stages of the menstrual cycle will be found more commonly in the lutein phase, for example, and yet the chart will show these same types during the follicular phase and *vice versa*. Only a trend is shown. Added to this there are other types of lobules that show no relation at all to the periodicity of the ovarian cycle, and, moreover, they embrace a wide variety of structure quite different from that of those lobules which seem more characteristic of either the follicular or lutein phase. In our lack of understanding of the significance of these latter structural types, we pursued their study under the premise that they may represent abnormal lobule configurations. Almost at once, it became obvious that the lobules adjacent to such expanding lesions as fibro-adenoma and cyst or lobules at the edge of a cancer showed a series of changes not encountered when these lesions were absent. Chief among the changes seen were intralobular edema, irregular contour and size of lobules and their epithelial components, lack of uniform layering of acinar epithelium and intralobular round cell infiltrate. These changes apparently represented an early stage in what can be called secondary lobule alteration. The later stage of this process was accented by decrease or nearly complete loss of lobular epithelial components, replacement by dense round cell infiltrate and decrease or disappearance of lobular edema. Finally, lobular units were completely effaced and their former sites marked only by residual round cell foci with perhaps hyalinized acinar remnants. Of all these changes the marked intralobular edema seemed most common. Often these alterations involved lobules as much as 2 cm. distant from the edge of a large, expanding lesion; they extended, as might be expected, a shorter distance when the expanding lesion was roughly 1 cm. in diameter. In any breast containing many cysts and/or other lesions causing peripheral pressure, it can be easily seen that lobule homogeneity will in some measure be disrupted.

FIG. 26

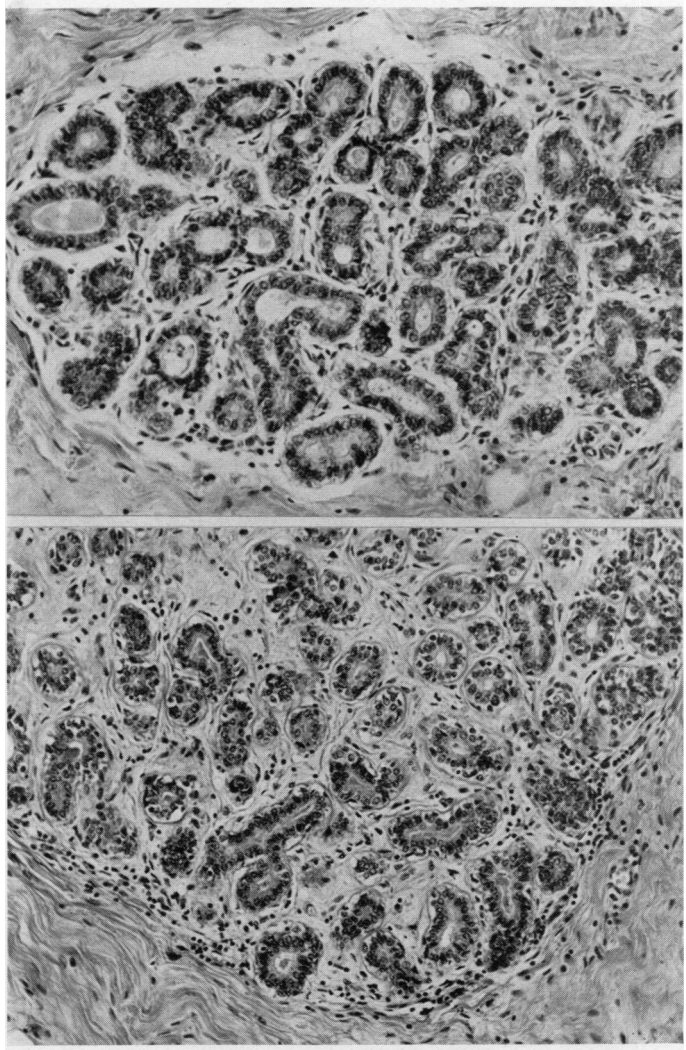
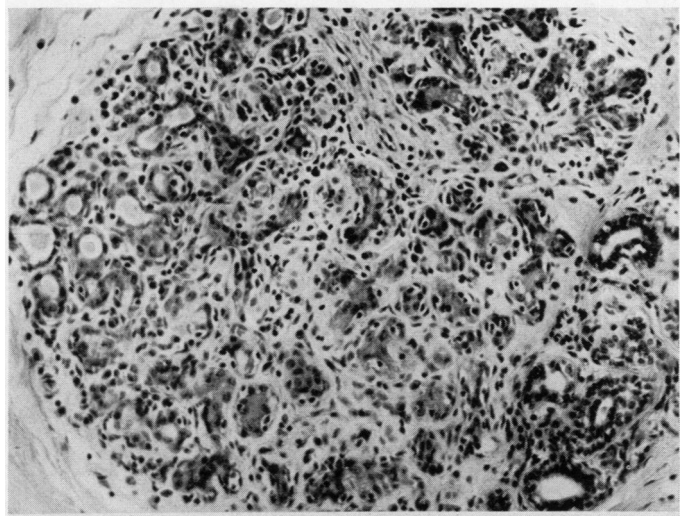


