

SWEAT GLAND CARCINOMA
OF THE BREAST
A MORPHO-HISTOLOGICAL STUDY
BY E.K. DAWSON



SWEAT GLAND CARCINOMA OF THE BREAST. A MORPHO-HISTOLOGICAL STUDY.

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- I. The Origin of "Sweat Gland Tissue" in the Breast: *A.* Sweat Gland Origin, *B.* Mammary Origin. II. The Significance of "Sweat Gland Tissue" in the Breast: *A.* The Possibility of Malignant Development, or *B.* Its Essentially Degenerative Character. III. Analysis of Material. IV. Findings and Discussion. V. Summary. VI. Conclusions.

Foreword.

DURING his last years in this laboratory, Dr James W. Dawson had built up a valuable collection of mammary material, with the intention of making an extensive study of pathological conditions in the breast. This material consists of over 1200 large breast sections, in addition to numerous small ones, from more than 600 cases of tumour and other conditions, as well as from normal tissue. Some time after his death, the study of this material was undertaken by me, with the assistance of a grant from the British Empire Cancer Campaign, and at the suggestion of, and in collaboration with, Professor Lorrain Smith. The initial problem we set ourselves was an attempt to correlate the incidence of malignant development in the breast with the various phases of growth and atrophy in the organ, and this involved a preliminary study of normal tissue at greater length than is usual in a pathological investigation. A detailed study of the actual malignant process was to follow. The death of Professor Lorrain Smith early last year left incomplete the analysis of both the biological aspect, in which he was particularly interested, and the problems more definitely associated with carcinoma, for the study of which the material was collected.

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The short general notes he left on the wide issues raised by a consideration of normal mammary growth I hope to expand later into a more detailed treatment of the subject. I am alone responsible for the following short paper.

The work is being done in the laboratory of the Royal College of Physicians, and I wish to express my gratitude for the courtesy and many facilities accorded me by the curator, Sir Robert Philip, and for the sympathetic interest and criticism of the Superintendent, Colonel M'Kendrick. I am specially indebted to Colonel Harvey, of the Histological Department, for many helpful suggestions, for much assistance with the literature, and for the invaluable opportunity of studying the extensive routine reporting material of his department. I wish also to pay a tribute to his assistant, Mr T. D. Hamilton, to whose skill is due the preparation of the very beautiful material which is now at my disposal.

I am greatly indebted to the Carnegie Trust for the Universities for their generous help towards defraying the cost of reproducing the plates in this work. The value of a histological study of this character is of necessity largely dependent on adequate illustration.

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One of the most obvious and striking histological features to be seen in sections of cystic breast material is the glandular tissue lined by large eosinophile cells. These glandular structures, when small, are usually arranged in groups, but they may be large and solitary; they are scattered irregularly through the breast substance and stand out in marked contrast to ordinary tissue. Figs. 1 and 2 show their appearance under low and high power magnification; Fig. 3 indicates their erratic distribution, the eosinophile structures being outlined. Borst¹ seems to have been the first to draw attention to them; von Saar² first used the term "pale epithelium," the term by which this cell-type is generally referred to in the German literature. It is perhaps more usually known elsewhere as epithelium of sweat gland type; French writers like Delbet³ call it idrosadenoid epithelium. In the following pages, I shall refer to these cells, for brevity, as *pale cells* and the glandular tissue they form as *pale structures*, without further qualification.

These cells and the structures they form will be described

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and illustrated in greater detail later in this study. The following general description will identify them at this stage. The cells are always larger than those of ordinary mammary epithelium, and may be very considerably so; the cytoplasm under low power magnification looks clearer, and the eosinophile staining gives it a paler appearance. The individual cells are usually well defined, unless marked degenerative appearances are present. An important and essential point to note is that in all cases this pale epithelium in the breast lines a definitely cystic structure, though the size of the cyst may vary within wide limits. Even the smallest pale structures are always larger than normal mammary acini.

It seems helpful, from the etiological aspect of mammary carcinoma, to study these structures more fully, since pale cells in the breast are mainly important in so far as they can be proved to be the starting point for malignant development or not. The origin and the significance of these structures have given rise to considerable diversity of opinion, and references to them in the literature are so numerous that only a few can be cited here.

I. The Origin of "Sweat Gland Tissue" (Pale Epithelium) in the Breast.

The main views with regard to the origin of glandular structures lined by pale epithelium are:—

- A. The structures represent actual or altered sweat gland tissue.
- B. They are derived from ordinary mammary tissue.

A. **Sweat Gland Origin.**—The view that these pale structures are derived from, or in some way associated with, sweat gland tissue arose apparently from their resemblance to the large sweat glands found in the axilla. These are more complex in structure than the simpler sweat glands met with in the skin generally, and by some writers are held to represent an intermediate position between these latter and true mammary tissue. The view is now generally accepted that the breast is genetically a modified sweat gland which has differentiated towards another function, though this would be a difficult matter to prove by histological examination of human foetal material. In the early months of foetal life, all the epidermal structures, sweat glands, sebaceous glands, hairs and the

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rudimentary mamma, appear in the epidermis as small solid masses or cords of epithelial cells; the mamma develops from such a solid mass of cells, and the ducts formed from its lower or inner surface show no resemblance to the neighbouring sweat gland structures in the skin, from the time when the two can be distinguished. Figs. 4 and 5 show ordinary sweat glands and the developing mammary ducts in the same eight months foetus and at the same magnification. These sweat glands do not appear as pale structures, and an examination of wide areas of skin in the anterior thoracic wall, in numerous whole breast sections, has failed to demonstrate the presence of pale epithelium in sweat glands, unless they show cystic enlargement, in which case they are not normal (Fig. 6). Even in the larger, more complex axillary sweat glands, the eosinophile character of the lining cells seems, from the limited material I have had opportunity to examine, definitely associated with a varying degree of cystic dilatation and epithelial degeneration.

