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A HISTOLOGICAL STUDY OF THE NORMAL MAMMA IN RELATION TO TUMOUR GROWTH.

II.—The Mature Gland in Pregnancy and Lactation.

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[*Continued from Vol. XLI., p.* 682.]

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THE previous paper in this series of studies of the normal breast described development and growth in mammary tissue from embryonic to adult life.[1] This paper deals with the mature gland, mainly in relation to activity in pregnancy and lactation, and the possibility of pathological growth during these periods.

An extensive review of the relevant literature has revealed no detailed illustrated investigation of normal pregnancy and lactation in the human breast, the cytology of the mamma at these periods being based very largely on examination of animal tissue and on experimental work. A knowledge of growth and function in human tissue is also necessary to an understanding and interpretation of its pathological developments and provides justification for this detailed study and its ample illustration.

The normal and pathological tissue on which my observations are based has come from several sources. Much of it, cut in whole breast sections, was selected by Dr J. W. Dawson and forms part of my permanent collection, but I am also indebted to the Pathology Department of the Royal Infirmary and to the Maternity Hospital, Edinburgh, and to various other hospitals and private sources for operation or autopsy material. I have, in addition, the privilege of examining the large amount of material received for routine reporting in the Histological Department of the Laboratory of the Royal College of Physicians. I wish to express my appreciation of the assistance given me by the British Empire Cancer Campaign, as a former grantee, in meeting the cost of illustration. The photographs, with a few exceptions, were prepared by Mr William Watson in this Laboratory. I am grateful to the Tumour Service of the Royal Infirmary for

follow-up notes and for the use of the Leica Camera in taking the small photographs reproduced on Plates VI. and X.

1. **Summary of Early Development to Maturity.**—After the main ducts and some smaller branches have been formed, the breast during childhood shows little growth activity until the onset of puberty (text Fig. 1). Mammary development in the years after puberty is evident as a slow progressive increase in the amount of glandular tissue, with a coincident connective tissue proliferation and a considerable new formation of fat both in and around the *corpus mammæ*. There is, however, a wide individual variation in the proportion and amount of the new tissue elements laid down. Glandular

FIG. 1.—Pre-puberty glandular structure (child of 8 years).

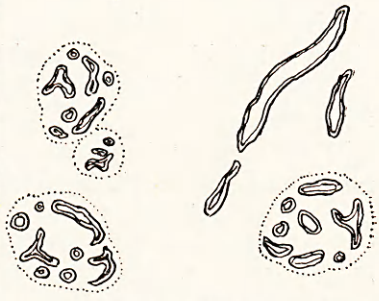

FIG. 2.—Post-puberty structure (girl of 17 years).

increase is brought about by budding from the ducts of epithelial outgrowths which lengthen, hollow out and form further subdivisions, and in this way produce more ducts and the complex groupings of ductules called lobules (text Fig. 2). Normal growth goes no further than this in the non-pregnant subject. On the analogy of melanosis, acanthosis etc., the term *adenosis* was suggested to indicate this glandular tissue increase, whenever it occurs, and emphasis was laid on the contrast between *adenosis* and *epitheliosis*, in which epithelial proliferation tends to fill up existing gland structures instead of forming new ones.[2] The term adenosis includes in its scope both physiological glandular increase, such as occurs after puberty and during pregnancy, as well as pathological increase, evident at other periods not obviously associated with normal proliferative stimuli. Though the term adenosis has since been used by Lewis and Geschickter [3]

to denote a variety of " chronic cystic mastitis," I use it here in my original sense as descriptive of *glandular tissue increase without any necessary implication of a pathological condition.*

After having reached a certain degree of development in the period between puberty and adult life, the mature virginal gland shows little apparent histological change and, in the absence of pathological growth, its glandular content remains in a state of functional rest. As already noted in the earlier study, no evidence has been found to suggest that menstruation is associated with the definite glandular growth and retrogression described by various other observers; there is, moreover, no true milk secretion in the proper sense of the term, as true secreting structures are normally absent from the quiescent gland. With pregnancy and lactation, when the breast reaches its full development, a series of histological changes is initiated, which will now be described in detail.

In the descriptive text I have, in general, avoided quotation from the literature of the subject. Those with special knowledge will be already conversant with the views of the writers mentioned in the bibliography, while those interested in the more general implications of mammary growth and function will thus obtain a more consecutive account of my own observations without distraction by the controversial issues.

2. **The Mamma during Pregnancy.**—During pregnancy, the breast undergoes a true hypertrophy which is more or less progressive until parturition, but it is convenient for histological description to divide this phase of growth into an early and a late period.

(a) *The Early Period.*—This period is characterized by a great increase in the amount of glandular tissue, an adenosis which is progressive and is associated with increased vascularity, evident as a new formation of fine capillaries in and about the expanding lobules. Examination of material removed at different periods of pregnancy indicates that this glandular increase is produced not only by hypertrophy of lobules already existing but also by the formation of new lobules, as the comparison of normal tissue, cut in small and large sections from quiescent and active mammæ at different stages, suggests that, in pregnancy, the branching of the smaller ducts into new lobules is much more complex than in quiescent tissue (see text Fig. 3). This new lobule formation and hypertrophy is merely an exaggeration of normal growth as seen in the

PLATE I

FIG. 4

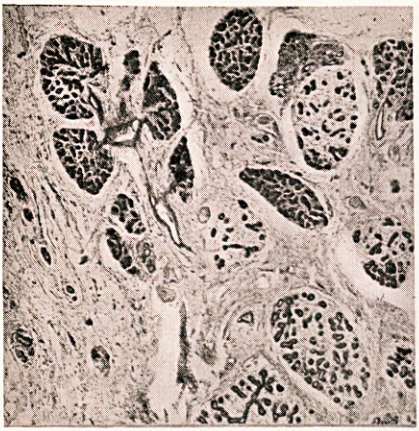

FIG. 5

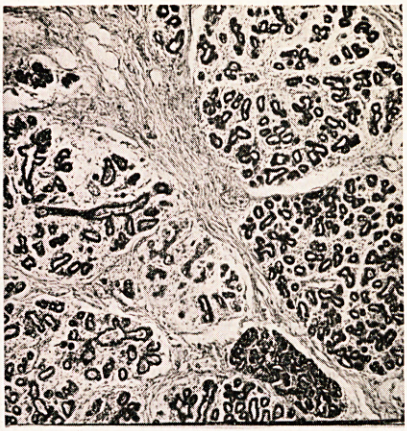

FIG. 6

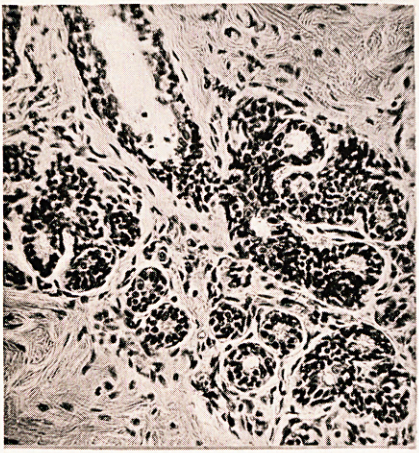

FIG. 9

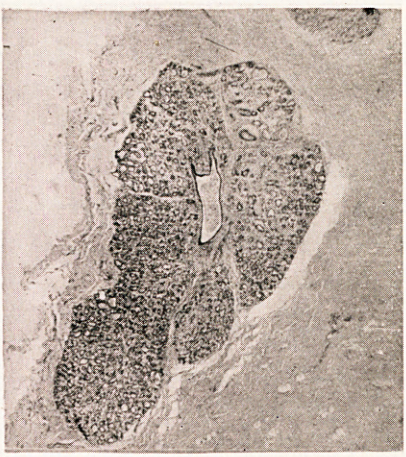

FIG. 10

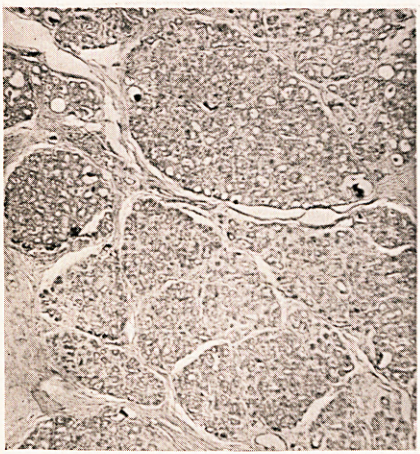

FIG. 11

The Mamma during Pregnancy.

developing mamma after puberty, and the type of structure produced—ductules—is similar. Tissue at the tenth week of pregnancy (Figs. 4 and 5, Plate I.) showed budding, elongation and subdivision of the ductules in expanding lobules; the two layers of epithelial cells which line the structures at

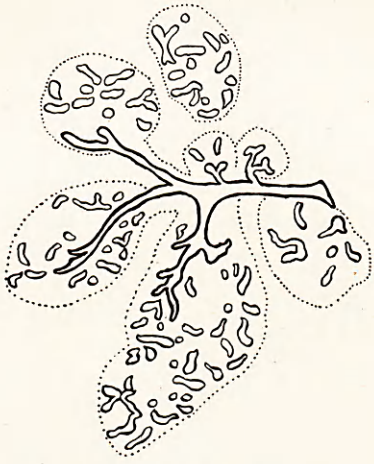

FIG. 3.—New lobule formation in mammary tissue, at 10th week of pregnancy.

this stage are shown in Fig. 6, at a higher magnification, in tissue at the third month of pregnancy.

In early pregnancy, the mamma thus gradually builds up a complex framework from which the abundant secreting tissue required for lactation will be produced. One has only

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PLATE I

The Mamma during Pregnancy

FIG. 4.—Mammary tissue, 10th week of pregnancy, showing early lobular growth (*cf.* text Fig. 3). ×20.

FIG. 5.—Mammary tissue, 10th week of pregnancy, showing budding of ductules in the lobules. ×40.