FIG. 27

FIG. 26.—Section taken on first day of menstruation. Acini are numerous and closely spaced. Lumina are open and contain secretion. Lining cells cuboidal to columnar, cyptoplasm rather abundant and pale. Cell arrangement orderly. Full size of lobule not shown in this cross-section. Stroma rather vascular and free from collagen. Occasional lymphocytes. Fully developed lutein phase of cycle. Appearance indistinguishable from many lobules seen in third month of pregnancy. Many lobules in this breast fail to show as marked luteinization.

FIG. 27.—Section taken on fourth day after onset of menstruation. Early involutional changes. Acini continue to be numerous. Some lumina remain open, some narrowed, many closed. Residual secretion can be seen. Fewer columnar cells. Orderly cell arrangement persists in some acini but with contracture of acini and obliteration of lumina, cells are piling-up in disorderly fashion. Stroma showing early condensation and increased numbers of lymphocytes as well as decreased vascularity.

FIG. 28



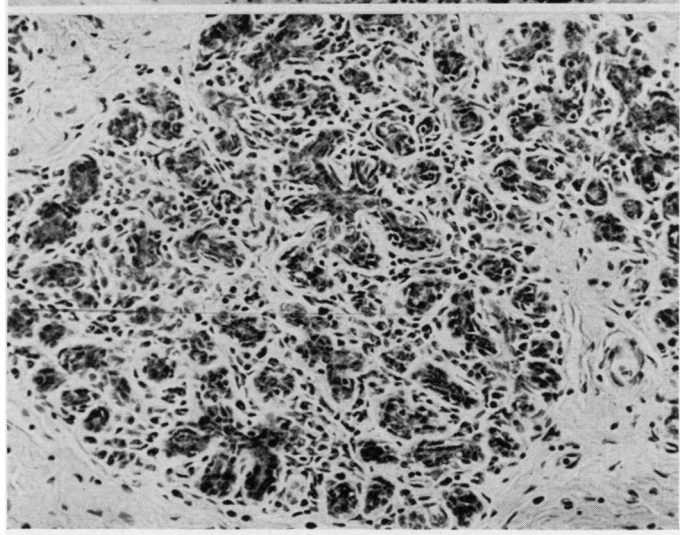


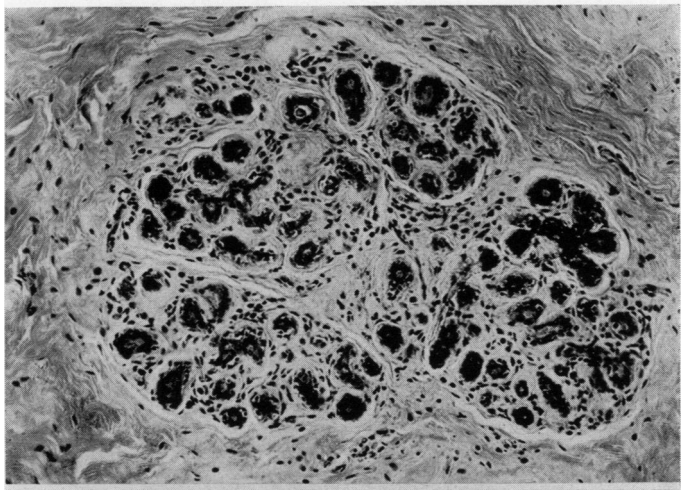
FIG. 29

FIG. 28.—Section taken eight days after onset of menstruation. Further involutional changes. Process not entirely uniform but this is not unexpected. Central portion of lobule in advance of periphery. Some acini almost extinct. Increasing numbers of lymphocytes. (Compare with Figures 27 and 29)

FIG. 29.—From same section as Figure 28. Uniform and rather advanced involution. Acini still numerous but collapsed. Condensation of acinar cells. Reduction in size and nuclear pyknosis. Abundant lymphocytic infiltrate. Stroma somewhat less dense than ordinarily found eight days after onset of menses.