FIG. 6.—Mammary tissue, 3 months' pregnancy, showing 2 cell layers of the ductules. ×200.

FIG. 9.—Mammary tissue, 5 months' pregnancy, showing a greatly enlarged lobule. ×20.

FIG. 10.—Mammary tissue, 8½ months' pregnancy, showing lobular enlargement (large fields almost entirely occupied with parenchyma). ×20.

FIG. 11.—Mammary tissue, 9 months' pregnancy, showing limited lobular growth, with periductal and interlobular lymph vessels (x). ×20.

to compare the amount of glandular tissue in an adult, well-developed mamma (text Fig. 7) with that found in late pregnancy and lactation to realise the enormous increase and elaboration of the permanent (resting) structure which is necessary to form the large secreting surface demanded in lactation (text Fig. 8). In the former, lobules surrounded by loose stroma are fairly widely scattered in a dense, comparatively acellular supporting tissue, while already by the middle of pregnancy, numerous large lobules dominate the histological field (*cf.* Fig. 9, at the fifth month of pregnancy), and both connective tissue and fat are decreasing in amount.

(b) *The Later Period.*—The histological picture during the later months of pregnancy varies considerably in different

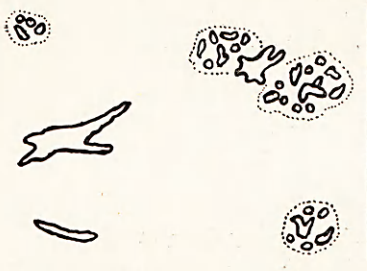


FIG. 7.—Adult glandular structure, nullipara of 21 years.

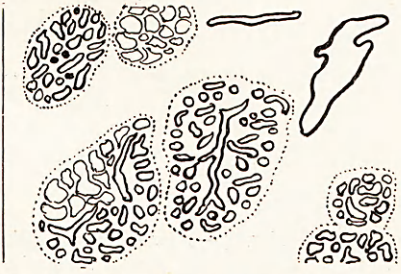


FIG. 8.—Glandular structure in pregnancy.

cases, so that it is difficult to draw a rigid line between the earlier and the later periods; but after the third month, simultaneously with continued glandular growth, the formation of true acini, the differentiated structures, is more and more apparent. The use of the terms *acinus* and *differentiation* needs comment, for both are ill-defined in mammary terminology. The writers who consider that secreting structures develop only during pregnancy, use the term *alveolus* to distinguish this new formation from the resting structure; others, in whose opinion the breast shows secretory activity apart from lactation, call the lobular elements *acini*, without distinguishing the quiescent and pregnant states. German pathologists, in general, call the terminal structures in the resting organ *acini* or *Endstücke* and the secreting components *alveoli* or *Endbläschen*. In the non-secreting breast, the structure of ducts and lobular elements is essentially similar as regards their epithelial cell arrangement and I therefore prefer the

term *ductule* for the latter ; for the secreting structures produced only during pregnancy and lactation, the term *acinus* is distinctive and appropriate and conforms to an accepted usage in this country. Alveolus is less satisfactory, since it is used indiscriminately for a secreting structure or simply for a gland-like formation, without reference to function or for solid, circumscribed epithelial formations, as, for example, in " alveolar carcinoma."

Differentiation, in the wide sense, includes all the cell and tissue changes which mark the transition from mere proliferation to function, or " the process by which cells advance from an immature to a mature or specialised state, or acquire a

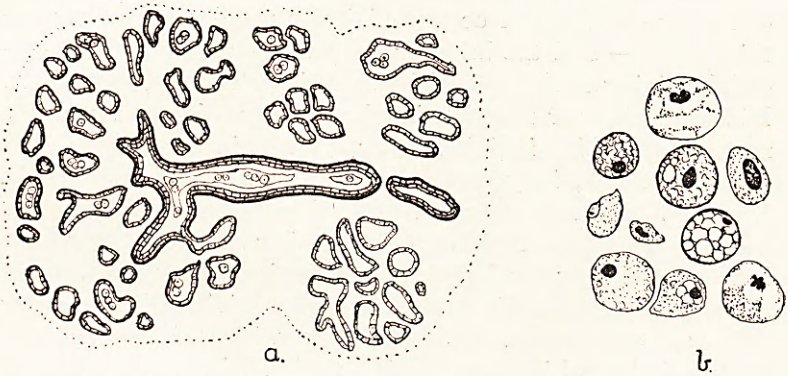


FIG. 12.—(*a*) Mammary lobule at term, differentiated for lactation. (*b*) Colostrum cells, highly magnified.

distinct or separate character " (Broders [4]). It does, therefore, logically include earlier stages of mammary development from nipple epithelium to normal duct and lobule formation, but full differentiation for function is not reached until true acini are formed. The function of the breast is milk secretion, and this implies the formation of differentiated tissue and the activity of specific secreting cells, which are normally evident only during reproduction (text Fig. 12*a*). Differentiation is used rather loosely in describing malignant mammary growth, as the antithesis of anaplasia, though little or no resemblance to lactating tissue is implied. This matter is discussed later in this paper, when malignant tumour emerging during pregnancy and lactation is described and illustrated, but physiologically the term differentiation is restricted to denote

the formation and functioning of acini, the secreting components of the mamma. During pregnancy, acini are more accurately described as *potentially* secreting structures, since true secretion of milk is not initiated until after delivery.

The formation of true acini during pregnancy is an uneven process and does not occur simultaneously throughout the whole breast or even a whole lobule. Loeb [15] observes that differentiation does not begin until a certain amount of new glandular tissue has been formed. I have found no detailed description of the formation of acini in human tissue in the relevant literature, but a careful study of my material suggests that about the third month of pregnancy, the newly formed ductules begin to throw off the superficial of their two lining cell layers—colostrum occurs clinically usually only after the third month—and the basal or deeper layer remains as a unicellular lining to the potentially secreting structure, the acinus. Differentiation for function involves changes in the basal cell metabolism which inhibit further growth, in accordance with the laws which, in general, regulate growth and function in the body. I have found no evidence that the one-layer structure —the true acinus—buds off other similar structures, nor have I found, during prolonged investigation of much human material at high magnification, evidence of division in the acinar cells at any stage. Concurrently with this progressive differentiation which forms acini, there is, in all the material I have examined at various stages of pregnancy, evidence of continued glandular (ductule) growth. The rarity with which mitoses are encountered in this proliferating tissue is not surprising, since this is also the case in rapidly enlarging benign adenomatous growth apart from pregnancy.

The composition of colostrum, as associated with the differentiation of ductules to form acini, has given rise to difference of opinion, a detailed discussion of which is not relevant here. Colostrum is not a secretion in the true sense of the term, though frequently described as such; it is apparently similar to the contents of ducts and ductules observed at other periods than pregnancy, when epithelial cell proliferation, desquamation and degeneration lead to the incursion of phagocytic cells into the lumen from the surrounding stroma. The older writers considered that these colostrum cells were, in the main, if not exclusively, epithelial; later observers ascribe a predominantly blood or stroma cell origin.

This difference of opinion may, in part, be explained by the stage at which the differentiating structures have been examined. In the early stage, following desquamation of the superficial cell layer, the ducts contain degenerating epithelium but later, phagocytic cells continue to find their way into the lumen, where they are more in evidence. Histologically, it is difficult to determine the origin of these " foamy cells " in the ducts and acini ; they may be derived apparently either from glandular epithelium which has undergone fatty degeneration, or from phagocytic cells which have ingested fatty débris. The foamy cells attain considerable size (text Fig. 12*b* and Fig. 66), as they do in other tissues of the body. The presence of fatty material, produced by epithelial degeneration and attracting phagocytic cells from blood and stroma, is supported by experimental work.[5, 6] The lysis of some of this epithelial débris is probably responsible for the appearance in fixed preparations of the finely granular coagulum which fills and may considerably distend the acini during the latter part of pregnancy. The colostrum which forms during pregnancy is removed, according to some observers, by early post-partum suckling ; others note that some of the colostrum cells may return to the connective tissue, to be carried away in the lymph stream to the lymph nodes, but I have not been able to identify them outside the acini in mammary tissue during pregnancy, though they are evident in lymph vessels and lymph node sinuses during post-lactation involution, when colostrum is again produced. The cells from the blood and from the stroma have apparently little difficulty in entering the lumen through the basement membrane which surrounds the acinus and appears to be a continuous homogeneous structure. They may be seen lying deep to the epithelial cells or making their way between them before actually entering the lumen and the hyperchromatism suggests that the nucleus may have been mistaken for the prophase stage of mitosis of the larger vesicular nucleus of the secreting cell. The entrant cells appear mainly lymphoid in morphology, but various other types of cell may be seen around the acini in later pregnancy, such as eosinophils, plasma cells, large mononuclears and even polymorphs ; of these, my material shows the plasma cell to be the most obvious.

Colostrum causes considerable acinar distension and

probably accounts for much of the mammary enlargement apparent in the later months of pregnancy, though progressive glandular growth, increased vascularity and congestion also play a part. In addition to the process which transforms newly formed ductules into acini, there is, as already mentioned, continued growth of the undifferentiated glandular fields, and even in the same lobule and during lactation the two processes of growth and differentiation may be observed side by side (Figs. 19 and 23).

With this lobular growth and acinar distension, the connective and fatty tissues of the breast decrease. The intralobular loose connective tissue is reduced to narrow strands, carrying fine capillaries between the closely adjacent acini, but the amount of supporting stroma shows great variation. In some cases, glandular growth is so extensive that large areas of the breast show little but parenchyma (Fig. 10), while in others, even at term, the lobules may be separated by much stroma (Fig. 11). The macroscopic distribution of the secreting tissue is also variable; it may be limited to the corpus mammæ and show a fairly well-defined boundary (Fig. 57, at D), or it may be seen in the suspensory ligaments and in the fibrous septa in the surrounding fat (Fig. 58). Altmann [7] found that the possibility of lactation was not negatived by small mammary development, as judged by the weight of the gland without surrounding fat, since the *corpus mammæ* at the end of pregnancy may, in some cases, be mainly lactating tissue, in others, still largely composed of stroma.