On further observation, secondary lobule alteration could be found in association with other breast lesions. Those lobules distal to an intraductal papilloma or comedocarcinoma were nearly always adversely affected. The general trend in these instances was toward atrophy following in the wake

FIG. 30



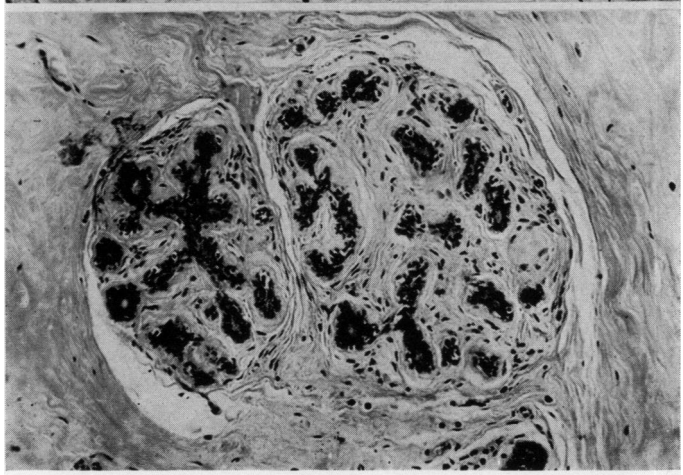


FIG. 31

FIG. 30.—Section taken 12 days after onset of menstruation. Involution nearly complete. Acini less numerous, more widely spaced. Intervening stroma denser. Lymphocytes still present.

FIG. 31.—From same section as Figure 30. End-point of physiologic involution. Few acini remain and these in collapsed state with hyaline connective tissue condensation about some. Remainder of stroma dense and practically free from lymphocytes.

of, and dependent upon the degree of the induced duct dilatation, stasis of duct content and periductal mastitis. In another section we have discussed the secondary formation of duct stasis, distention and periductal mastitis due to pressure from cyst, fibro-adenoma and cancer. Thus, any expanding

lesion of the breast may not only cause lobule alteration locally through pressure alone, but also at a greater distance by interference with adjacent ducts, the effects of which interference are detected in their corresponding lobular terminations. As expected, when the lesion complex of duct stasis,

FIG. 32

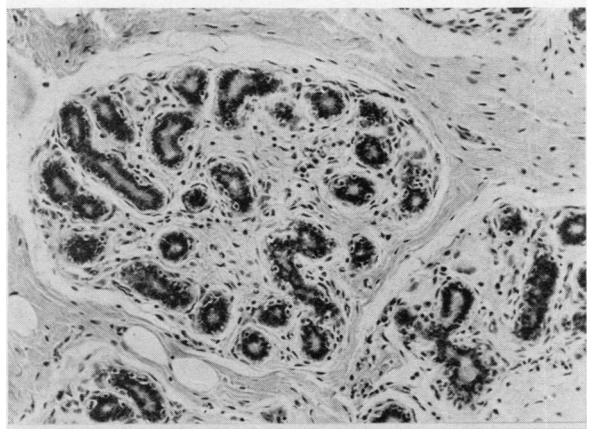


FIG. 33

FIG. 32.—Section taken 15 days after onset of menstruation. Stage of reactivation. Note loosening of stroma as if in preparation for acinar hyperplasia. Connective tissue cells larger and less elongated. Occasional mitoses of these cells present but not visible at this magnification. Acinar lumina reestablished with lining cells assuming coherent arrangement. Nuclei remain dark.

FIG. 33.—Section taken 22 days after onset of menstruation. Characteristic corpus luteum effect. Multiplication of acini. Lumina present but not yet crowded with secretion. Lining cells larger and taller. Cytoplasm more abundant and nuclei relatively pale. Occasional mitoses can be seen with difficulty.

dilatation and periductal mastitis occurs in primary form, the lobules supplied by these ducts show the same changes as seen when the aforesaid lesion-complex of duct dilatation, stasis and periductal mastitis is of secondary type.

Those portions of breast tissue free from expanding lesions did not show the type of change referred to as secondary lobule alteration. In

sections of such tissue, however, it was common to see lobule patterns that did not fit the pictures associated with expected cyclic changes. The structural types seen were several in number, and as a general group may be referred to as primary lobule alteration. In some instances the lobules were uniform in appearance, and when such was the case, they tended to assume one of two forms. In the first of these the lobules were very few, they were quite small, the acini were scanty and reduced in size. The intralobular connective tissue was neither edematous nor dense, and periacinar hyaline was inconspicuous. Often there was considerable fat replacement of fibrous stroma. In short, this was a reproduction of an atrophic breast, and was what would be seen in the breast of a postmenopausal woman. On repeated occasions this sort of lobule pattern has been seen in women far short of the menopause. Extreme examples may be seen in the early twenties. Little or no difference was apparent regardless of the stage of the menstrual cycle during which the tissue was obtained. No accurate explanation can be made when such cases have normal menstrual histories, and such is usual in the cases seen thus far. The general impression is that such breast tissue may be refractory to hormonal influences. Verification of this hypothesis obviously depends upon demonstration of at least normal cyclic output of both the follicular and luteinizing hormones, since the mere existence of a normal menstrual cycle clinically perhaps tells us nothing of actual hormone patterns.

In the second type of primary lobule alteration where homogeneity of structure existed, the following was seen: The number of lobules was neither increased nor decreased. They were chiefly of average size. The intralobular connective tissue was abundant, loose and edematous. The epithelial components were very few in number but of large size, and the lining cells were often piled up in three to four layers and were rather apolar in arrangement. Seldom was periacinar hyaline a prominent feature. The most extreme examples of this type furnished at least a superficial resemblance to gynecomastia, particularly when the epithelial components of the lobule were very few in number. Again, this type of lobule structure has been encountered repeatedly without relation to any particular phase of the menstrual cycle. Any proposal that such a picture is the result of excess follicular hormone meets the embarrassment of one's inability to present the required proof by chemical assay.

The two types of primary lobule alteration just discussed are relatively infrequent, each being seen in about 5 per cent of surgical breasts. Far more common is a third form of primary lobule alteration in which the lobule pattern is unbalanced and irregular. A description of these changes is extremely difficult to put into words. The principal character is the heterogeneity which makes it utterly impossible to predict from sections at what stage of the menstrual cycle the tissue was obtained. Certain lobular groups suggest the lutein phase, while adjacent ones seem more characteristic of the follicular phase. Still others partake of neither of these phasic types. Sometimes the structure resembles the florid phase of lobular sclerosing adenosis, and in the

same section foci may occur that demonstrate the regressive phase of the same process. Still other lobules appear to be undergoing atrophy very much as in a senile breast, while others suggest an early phase of cyst formation as manifested by marked acinar dilatation. Intralobular epithelial hyperplasia of "nonphysiologic" kind is seen. This is commented on at a further point in this section. Added to these are "metaplastic" changes in which the acinar epithelium becomes flattened and almost epidermoid in character; or perhaps the acinar epithelium is seen in various easily traced stages of transformation to the so-called apocrine type. It is reasonable to assume that when such complex lobule arrangements are met, they represent multiple epochs of abnormal proliferation and involution, some of which may have occurred long before the specimen was secured.

To refer such changes as these to hormone imbalance is still problematical, and practically all of the evidence on human breasts comes from somewhat indirect sources. These sources include (1) the résumé of material which indicates certain types of lobules to be more characteristic of the follicular or lutein phase of the cycle; (2) the study of the human female breast under known preponderance of the corpus luteum hormone, that is, in pregnancy; and (3) the study of the male breast under conditions of known excess of female hormone, that is, in gynecomastia. Interesting observations could be made if one could secure breast tissue from patients who, on curettage, are shown to have glandular and cystic endometrial hyperplasia. The number of cases required to enable proper evaluation is discouraging. When one applies the structural evidence from sources that are available and makes comparisons with surgical breast preparations, it is difficult to deny a probable relationship to hormone imbalance. It seems possible that the implied imbalance need not require an excess of one or the other ovarian hormone; perhaps a subnormal amount of one or the other is sufficient. There is evidence that certain lobules are either more or less liable to hormone stimulation than are others. This is partially demonstrated by sections of the breast in various stages of pregnancy. Not every breast in the fifth to sixth week after the last menstruation shows the same degree of response, and as a matter of fact in some cases, one could not be sure of the existence of pregnancy from the sections, the appearance being so similar to that seen in a normal premenstrual breast. Even in the third trimester of pregnancy very small numbers of lobules may either appear almost totally unresponsive or much less well-developed than the vast majority of the lobular units. The rate of involution of individual lobules following pregnancy is also subject to demonstrable variation. Moreover, in examining a large number of breasts taken from one to ten years after the menopause, it is remarkable to note how capricious may be the rate of lobular atrophy.