The nipple becomes more prominent during pregnancy. Its enlargement during lactation is due, according to some observers, to multiplication of acini, but my examination of a number of nipples during pregnancy and lactation indicates that in this also there is much variation. Three, at different stages of lactation, are illustrated in text Fig. 13 and show little acinar tissue lying near the large milk ducts. Increased areolar pigmentation is a clinical sign of pregnancy and histologically is evident as much melanin in the basal epithelium of the skin in that area; hypertrophy of the large sebaceous glands of the nipple and areola—the so-called Montgomery's tubercles—is described as present during pregnancy and lactation, but my sections do not show these structures as particularly prominent.

(c) *Discussion.*—The increase of glandular tissue—adenosis—which is characteristic of pregnancy is clinically apparent in the human breast about ten weeks after conception, according to Cheatle and Cutler [8]; Starling [9] observed, in rabbits, that rapid growth of the gland appears to begin at once and five days after conception, when the impregnated ovum is still unrecognisable by the naked eye, the mammæ are visibly enlarged. Steinhaus [10] found, in the guinea-pig, the structure of the newly formed glandular tissue of the first half of pregnancy very little different from that of the resting breast, except that more mitoses were observed. Coen [11] and Prym [12] described solid budding and two-layer gland formations at two months, and Gruber [13] and Berka [14] at three months of pregnancy, findings which support my observations that the activity of early pregnancy is mainly the laying down of new

FIG. 13.—Three nipples in lactation, to show lactating tissue in relation to large milk ducts.

structures similar to those produced at other phases of normal mammary growth.

The differentiation characteristic of the later half of pregnancy is, according to Loeb,[15] a gradual process, and the loss of power to multiply a gradual change in the cell; Steinhaus [10] also finds the acini passing through a series of changes to reach the fully differentiated state. Several references to mitosis in differentiated tissue [16 *et al*] are probably explained by the finding already noted that, coincidently with cellular differentiation, epithelial proliferation to form additional gland tissue continues, even during lactation.

The difference of opinion in the literature with regard to the origin of the colostrum cell has been mentioned. Loeb [15] has observed colostrum formation in terminal tubes (ductules) associated with preceding growth processes, at a time when "alveoli" (acini) are not yet formed, and Gruber [13] found colostrum cells at the third month of pregnancy when the glandular tissue was still almost all of two-layer structure,

that is, still undifferentiated. The colostrum or foamy cells are very much in evidence in older mammary tissue, especially when glandular structures are being removed by menopausal involution, with marked epithelial degeneration. I am unable to detect histologically any structural differences which would distinguish from which of the possible sources—epithelium, blood or stroma—the cells are derived. Maximow [17] considered that the majority of the colostrum cells undergo lysis in the acinar or duct lumen and are removed in the milk during lactation, but Gruber also observed them in the lymph channels and axillary lymph nodes. The large pigmented macrophage, formed subsequent to the appearance of the foamy cell in the gland lumen, may be observed in great numbers in the stroma in menopausal involuting tissue and will be referred to again in a later study of the breast at that period.

3. **The Mamma during Lactation.**—With delivery, the mamma is prepared to begin secreting, but the process is not usually initiated until a few days after child-birth. This initial check on milk secretion finds adequate explanation in the pressure on the secreting cells by the colostrum which distends the acini; when this is removed by early suckling, secretion begins and, with regular nursing, becomes a rhythmic process which normally persists during the lactation period. In the human breast, the ducts do not form part of the secreting surface of the gland (Figs. 16, 18, 21 *et al*). The actual site of change from non-secreting to secreting structure seems somewhat variable, though the transition from two-layer duct to one-layer acinus may be fairly abrupt, when seen in favourable sections, as in Fig. 14, Plate II.

PLATE II

The Mamma in Lactation

FIG. 14.—Mammary tissue, 6th week of lactation, showing transition of 2-layer formation of duct (d) to single-layer secreting acini. ×65.

FIG. 15.—Mammary tissue, 10th week of lactation, showing single-layer structure of acinus. ×900.

FIG. 16.—Mammary tissue, 10th week of lactation, showing non-secreting ducts (d) and secreting lobules. ×25.

FIG. 17.—Mammary tissue, 10th week of lactation, showing discharge of secretion (fat). ×200.

FIG. 18.—Mammary tissue, 10th week of lactation, showing duct (d), secreting lobules at different phases and perilobular lymph vessels (x). ×30.

FIG. 19.—Mammary tissue, 10th week of lactation, with much undifferentiated lobular tissue (x) and few secreting lobules (y). ×20.

FIG. 14

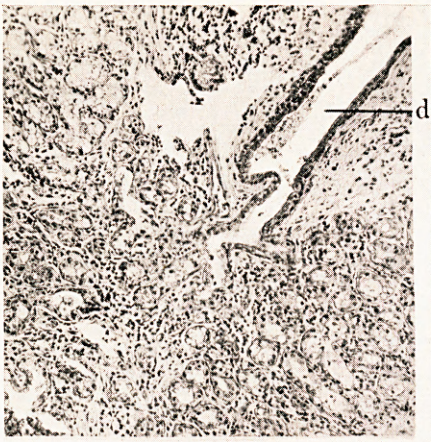


FIG. 15

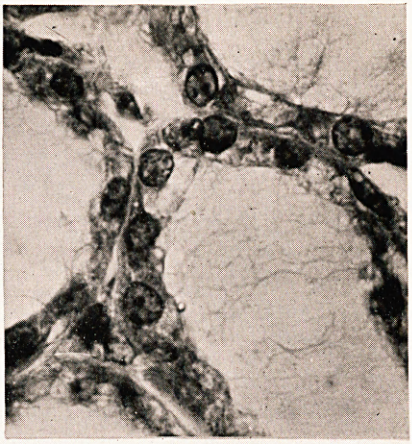


FIG. 16

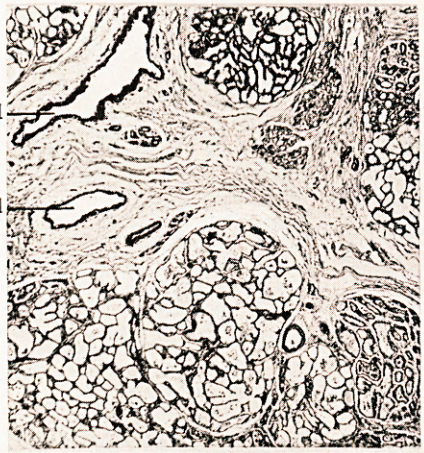


FIG. 17

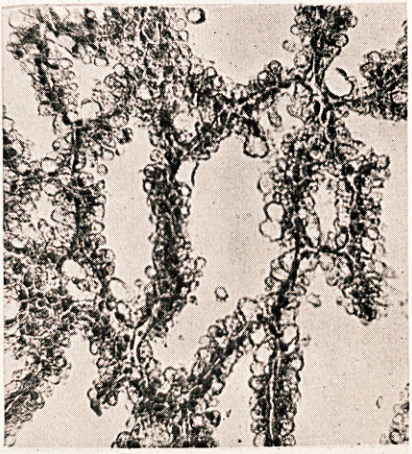


FIG. 18

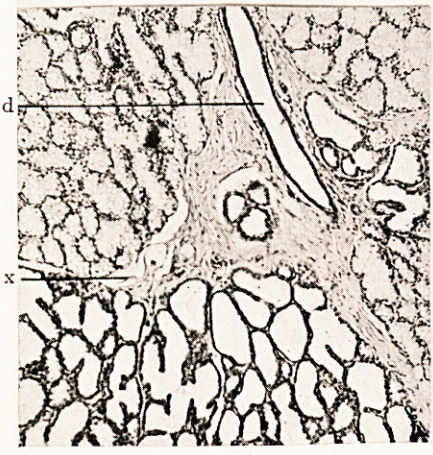
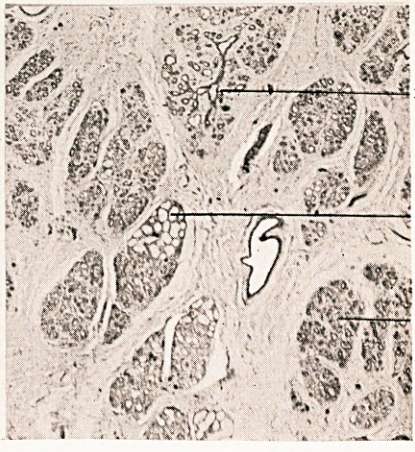


FIG. 19



The Mamma in Lactation.

(a) *The Histological Picture in Lactation* (text Fig. 20).—I have defined the acinus, formed during pregnancy and secreting in lactation, as the terminal outgrowth which marks the end of glandular growth. It is lined only by a single layer of cubical epithelium, bounded by a fine basement membrane and in close contact with capillaries in the scanty surrounding connective tissue (Figs. 15, 17). The acinus varies in size and cell behaviour according to the phase of secretion at which it is examined. The presence of a second layer of epithelial cells has been described by some observers, but my examination of much normal material at high magnification supports the observations of those who point to the essentially one-layer lining of the acinus (Fig. 15 and Fig. 27, *a-f*, in text).

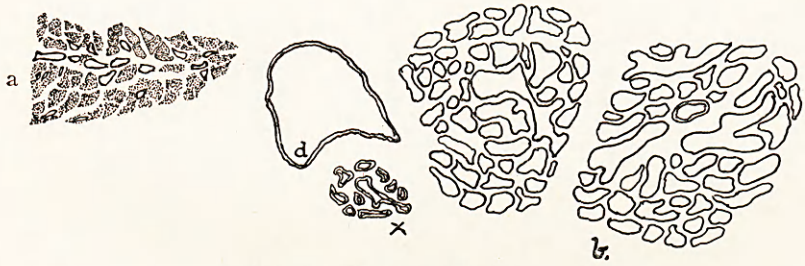


FIG. 20.—Lactating tissue.

a. Diagram from a section. (×1.)
b. Diagram (×60), with duct (*d*), differentiated and undifferentiated (*x*) lobules.