The implications brought forward in the foregoing received some support when, late during the progress of this general study, we had the opportunity to examine breast material from another source. Through the aid of Doctor Sophie Spitz, and the courtesy of the Medical Examiner's Office of New

York City, specimens of both breasts and the endometrium were obtained. These were from cases of sudden death due to accident, homicide, or natural diseases, the latter being noninfectious in nature. There were two interrelated purposes in securing this material from cases of sudden death. First of these was to gain a more accurate insight into the frequency of the lesions of so-called chronic cystic mastitis in the breasts of the female population at large. The second was to ascertain the "average" appearance of the mammary lobules during the various phases of the menstrual cycle, as indicated by comparison with simultaneously taken sections of endometrium in cases without debilitating chronic disease. There were 27 such cases aggregating 54 breasts. Two of the cases were in the decade 10–20, three in the decade 20–30, thirteen in the decade 30–40, and nine in the decade 40–50. Not less than eight and an average of ten blocks were cut in each case, considerably more abundant sectioning than was done in the series of 500 cases reported here in detail. A thorough summary of this additional material will not be made here, but will be reported at a later date. The total number of cases is admittedly small, but there was so much structural contrast with the group of surgical breasts that some general comment seems warranted.

The lesions that have been presented in previous sections as constituting the complex of so-called chronic cystic mastitis were not absent in the material from cases of sudden death, but they were far less plentiful and by no means of as marked degree as seen in the cancerous or noncancerous surgical breasts. This was preeminently true in regard to gross lesions and equally true as regards microscopic lesions. The more plentiful sectioning of the material from instances of sudden death is, in our opinion, reinforcing, in that it affords less chance of failure to detect abnormalities.

The lobule status in the postmortem material was vastly different from that in the surgical material. In surgical breast material from premenopausal women, we find only about 10 per cent of cases that have enough homogeneity of lobule structure to justify a prediction of the phase of the menstrual cycle. After a certain degree of lobule imbalance is attained, any estimate is pure guesswork. Two of the 27 cases of sudden death showed advanced postmortem changes and were unsuitable for lobule or endometrial determinations. Three of these cases had atrophic endometria and were regarded as postmenopausal. Of the 22 remaining cases, two showed primary lobule alteration which made estimate of the stage of ovarian cycle unfeasible. Three of the cases showed the atrophic type of breast unsuitable for determining cyclic phases. There were 17 cases with uniform lobule structure which enabled one to estimate the phase of the menstrual cycle. In 16 of these 17 cases, the independent predictions of the cyclic phase by two observers proved correct, as controlled by the accompanying endometrial pattern. The prediction reported as a failure was correctly made by one observer. The sections of endometrium were, of course, not consulted until after the examination of the breast tissue. Excluding breasts and endometria showing too advanced postmorten change and those that were postmenopausal, there

were 22 cases. In 16 of these (72 per cent) it was possible to predict from the breast sections the phase of the menstrual cycle. This is in high contrast to the figure of 10 per cent obtainable by us in surgical breasts. In short, the homogeneity of the lobular structure of these breasts from cases of sudden death was directly contrary to the disordered lobular structure found in the surgical breasts. The far lesser incidence of the lesions of "chronic cystic mastitis" and the comparative absence of lobule alteration in the control (sudden death) breasts, combined with the high frequency of these lesions in the surgical breasts, suggests a close relationship between lobular alteration and the lesions we have presented in another section as constituting the complex of so-called chronic cystic mastitis. Perhaps certain forms of lobule alteration are an integral part of that complex.

In studying the occurrence of lobule alteration in the group of 300 cancerous and the 200 noncancerous breasts, observations were limited to the decades 30–40 and 40–50. Secondary lobule alteration was so common that no figures are given, and, moreover, it has already been stated that, anatomically, such changes seem secondary to pressure or duct stasis and associated lesions. The figures given in Table XIX concern only primary lobule alteration, as it has been described in the foregoing.

Table XIX indicates little except that in surgical material these lobule alterations are common, and that they are considerably more frequent in the later decade, as has been shown in preceding tabulations to be true of other lesions concerned in so-called chronic cystic mastitis.

TABLE XIX

INCIDENCE OF PRIMARY LOBULE ALTERATION

Decade	In Noncancerous Breasts Frequency in Per Cent	In Cancerous Breasts Frequency in Fer Cent
30–40	36	34
40–50	52	48

The previous comments on lobule structure have referred to two general types of lobule alteration, primary and secondary, and were intended to direct attention to what may be considered abnormal lobule structure. It seems necessary here to discuss in some detail the problem of epithelial hyperplasia in lobules. Epithelial hyperplasia can be seen in lobules that show either primary or secondary alteration. A good deal of effort has been put forward in trying to establish what constitutes pathologic hyperplasia of lobular epithelium. The necessary criteria arrived at after prolonged consideration demand that the lobule under examination have an appearance dissimilar to that seen as a phasic pattern of the menstrual cycle or of pregnancy; the number of layers of lining epithelium must be greater than two (unless there is obviously a focal pile-up). If any part of a lobule shows such changes, epithelial hyperplasia is considered present. If such changes are limited to a single acinus, it is extremely uncommon in our experience. On many occasions, however, a relatively small part of a lobule may be affected. The occurrence of this sort of epithelial hyperplasia was

tabulated for the same material in which the incidence of lobule alteration was determined (Table XX).

TABLE XX

INCIDENCE OF INTRALOBULAR EPITHELIAL HYPERPLASIA

Decade	Noncancerous Breasts Frequency in Per Cent	Cancerous Breasts Frequency in Per Cent
30–40	14	16
40–50	22	34

FIG. 34

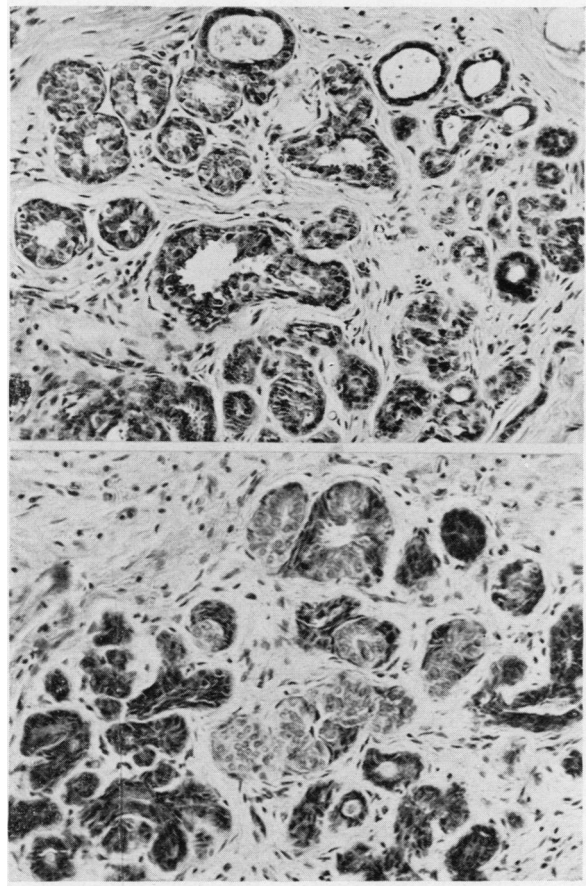


FIG. 35

FIGS. 34 and 35.—Lobule patterns dissimilar to any seen as phasic variants of the ovarian cycle. Structural imbalance with multilayered lining cells in disorderly arrangement.

The degree of epithelial hyperplasia in lobules, as one would anticipate, varied between broad limits from simple multiplication of lining layers to complete plugging of acinar lumina. A considerable experience is necessary before one's designations of epithelial hyperplasia in lobules are accurate and repeatable. Our plan was for each observer to make independent

recordings, compare results, review material where discrepancies occurred, and continue until each individual's observations were reproducable by the other. Several hundred breasts were studied in this manner before the above tabulations were made.