This is an important finding in regard to the possibility of pathological growth arising in secreting tissue in the breast.

If the acinus is essentially a single layer formation without even the occasional presence of "reserve" or "generative" cells, and if mitotic figures are not observed in the secreting cells themselves, it may be asked how cell renewal during lactation is provided for. Since secretion is formed and liberated with little or no apparent injury to the cell, a process which is continually repeated, we can assume that the secreting cell in the breast, as in other merokrine glands, such as the liver, thyreoid, etc., has a considerable life duration. Should the cell be exhausted, desquamated or destroyed, tissue regeneration seems adequately provided for by the continued growth and differentiation of the non-secreting lobules which, in my material, may be observed at all stages of later pregnancy and during lactation. In tissue removed from women still

lactating after 12 and 15 months, sections in both cases showed many undifferentiated lobules, scattered among and at the periphery of the secreting tissue (Figs. 23 and 72). Lewis and Geschickter [3] consider these undifferentiated ductules are "virginal" lobules "refractory to endocrine stimulation," which "may respond abnormally during the menstrual cycle to form the basis for the later development of cystic disease." It would be difficult to present histological proof of this

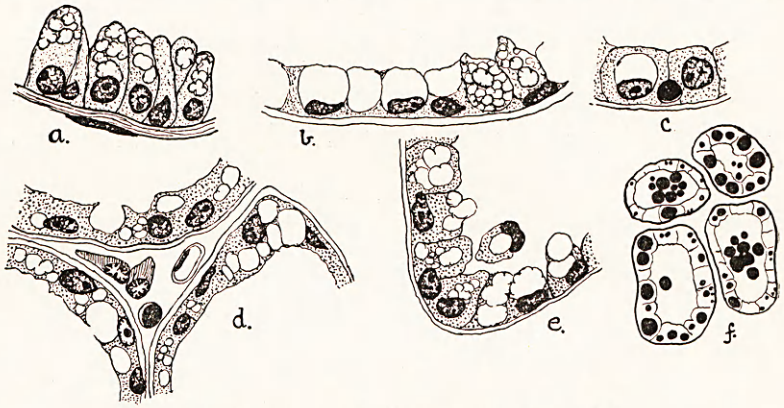


FIG. 27.—Fat secretion in lactating mammary cells.
a-e. Stained by H. and E. *f.* Osmic acid stain.

assumption. All the normal tissue of pregnancy and lactation which I have examined shows some of these "virginal" lobules, and it seems justifiable to assume that they provide for the replacement of exhausted and degenerating secreting cells, as well as supply the additional tissue needed to cope with the nutritional demands of the growing infant.

PLATE III

Lactating Mammary Tissue

FIG. 21.—Secreting acini, showing discharge of secretion (fat), and duct (d), which does not share in secretory activity. ×200.

FIG. 22.—The resting stage of the secreting cell, with acini (a) and duct (d) distended with secretion. ×65.

FIG. 23.—Mammary tissue after 12 months' lactation, showing undifferentiated lobules (x). ×20.

Lymph Vessels in Mammary Tissue

FIG. 24.—Lymph vessels (x), 5th month of pregnancy. ×20.

FIG. 25.—Afferent lymph vessels (x) entering axillary lymph node removed during lactation. ×20.

FIG. 26.—Greatly distended lymph vessel (x) 3 months after lactation. ×40.

FIG. 21

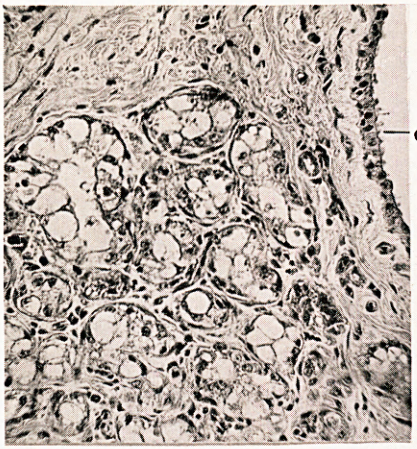


FIG. 22

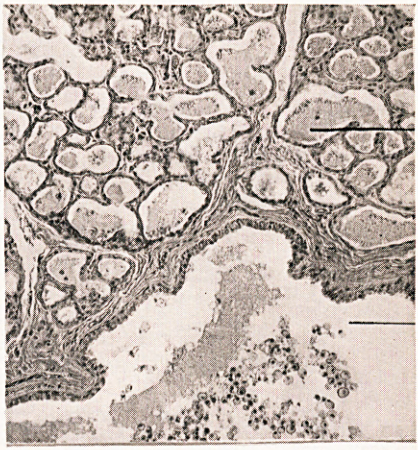


FIG. 23

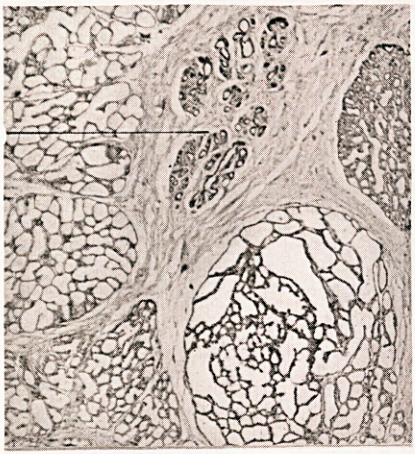


FIG. 24

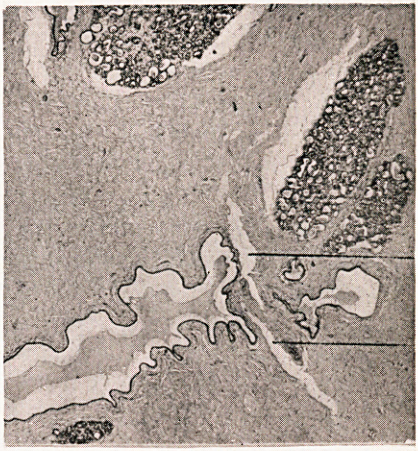


FIG. 25

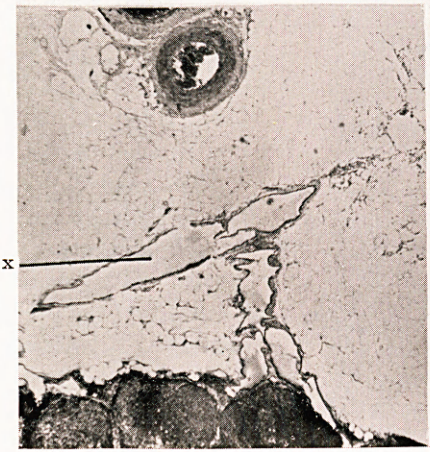
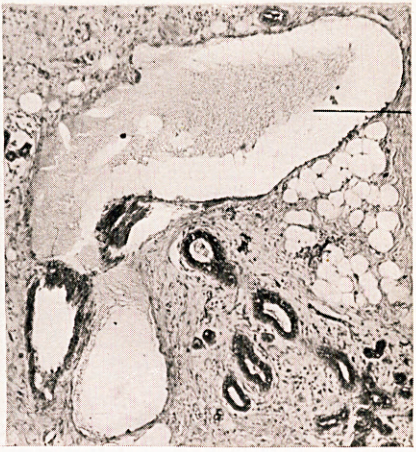


FIG. 26



Lactating Tissue and Lymph Vessels.

(b) *The Process of Lactation.*—I have divided, somewhat arbitrarily, the picture and the process of lactation. When lactation is established after the removal of the colostrum of pregnancy, the acinar cells, now fully differentiated, begin the rhythmic process of the formation and release of secretion. Within these cells, the amino-acid, lecithin and dextrose brought to them by the blood stream are elaborated into the casein, fat and lactose of the milk. Tissue in fixed and stained sections gives little evidence of protein secretion in the cell body, though homogeneous droplets interpreted as such are described by several observers. Fat secretion is, however, obvious at all stages in microscopic preparations (text Fig. 27). Small globules appear as vacuoles round the nucleus which lies at the base of the cell; these increase in size, usually coalesce to form larger drops and move towards the free end of the cell, to be liberated into the lumen through the cell wall. The appearance of rupture and re-formation of the cell wall, in the process of fat extrusion, is probably due to artefact. After a resting period, during which the nucleus, flattened by accumulation of fat within the cytoplasm, regains its normal spheroidal shape, the process is repeated. These phases are sometimes described as resting, developmental (with small drops), secreting (with larger drops) and discharging (see Figs. 14-18, 21, 22, text Fig. 27 and Fig. 40). In stained sections, milk appears as an evenly granular coagulum—the albuminoid constituent—with fat drops and some colostrum cells embedded in it. In the ducts, there is frequently a sharp demarcation evident between the fatty and the non-fatty content, as though the different constituents had been secreted at different phases of the cycle (Figs. 22, 73 and 74). Distension of the acinus by milk flattens the lining cells and inhibits their activity; when emptied by nursing, the cell expands and the secretion cycle begins anew. The period during which secretory activity can remain inhibited by acinar distension, with the possibility of being resumed by drainage, is an important practical point and apparently varies within considerable limits for human tissue. Some observers have noted that where there is no lactation, the glandular tissue shows almost at once a confused cellular picture which indicates acinar collapse and the beginning of involution, but lactation has been established as long as ten weeks after delivery, in cases where there had been no initial attempt at nursing.[18]

This indicates that the secreting cells survive even prolonged pressure and inactivity without irreparable damage; these, however, may be exceptional cases, and if so, they suggest that regular and adequate aspiration must play an important rôle in the maintenance of secretory function.

This brief description of the process of lactation, supported by the histological appearances observed, is now the generally accepted one. Two other hypotheses have been put forward regarding milk secretion—(i) the disintegration of the acinar cells to form the milk solids, a conception negatived by the absence of rapid cell renewal, and (ii) the breaking off into the lumen of the inner part of the epithelial cell, with its secreted substances. The theory of secretion without cell injury best accounts, in my opinion, for the whole process as it is evidenced in microscopic preparations.

Secretion in the breast raises many interesting questions, which are only indirectly concerned with a histological study, but two points may be noted here. Weatherford's studies of secretion by mammary cells [19] in relation to changes in form and distribution of the finer cytological constituents—mitochondria and Golgi apparatus—lay emphasis on the profound changes in the cell necessitated by the secretory function, and indirectly support the thesis, brought forward later in this paper, of the unlikelihood of purely proliferative changes being assumed by true acinar cells. The second point is the prominence, probably due to dilatation, of the lymph vessels, not only in lactating tissue and the axillary area (Fig. 25), but also in pregnancy tissue (Fig. 24, at five months) and in post-lactation involuting tissue (Fig. 26, three months after nursing ceased).

(c) *The Duration of Lactation.*—Lactation is influenced by various conditions which shorten or prolong its duration, and the effect of these, in the absence of exact clinical and microscopic data, is difficult to assess. Both under- and over-lactation have been incriminated in the origin of later pathological growth in the breast, so it is relevant to enquire what is the optimum period under normal conditions. Opinions vary to a surprising degree. Some writers consider that 12 to 18 months is the normal time,[20] others, at least 6 months.[21] Others consider that, as milk secretion increases in quantity up to the 6th or 7th month and then gradually decreases, in most cases, lactation is inadvisable beyond 9 months.[22] This

opinion seems fairly general in most Western countries, but in the Orient, nursing for considerably longer periods seems usual. The Koran instructs the mother to nurse the child 2 full years, and 3 years is mentioned in the Apocrypha [23]; Goebel found lactation usual for 3 or 4 years in Egypt,[24] and in China, the period may be even longer.[25] Lane-Claypon [26] found surprisingly large numbers of children fed for one or more years in a breast cancer series and in a control series of women investigated at hospitals in this country—19·8 per cent. for the cancer series, and 34·2 per cent. for the controls—she observes that the view which regards lactation for more than 9 months as constituting some degree of over-lactation has been based on consideration of the interests of the child rather than those of the mother.

The question of the optimum duration of lactation involves that of the varying ability of the mother to provide enough milk for the nourishment of the child. Some observers consider that this may depend primarily on the glandular content of the mammary tissue, that is, on both the original quantity of lobular structure in the breast, a point raised in my earlier paper when discussing the "infantile type" of mammary development after puberty, and on the amount of new lobular tissue formed in the breast of the pregnant woman; a third factor is the adequacy of the stimulus to secretion during lactation. Cases are on record where mammary growth during pregnancy has been normal or even excessive, yet without later milk formation. The modern outlook tends towards the view that lactation, in most cases, is possible, if the co-operation of the mother be secured and there be no physical or temperamental contra-indications.

Lactation in infants, in non-parturient women, in women after the menopause and in male subjects is described in the literature, though without histological findings, and what is called by some observers pathological lactation may be associated with prolonged sterility, derangements of the genital tract and cystic or adenomatous mammary tumours; but apart from definitely post-partum milk retention, the fluid in mammary cysts has, in my opinion, no necessary connection with an earlier pregnancy or lactation.

(d) *The Coincidence of Pregnancy and Lactation.*—It is sometimes stated that lactation and pregnancy are incompatible,[27, 28] and prolonged nursing may be attributable to this

belief. There is, however, much clinical evidence that lactation does not cease when a new pregnancy begins, and it may continue until the second child is brought to term.[18] Seifert [29] observed that the concurrence of pregnancy and lactation was comparatively common. Fordyce [30] found, in a series of 100 mothers with 405 children, investigated at a maternity clinic, that menstruation and, therefore, the possibility of a new pregnancy returned within two months of delivery in 27 per cent.; within nine months, 92 per cent. of the mothers were menstruating. There was menstruation during lactation in 47, and in 24 of the 100, overlapping of pregnancy and lactation. It was frequently found in his series that the mother was unable to nurse the later child, as the milk was poor and insufficient, but nourishment of the earlier infant was not seriously affected. As the two conditions may co-exist for some time without being suspected, Fordyce considers weaning advisable early in the eighth month, as the new pregnancy rarely began within six months of delivery. Loeb [15] observes that a new pregnancy arising during lactation is unable to stimulate new glandular growth, a finding which may explain the insufficient nourishment of the later child. I have no mammary material for histological examination in cases where pregnancy and lactation coincided.

(e) *Discussion.*—The histological appearance of lactating tissue has been dealt with in some detail here, as it is an important matter in microscopical diagnosis. The one-cell layer structure has been described by Loeb,[15] Prym,[12] Maximow [17] and others, in human tissue, and by Steinhaus,[10] Corner,[31] Weatherford [19] and others, in animal tissue. Benda thought that the superficial cells of the two-layer ductule, instead of desquamating and forming part of the colostrum of pregnancy, as described above, develop into the acinus, while the deeper (basal) layer produces the isolated elongated cells lying in the basement membrane—the " myo-epithelium " of Krompecher and other observers. Berka,[14] on the other hand, considered that these isolated cells, sometimes also called " basket cells," have nothing to do with the essential structure of the secreting unit which, when fully developed is, in his opinion, always of one-cell layer. This is also the view of Dieckmann,[32] who does not consider that Benda's outer layer of flattened cells represents the basal layer of the non-secreting ductule. MacCarty, in a diagram of an acinus,[33] shows

scattered "generative" or "reserve" cells between the continuous layer of differentiated (secreting) cells and the basement membrane in the lactating breast. He considers that "in differentiation and specialisation, destruction and regeneration must be provided for"; two layers are therefore always present, in his opinion. My observations, however, support the findings of Loeb, Weatherford, Steinhaus and others regarding the one-cell layer of the secreting acinus, and show that regeneration seems amply provided for by continued ductule proliferation. Some areas of lactating tissue I have examined show almost a preponderance of this undifferentiated tissue (*cf.* Fig. 19). Cheatle includes in his description of *mazoplasia* the glandular picture seen in pregnancy and in the less active parts of the breast during lactation, as well as at other times when mammary tissue is active; he thus implies the presence of undifferentiated tissue in the lactating breast. Deaver and McFarland [34] consider that the variation in lactating tissue showing both secreting and inactive lobules, may explain differences in the volume of milk secretion; a preponderance of inactive tissue would suggest an inadequate function of the secretory stimulus. McFarland [35] and Trinca [36] also suggest that the undifferentiated lobules provide additional lactating tissue by their continued growth. I have mentioned that the ducts in human mammary tissue show no evidence of secretion, but in the rat, Maeder [37] and Weatherford [19] observed that the ducts, lined by two-cell layers in the resting stage, become one-layer structures during the last days of pregnancy and then show some secretory activity. Loeb,[15] however, thinks this apparent difference between human and animal tissue may be explained by appearances which indicate the absorption rather than the secretion of fat by the epithelium lining the ducts. The non-participation of the ducts in secretory function in human tissue is an important point with regard both to the continued formation of glandular tissue during lactation and to the genesis of pathological epithelial growth during reproduction.

4. **The Stimuli to Growth and Secretion.**—As mentioned in the earlier study, discussion of the stimuli responsible for mammary activity is purposely omitted from this histological investigation. Much of the animal experimental work on record is inconclusive, while reports in human cases are rare

and, because therapeutic, necessarily lack histological details. Attempts to define the part taken by the follicular, luteal and pituitary factors are rendered more difficult by the simultaneous finding of different histological phases of growth and function in mammary tissue, but, stated briefly, there seems considerable agreement of opinion that the anterior pituitary hormone is responsible for secretion, but its effect is observed only on glandular tissue developed and sensitized by ovarian influence, follicular in the early stages, luteal in the later stages of pregnancy. The stimuli are blood-borne, as they can influence mammary tissue transplanted in other parts of the body [38]; the influence of the autonomic nervous system, both stimulant and inhibitory, finds probable explanation in its vasomotor control.

5. **Post-lactation Involution.**—When lactation ceases, the secreting structures, newly formed and differentiated during pregnancy, degenerate and gradually disappear. This glandular atrophy is not a uniform process throughout the whole breast and the varied cytological picture may be, in some cases, difficult to interpret. Various points are raised by a consideration of this glandular involution.

(a) *The Histological Picture in Normal Post-lactation Involution.*—In the description of the formation and differentiation of secreting tissue, the view was put forward that the acini represent the final stage of growth of the glandular epithelium. The basal or "reserve" or "generative" cells, which in the ducts and ductules of the resting breast are capable of proliferation to form new glandular tissue, in the acini have themselves differentiated for secretory function, and this process is apparently irreversible. The involution

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PLATE IV

The Mamma in Post-Lactation Involution

FIG. 28.—Mammary tissue, one month after lactation, showing early acinar distension, with flattening of the lining cells.

FIG. 29.—Mammary tissue, 3 months after lactation, showing epithelial cell desquamation and disintegration of the secreting lobule.

FIG. 30.—Mammary tissue, low power view, 3 months after lactation, showing different stages of involution.

FIG. 31.—Mammary tissue, 4 months after lactation, showing epithelial cell atrophy and disappearance of the basement membrane of the acini.

FIG. 32.—Mammary tissue, 5 months after lactation, showing colostrum cells (x) in the nucleated tissue mass of the involuting lobule.

FIG. 33.—Mammary tissue, 13 months after lactation, showing considerable vascularity and active fibrosis.