In a former paper[7] the existence of and the histologic features of lobular

FIG. 36

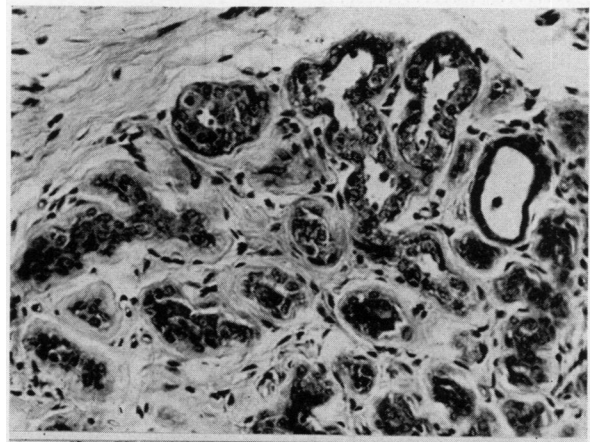


FIG. 37

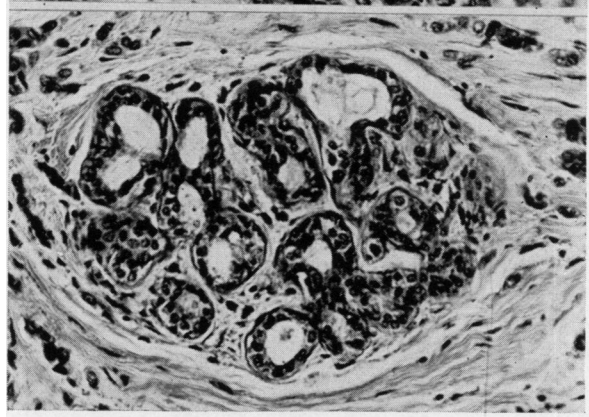
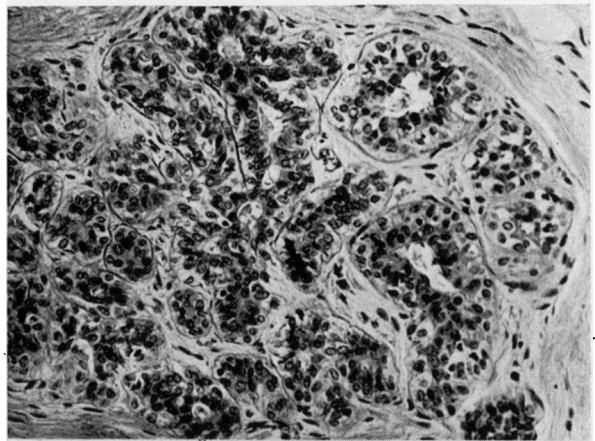


FIG. 36.—Lobular alteration, with pathologic hyperplasia of epithelium.

FIG. 37.—Appearance superficially suggesting corpus luteum phase of menstrual cycle, but there is stratification of lining cells, lack of coherent grouping and difference in cell size and staining properties. Moreover, patient beyond the menopause.

mammary carcinoma *in situ* were discussed. In addition, a brief description of the infiltrating phase of this type of mammary carcinoma was given. At that time no effort was made to depict histologic levels of lobular epithelial change that fell short of the fully developed *in situ* lesion. It was felt that such changes must exist, but we were not sure of their identity. The large mass of material examined in the past few years has made us much more confident of the earlier transitions to lobular mammary carcinoma *in situ*.

FIG. 38



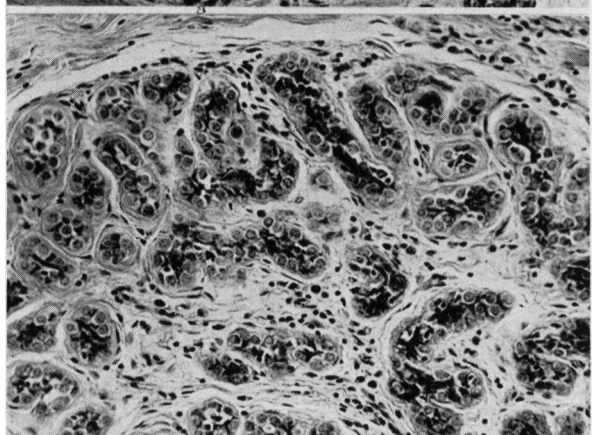
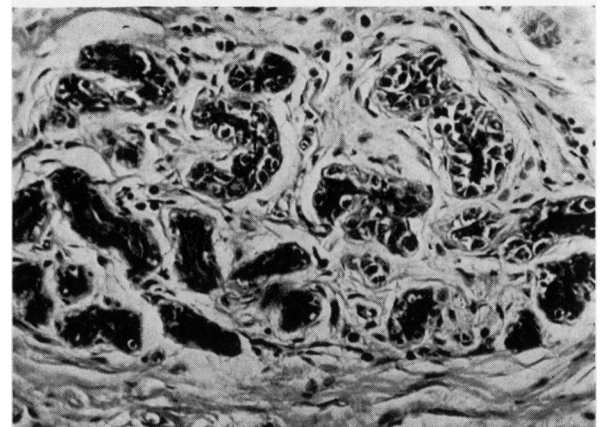


FIG. 39

FIG. 38.—More advanced stage in hyperplasia of lobular epithelium. Structure distinctly atypical with deep stratification or plugging of lumina. Lack of polarity with pleomorphism and variable staining qualities. Mitoses seen, but not at this magnification. (Compare with Figures 37 and 39)

FIG. 39.—Interpreted as an early stage of lobular carcinoma *in situ*.

FIG. 40



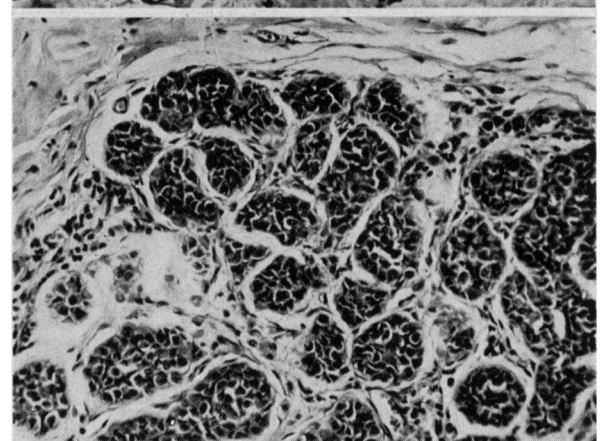


FIG. 41

FIG. 40.—Another early phase of lobular carcinoma *in situ*. Note partial involvement.

FIG. 41.—Fully developed lobular carcinoma *in situ*. Acinar outlines still distinctly maintained.

To write a word-formula for the identification of these subtle alterations is beyond our powers. The photomicrographs shown in Figures 34 through 43 illustrate variable degrees of lobule alteration with progression to lobular mammary carcinoma both *in situ* and in an early infiltrative phase. These may suffice in part, but they cannot substitute for actual retinal images. Once the actual histologic pictures are grasped, they appear to one as highly

FIG. 42

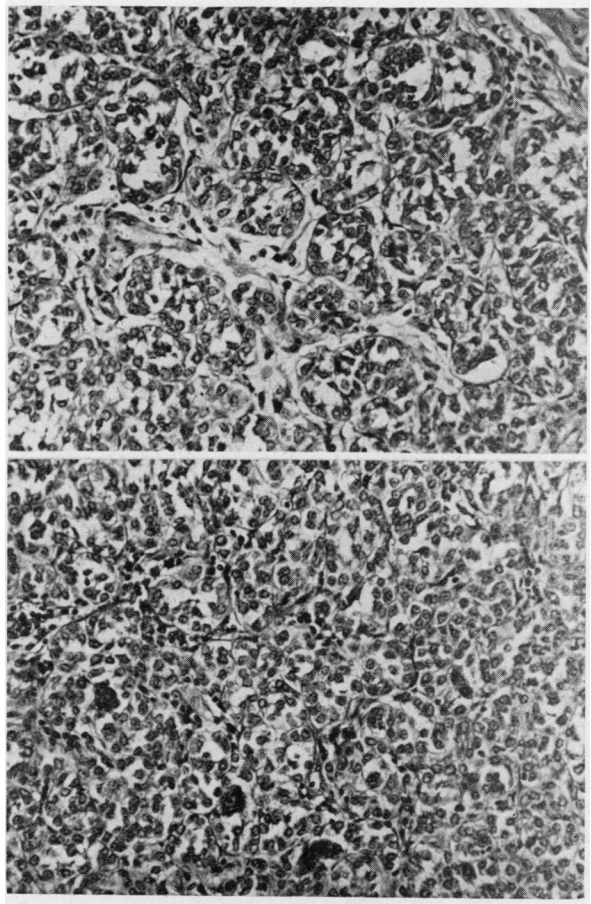


FIG. 43

FIG. 42.—Further progression of lobular carcinoma *in situ*. Integrity of individual acini difficult to detect at all points.
FIG. 43.—Merging of acini and start of infiltrative stage.

characteristic and separable from other more common pictures of hyperplasia in lobules.

We regard certain atypical hyperplasias as transitional stages in the development of *in situ* lobule cancer. In a preceding section, it has been shown that one of the chief differences between cancerous and noncancerous breasts was the far greater likelihood that the cancerous breasts would show

duct papillomatosis of atypical structure. For this reason it seemed necessary to investigate atypical hyperplasia in lobules for the same relationship. In the material used for other lobule studies, there were 100 noncancerous breasts equally divided between the decades between 30 and 50 years. Not a single case was found in which there was atypical hyperplasia in lobules. This absolute absence is one of chance, since in about 500 noncancerous breasts seen yearly at Memorial Hospital, this atypical form of hyperplasia is seen about half a dozen times. We do not refer here to true lobular carcinoma *in situ* but the less advanced lobular alteration.

In 32 cancer cases between the ages of 30–40 and 50 cancer cases between the ages 40–50 there were six which showed the atypical form of intralobular epithelial hyperplasia. In four of these six cases, the cancers had the infiltration pattern so characteristic of cancers of lobule origin. In this group of 82 cancers, some form of epithelial hyperplasia in lobules was seen in 22 cases. In those 22 cases there were nine lobular mammary carcinomas, an incidence of 40 per cent, while the over-all incidence of lobular carcinoma is only about 5 per cent. These findings lead us to believe that the epithelial hyperplasias discussed do have a positive relationship in the development of mammary carcinoma of lobule origin.

In comparing the lobular structure of cancerous and noncancerous breasts, abnormal types are common in each group. One fundamental difference is found. This is the much more pronounced tendency for the lobules of breasts with cancer to show intralobular epithelial hyperplasia of atypical sort.

(To be continued)