FIG. 28

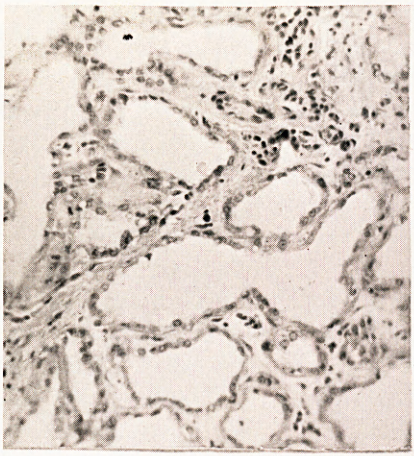


FIG. 29

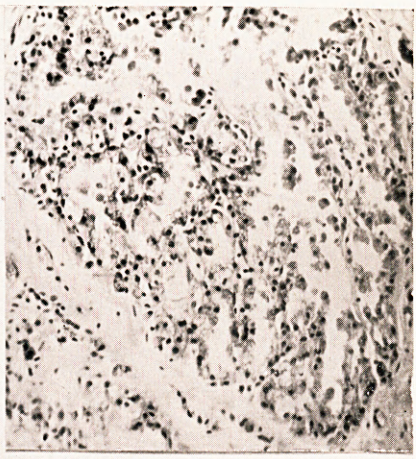


FIG. 30

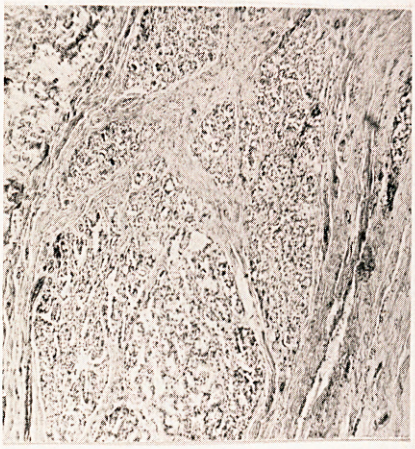


FIG. 31

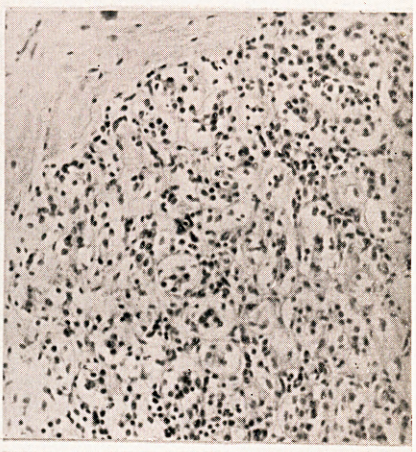


FIG. 32

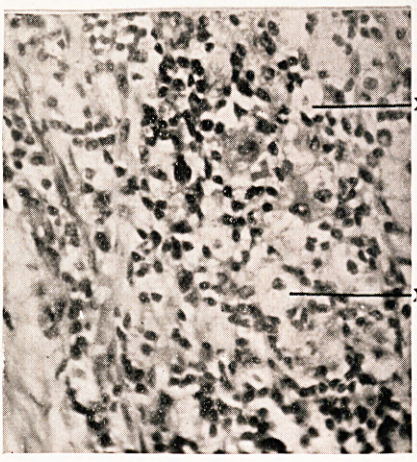
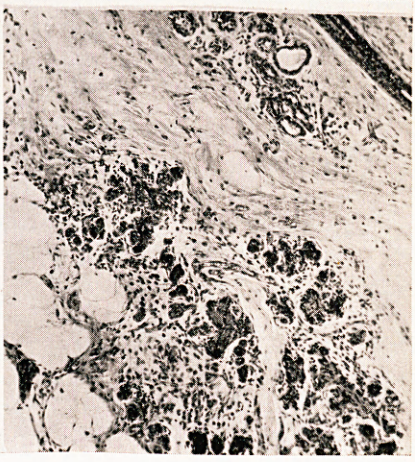


FIG. 33



The Mamma in Post-Lactation Involution.

process after lactation is "not a reversed differentiation" (Loeb [15]) in the sense that acini change back into ductules; they degenerate and disappear and the breast reverts to a resting condition. My examination of post-lactation tissue at various phases of retrogression suggests that the stages in this atrophy are, in general, as follows :—

i. The acini become distended with retained secretion, which may, in places, cause rupture of adjacent walls to form larger lumina.

ii. This distension flattens the epithelial cells, inhibits the changes associated with secretion and gradually prevents its formation (Figs. 28 and 75, one month after lactation). Distension also causes interference with the capillary circulation surrounding the secreting acini and thus furthers epithelial inactivity and retrogression.

iii. Colostrum formation is again evident, and phagocytic cells migrate into the acinar lumen, attracted by stagnating secretion and degenerating epithelium.

iv. Secretion is gradually removed and absorbed by phagocytosis and lysis and acinar distension diminishes; later, the dividing walls collapse with desquamation of the lining cells (Figs. 29 and 76). These are pushed towards the centre of the distorted lumen, where they gradually disintegrate. The desquamated epithelial cells may form clumps very similar to the solid buds observed in the adenosis of early pregnancy. Later stages show cytoplasmic atrophy, with nuclear pyknosis and lysis, disappearance of the basement membrane and loss of definition of the whole lobule (Fig. 31). Even in the same lobule, acini may be observed at different stages of degeneration (Fig. 30), but those at the periphery of the lobule seem to disintegrate first.

v. With retrogression of the epithelium, fibrous tissue takes the place of the dead secreting elements. Analysis of the somewhat confused microscopic picture at this stage shows epithelium in small clumps or still lining contracted acini, numerous active fibroblasts, lymphoid and occasionally other stroma cells and fine blood vessels with prominent endothelium. It is difficult to say whether the capillaries are those of the fine septa between the secreting structures or of new formation associated with the active fibrosis. Colostrum may also occasionally be seen in this nucleated tissue mass (Fig. 32 *x*). Though a considerable amount of fatty débris has to be

removed, at this early stage the transport of this has been difficult to demonstrate in my sections, though other observers have described, at the periphery of the involuting lobules, cells laden with very fine fat granules in the stroma, as well as in the lymph and blood vessels and in the lymph nodes.[13]

vi. At a later stage, fatty tissue reappears in the supporting stroma. This new fat formation in and around the *corpus mammæ*, in the fifth month after lactation, is shown in Fig. 77, Plate X.

The abundant glandular tissue of pregnancy and lactation is thus gradually replaced by fibrous and fatty tissue. Some observers consider that if involution is complete, the mammary picture is histologically very similar to that of the virgin breast, with ducts and sparse groupings of ductules; but others think that until menopausal involution sets in, the parous organ shows more glandular tissue than if lactation had never occurred. The clinical increase in the size of the post-lactation breast, in any particular case, might be due in part to a permanent increase of glandular structure, or in part to replacement of stroma by larger areas of fatty tissue. Any statement regarding the degree of involution, whether only the ductules of the original (pre-pregnancy) lobule remain, or whether the lobule left is more complex than that in which pregnancy growth first started, would be difficult to substantiate, for occasions which allow examination of mammary tissue before and after pregnancy from the same breast, or even the same person, must be rare. The degree of involution would appear to be of less importance than evidence of delayed or perverted retrogression.

(b) *The Time taken in Normal Post-lactation Involution.*—I have no data for estimating the time normally occupied by these various stages of involution after lactation in the human subject. A detailed lactation-history is rarely available for the pathologist, and the circumstances which hinder or hasten involution cannot therefore be defined. Berka found, in mammary tissue three months after child-birth, where there had been lactation for three days only, that while some small lobules were still distinguishable, from other areas they had already almost completely disappeared and their place was indicated by cell infiltrates and fine elastic fibrils. This picture is in marked contrast to that illustrated in Figs. 29 and 30, already referred to, which show tissue at the same, three months, post-

lactation stage. It is stated that involution in the human breast should normally take from nine to twelve months, but other opinion in the literature suggests that one to two years is more usual, and that pregnancies should be spaced out to correspond. Considerable stroma activity was noted thirteen months after lactation (Fig. 33). Many observers describe incomplete involution apparent years after the last child-birth, but usually the histological picture is not submitted and no data regarding lactation or coincident infection are given.

(c) *Abnormal (Delayed or Incomplete) Involution :—*

i. *Possible Causes.*—Most writers, in describing post-lactation glandular retrogression, mention the possibility of " incomplete involution." Some associate it with frequent pregnancies, especially if in rapid succession, others with retention of secretion delaying and modifying glandular atrophy ; others, again, consider that in the older mother, the gradual increase of elastic tissue in the breast may be a hindrance to involution. Examination of my material, in relation to the available clinical data, suggests that absence or inadequacy of lactation or an infective condition tends to delay involution, the former by increasing the amount of secretion to be absorbed, the latter by augmenting the cellular débris to be removed. It is probable that absorption of secretion after lactation varies greatly in different individuals, and any conclusion regarding causes of delay would require clinical details rarely available in human cases. The following three of a number of examples in my material may be mentioned. The first, a woman aged 42, had her last child seven years previously; the child was not nursed, and in the intervening years the breasts had shown a slow progressive hypertrophy, more evident on one side. Both breasts were amputated and showed a microscopic picture of large lobules of indefinite outline and much fibrous tissue, in parts quiescent, in parts still very active and apparently an exaggeration of the fibrosis which normally accompanies involution (Figs. 78-80, Plate X.). Some areas showed a few small ducts filling with an active epithelium, but this proliferation might have been associated with early menopausal hyperplasia. The second case illustrates the possible result of an infective condition. This woman, aged 31 years, had a breast removed for small multiple " suspicious " nodules, which she stated began to form three months before examination, at the end of eleven months' lactation. The mammary tissue,

cut in small and whole-breast sections, showed several small defined sub-acute abscesses and little indication of glandular retrogression. In the third case, without lactation or obvious infection, tissue removed eighteen months after delivery showed a glandular content not unlike that of mid-pregnancy, but associated with pronounced fibroblastic activity and stroma cell infiltrations. This patient was 37 years old and there had been more than eight years' interval between the last and previous pregnancy.

Reference may be made to over-involution, where excessive glandular atrophy reduces the mamma to a size less than that of the resting organ. Cases are on record where, after neglect to nurse successive children, the breasts underwent such excess of involution that they almost disappeared, though there had been normal growth during pregnancy and milk secretion at term. Altmann [7] tried to prove that this " inactivity atrophy " was a heritable character among Bavarian women who rarely nursed their children.

ii. *The Histological Picture in Abnormal (Delayed or Incomplete) Involution.*—Examination of tissue from mammæ in which return to the resting condition seemed unduly delayed suggests that excessive and active fibrosis is largely responsible for the clinical picture, though non-involuted lactating lobules with acinar distension even to small cyst formation, are usually also evident. This fibrosis, associated with persisting adenosis, may, if progressive, lead to fibro-adenomatosis or to small multiple fibro-adenomata (Fig. 34, Plate V.), as noted in the

PLATE V

Abnormal Post-Lactation Involution

FIG. 34.—Small active fibro-adenoma, one of several, in post-lactation involuting mammary tissue.

FIG. 35.—Mammary tissue showing genesis of eosinophile (" pale " or so-called sweat-gland) epithelium (e) in a duct. The partial nature of this degenerative change is well shown, contrasted with the normal cell lining (n).

FIG. 36.—Mammary tissue (same case as in Fig. 35) showing delayed post-lactation involution (l) in a superficial lobule, adjacent to dilated sweat-glands with eosinophile epithelium (s).

FIG. 37.—Mammary tissue, showing a later stage of delayed involution, with acinar dilatation (x) and small cystic ducts (c).

FIG. 38.—Mammary tissue, showing another type of abnormal involution, with much fibrosis. Similar pictures are shown in the literature as a " pre-cancerous " condition.

FIG. 39.—A cystic adenoma, post-lactation, showing irregular acinar dilatation, with epithelial cell atrophy. This was a defined tumour, which enlarged and became painful during lactation.

FIG. 34

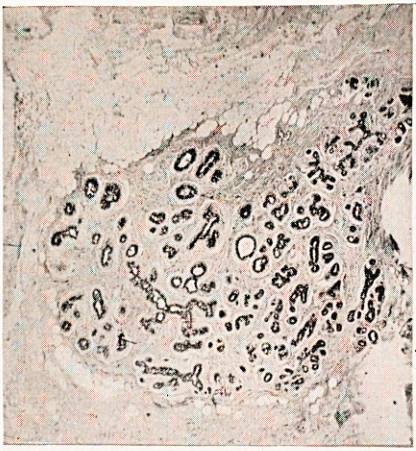


FIG. 35

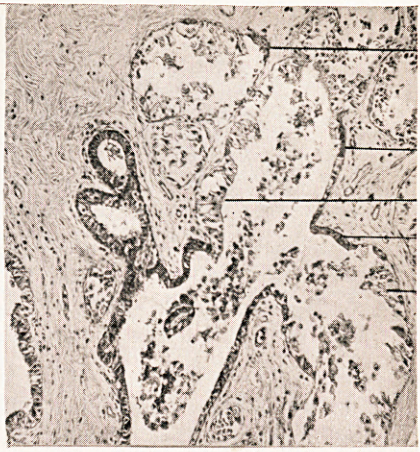


FIG. 36

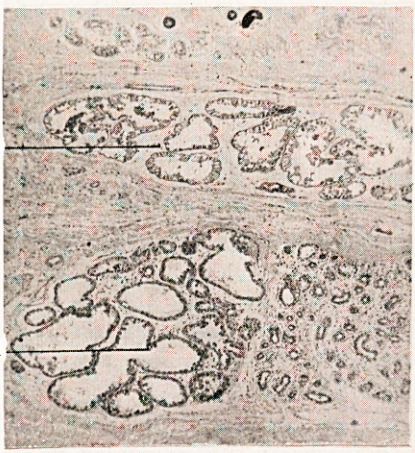


FIG. 37

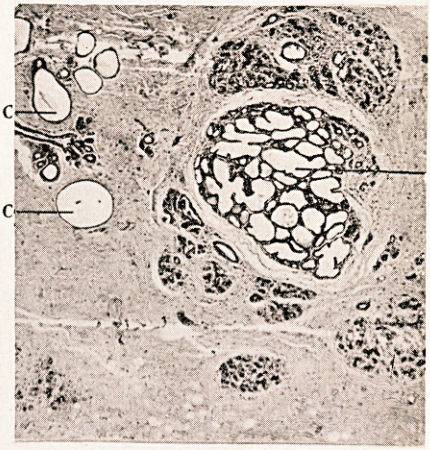


FIG. 38

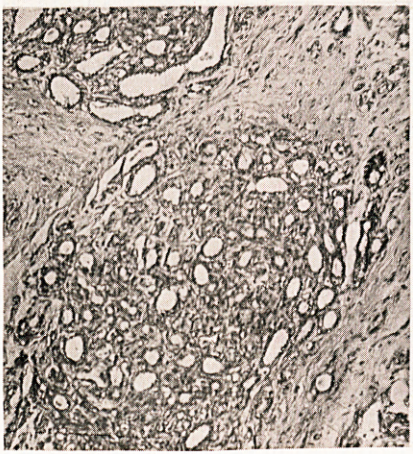
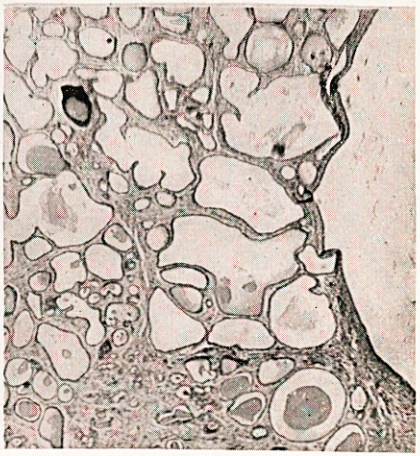


FIG. 39



Abnormal Post-Lactation Involution.

following section, sequelæ of abnormal involution. Another type of abnormal involution is seen in Fig. 38. Other appearances are, however, included in the histological picture of abnormal involution by various observers, who describe "residual lactation acini" forming eosinophile ("pale") cysts which gradually enlarge and may, in some cases, become prominent and numerous enough to produce the condition usually called "chronic cystic mastitis." I have discussed elsewhere [39] the origin of these eosinophile glandular structures —Krompecher's and Ewing's "sweat gland tissue"—and I am unable to support the findings which identify them with surviving lactation tissue. The genesis of this type of epithelium from normal non-secreting *duct* cells is illustrated in Fig. 35; this breast tissue also showed, in a superficial area adjacent to sweat glands (Fig. 36, *s*) in the overlying corium, non-involuted lactation acini, with no evidence of the eosinophile change (Fig. 36, *l*).

iii. *Sequelæ of Abnormal Involution.*—Where the normal course of involution and the possible factors influencing it are difficult to define, any consideration of the sequelæ of abnormal retrogression after lactation is necessarily somewhat speculative and has led to considerable difference of opinion.

When there has been no lactation there may be a persistence of glandular tissue, with active fibrosis, at a time when the breast should have returned to the resting condition. This may become clinically evident as a diffuse fibro-adenomatosis, as in the case mentioned on p. 591, where, after seven years of slow progressive hypertrophy, mainly due to fibrosis, more definitely pathological growth might have emerged; on the other hand, later retrogressive changes coincident with the menopause might have inhibited this, as seen in uterine fibroblastic activity at this period. The fibro-adenosis may, in other cases, produce small single or multiple fibro-adenomata, as shown in Fig. 34, from breast tissue which in other areas showed several non-involuted lactating lobules (Fig. 37, *x*). There is also experimental evidence to connect abnormal lactation and anomalies of involution with such benign tumour formation.[40] The presence of cysts in mammary tissue has been associated by some observers with irregular involution, but cysts are frequently found in nulliparous subjects as well as in parous women with a normal lactation history. In a small series of mammæ I examined from mice with normal

pregnancies and lactations, the resting breast tissue cut in serial sections showed many of the larger ducts widely distended with coagulum, but with no evidence of any pathological activity. Keynes [41] describes a condition which he says "may be called a 'stagnation mastitis,' seen clinically in women who have for some reason been compelled to cease nursing a child soon after its birth. Reabsorption of secretion is then attended by acute pain and inflammation, which may initiate a chronic mastitis and give rise to considerable suffering in a subsequent pregnancy." A similar condition may, in his opinion, be produced if pregnancy growth supervene in a breast which already shows "chronic mastitis," as normal hypertrophy does not take place in the presence of the fibrosis, epithelial proliferation and round cell infiltration characteristic of this lesion. Only rarely is there opportunity of examining the histological condition at different periods in the same breast, and such statements therefore need confirmation, in view of other opinions that cysts and fibro-adenosis disappear when a new pregnancy hypertrophy begins. There is, moreover, both clinical and histological evidence against any necessary association between absence or curtailment of lactation and later pathological development. Bradley [42] considers that leaving the breast partly distended with milk hastens epithelial atrophy through pressure. Frequently no clinical sign of disturbance is evident where there has been no lactation and no effort to establish it, a finding which may, in part, be explained by the abundant lymph drainage in the lactating mamma and the consequently rapid absorption of secretion, should lactation be avoided. The patency of the lymph vessels several months after glandular involution had begun has been already referred to (see Fig. 26, from tissue three months after lactation). The following case illustrates the comparative absence of histological disturbance with lactation anomalies. A woman of 51 years, 12-para, had a breast amputated because of serous discharge from the nipple of three months' duration. She had nursed none of her children; five had died in infancy. The breast tissue was cut in a series of small and whole breast sections and showed an almost complete replacement of the *corpus mammæ* by fat, in which were fibrous strands containing distorted quiescent lobules (Fig. 81), small areas of active fibrosis (Fig. 82) and some small cysts; the larger ducts near the nipple were dilated

and showed extensive desquamation and lysis of proliferated lining cells. Discharge from the nipple during post-menopausal mammary involution may, in rare cases, as here, be associated with catarrhal proliferation in the larger ducts, and little other evidence of pathological activity.

These findings in regard to anomalies of lactation, possible abnormal involution and benign tumour formation, are inconclusive; the association with malignant development is equally so. There is much opinion in the literature which associates milk stasis and decomposition with later cancer development. Experimental work, however, which demonstrated increased malignant tumour incidence in mice subjected to rapidly successive pregnancies without lactation and therefore presumably absence or perversion of involution, though it introduces an essential time factor, postulates conditions too abnormal to throw much light on carcinogenesis in human mammary tissue. Moreover, when mammary adenomata in the rat are transplanted to other areas of the body, lactation and post-lactation involution are concurrent in the breast and in the transplanted tissue, even when the transplant is intraperitoneal or intramuscular. The inspissated milk gradually disappears without exercising a stimulant effect on the duct epithelium.[38] Though there is some statistical evidence of connection between absence of lactation and later cancer development, it is generally agreed that malignant growth in the breast occurs more frequently in nulliparous subjects, where no lactation hypertrophy and secretion have taken place.

The formation of eosinophile glandular structures, interpreted by some observers as derived from surviving lactation tissue, has been already referred to. My material shows their presence in mammary tissue which has never undergone pregnancy and lactation changes; I have found no evidence in support of the proposition that eosinophile epithelium indicates a proliferative change with a more or less definite possibility of later malignant development. Later developments from these structures do not therefore concern us here.

Infective conditions associated with pregnancy and lactation have been mentioned as a possible cause of abnormal involution, and the later histological picture in these cases needs attention. Chronic lactation mastitis has been described as " characterized

microscopically by evidence of lactation hypertrophy, varying from the fully developed lobule of lactation to small areas of residual lactation hypertrophy, associated with infection." [43] The "tumour" formed begins as an area of induration, and there may have been at no stage any clinical evidence of an infective process. The diffuse induration, associated with a microscopical picture of lactation hypertrophy, has frequently led to a diagnosis, from frozen sections of biopsy tissue, of "adenocarcinoma" and to radical mastectomy, but a knowledge of normal lactation and involution histology would have avoided both the diagnostic and the therapeutic error. I am not convinced, however, that there was *necessarily* bacterial infection, at any stage, in some of the cases of "chronic lactation mastitis" described as "lactation hypertrophy persisting for years and appearing later as a non-encapsulated tumour." The absorption of secretion and colostrum, especially in quantity, may be a very slow process, especially where, according to the mother, "the milk dried up slowly," and cases are on record where milk has continued to be secreted in measurable amount several years after weaning the last child. Absorption may also be an "irritative" process, in the sense that it causes extensive periductal fibroblastic activity and stroma cell infiltration round the distended ducts, and may even be attended by "acute pain and signs of inflammation." [41] The later histological picture varies with the stage at which the process is examined. Early, it may show a belt of active, very vascular granulation tissue, with giant cells surrounding a duct denuded of epithelium (Figs. 41, 42 and 45, Plate VI.); at a later stage, there is a

PLATE VI

FIG. 40.—Mammary tissue showing normal lactating lobules, 4 days post-partum. All the lobules in this tissue were very defined and separated by much supporting stroma (*cf.* Fig. 11, Plate I).

FIG. 41.—Mammary tissue, with atrophic cyst surrounded by granulation tissue, with giant cells.

FIG. 42.—An area of the cyst wall shown in Fig. 41, with stroma cell and capillary activity and giant cell formation.

FIGS. 43-45.—Infected areas in mammary tissue, showing defined edge of the areas (x) and giant cells (g) bordering an abscess cavity (c).

Benign Tumour in Lactation

FIG. 46.—Mammary adenoma, removed during lactation, a defined rounded tumour easily enucleated.

FIG. 47.—High power view of the adenoma seen in Fig. 46, showing secretory activity, as in normal mammary tissue.

FIG. 40

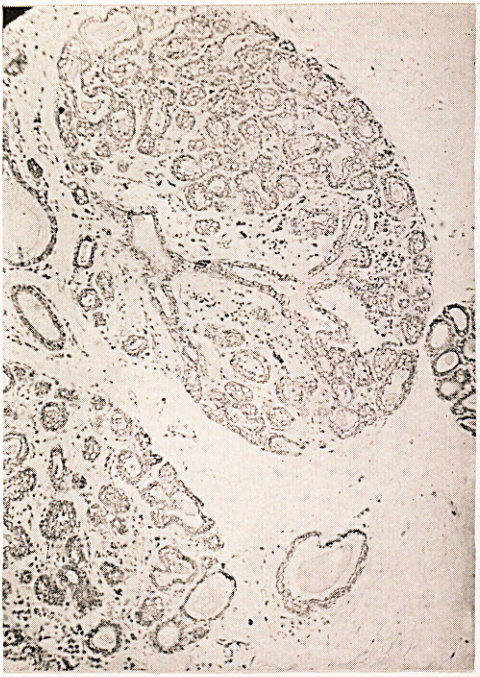
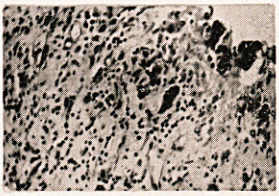
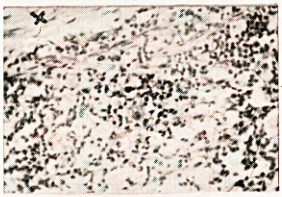


FIG. 41

FIG. 42



FIGS. 43 and 44



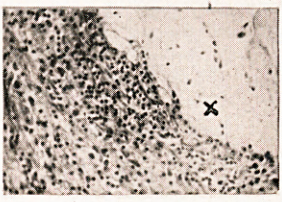


FIG. 45

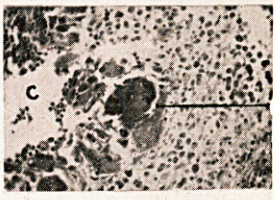


FIG. 46

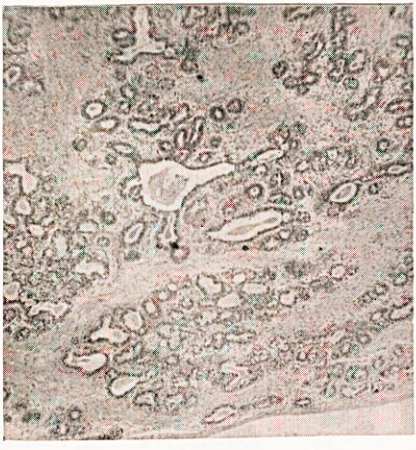
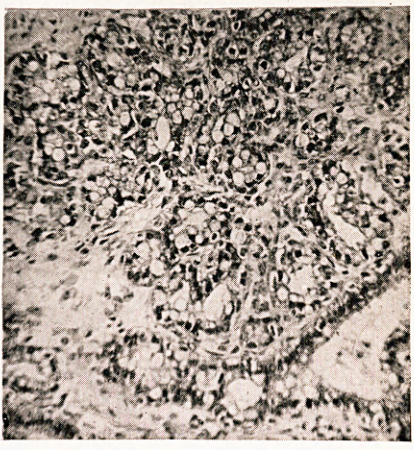


FIG. 47



dense fibrous band with hyaline degeneration, tending to form convolutions as it contracts and pulls on surrounding tissues. This picture, frequently called a chronic abscess cavity, is microscopically similar to, if not identical with, that seen in the late stages of a definitely infective condition associated with lactation, which earlier was an acute mastitis or a "sub-acute retention mastitis." The same picture is, however, also seen in both nulliparous and multiparous breasts about the time of the menopause, and in the absence of a detailed relevant clinical history, it is difficult to determine the origin of the thick-walled atrophic cyst in these cases. It may have been a milk cyst (galactocele) associated with lactation, or an acute or sub-acute infective condition which resolved without incision, or, in older women, it may be evidence of the late phase of menopausal epithelial proliferation in ducts with fatty degeneration, phagocytic cell activity and fibrosis. An understanding of the benign character of these histological appearances is essential, because of the frequent difficulty of clinical diagnosis. In a considerable number of cases in my material, where the clinical history gave no indication of an earlier infection, a quiescent thick-walled cyst had given rise to a hard, more or less circumscribed tumour, with fixation in the breast tissue and nipple retraction, for which a radical operation had been performed. Figs. 43 and 44, at *x*, show how defined the infective area may be, in the acute stage. The frequency of error in both clinical and histological diagnosis in these cases makes one chary of accepting as "cured carcinoma" any mammary tumour arising in association with reproductive activity, unless adequate data and illustration are submitted. Such pictures as Fig. 38 are not infrequently published as "pre-cancerous."

(d) *Subsequent Pregnancies.*—As normal post-lactation involution implies the more or less complete degeneration and removal of the new secreting tissue formed during pregnancy, a subsequent pregnancy involves a repetition of glandular proliferation and differentiation for a new lactation. Some observers consider that less fat is re-formed after lactation, the breast therefore becoming increasingly pendulous with successive pregnancies; others describe, in multiparæ, an increase of fatty tissue in and around the *corpus mammæ*. In older multiparous subjects, the addition of fat in the mammary area may be a menopausal change, that is, part of

a systemic rather than a local and post-lactation deposition. An increase of the normal elastic tissue round the larger ducts with successive pregnancies has also been described. My material provides little comparative evidence on this point. With appropriate staining, the elastica round the larger and smaller ducts is well shown in my sections of lactating tissue (Fig. 70), while few scattered elastic fibres are seen in the lobule itself.

[*To be continued.*]