Among those observers who support the sweat gland theory of origin of these pale structures in mammary tissue, several different views are held, not always sharply distinct; for example: (a) they are considered aberrant sweat glands, or accidental inclusions in the breast substance; (b) they indicate incomplete differentiation or metaplastic changes, or (c) they are evidence of the normal presence of sweat gland tissue in the breast.

(a) Their presence is considered to be due to a developmental anomaly, indicating accidental inclusion in the *corpus mammae*. This was, apparently, Creighton's view,⁴ but it is opposed by Delbet among others, on the ground that the structures are too constantly present, and by Nicholson,⁵ who mentions a case in which ducts and acini lined by these cells were to be seen everywhere in the breast. Fig. 3 indicates a similar widespread incidence. Nicholson remarks that in such cases the theory of developmental anomaly is reduced to an absurdity "unless we grant that practically every lobule of the whole breast contained a displaced sweat gland." Berka⁶ has also described sections of mammary tissue in which almost all the glandular structures showed this pale change in the epithelium.

(b) The pale structures are held to indicate either (1) a development of normal breast epithelium to sweat gland type, *i.e.* a metaplastic change to an embryologically earlier cell-type, or (2) a result of incomplete mammary differentiation.

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These two views, metaplasia and incomplete differentiation, seem combined in Krompecher's observations.⁷ He considers that metaplasia explains the formations lined with pale epithelium so frequently met with in mammary cystic disease, and the proliferative appearances they show imply "metaplastic regeneration." Prym⁸ and Dreyfuss⁹ support this view of metaplasia, but Krompecher speaks also of "an original anomaly of the breast tissue following developmental upset and indicating a faulty state of differentiation." This leads to the formation of what he calls "the hydrocystic breast," which he considers "a malformation of the primitive foundation" (Grundlage). Von Saar,² who first used the term "pale epithelium," without committing himself to views regarding its origin, pointed out the analogy between these structures and sweat glands, and assumed that they indicated "a phylogenetic level at which the breast tissue had differentiated itself from sweat glands."

(c) Another view is that actual sweat glands are normally present in the breast and the pale structures indicate their presence. This seems to be Ewing's position,¹⁰ who apparently endorses the opinion of Dreyfuss, Krompecher and others that "sweat glands are distributed throughout the breast . . . their number is very variable . . . their secretion is apparently discharged into the interlobular mammary ducts." I have not yet found histological support for this view of "normal inclusion," or for the slightly different one held by Fraser, who observes¹¹ that in the suspensory ligaments are occasionally found "small deposits of epiblastic cells resembling sweat gland epithelium and arranged as a rudimentary acinar tissue, embryonic "rests" which have failed to establish continuity with the proper breast tissue." In an earlier paper on the breast,¹² Fraser mentions "nests of imperfectly developed mammary tissue," not from actual sweat glands, but "epithelium of a foetal or infantile type," which is nearer Krompecher's view of a faulty state of differentiation. With regard to the cells in the suspensory ligaments, in whole breast sections of a normal mammary gland from a child of eight, I find the developing ducts growing into the base of the ligaments and along them upwards through the adipose layer between breast and dermis, a finding amply confirmed by the presence in mature breasts of normal small ducts and acini in this position. This suggests that the presence of glandular tissue here is not

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necessarily evidence of lack of continuity with the breast proper, nor of origin from sweat glands.

In my material, no sweat glands have been found in the actual nipple area, a fact adequately explained by the embryological growth of the primitive mamma. This has been studied by Lustig¹³ among others, in great detail, in foetuses from 8 mm. onwards; she emphasises the finding that no other glands are to be observed early in the immediate neighbourhood of the primary breast area (Anlage); later, sebaceous glands develop in the nipple area, but no sweat glands or hairs. The early downgrowth and later development of sweat glands in the areola and surrounding skin does not, in any section I have examined, extend deeper than the subcutaneous tissue lying over the breast substance and separated from it by a varying depth of adipose tissue. Cheatle and Cutler,¹⁴ in their extensive experience with whole breast sections, confirm this finding. "Whenever we have found sweat glands resembling breast structures, they have always been in the subcutaneous tissue outside the breast and not in the gland itself." It is not easy to see how the possibility of such a combination of glandular elements, mammary and sweat gland, could be upheld or disproved by histological examination of mature tissue, but my sections of normal developing breast material from the embryonic stage (fourth month) onwards, have so far given no support to this view of the normal inclusion of sweat glands. Cheatle and Cutler "have never failed to trace a direct anatomical continuity between them (the pale structures) and the ducts of the breasts." This finding in itself would not negative their sweat gland character from Ewing's point of view, according to which these "sweat glands" discharge their secretion into the mammary ducts, but it raises another difficult problem of how and when such "anatomical continuity" of sweat gland acini and mammary duct was effected.

There seems indeed so much against the view that these pale structures are in any way associated with sweat gland tissue, either as accidental inclusions, as metaplastic changes or faulty differentiation, or as normal inclusions, that from the evidence so far available, I am of the opinion that all glandular tissue in the breast substance—the *corpus mammae*—whether showing these pale cells or not, is true mammary glandular tissue. Embryological assumptions based on morphological

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tissue resemblances admit of little proof either way; it seems a more cogent argument against this sweat gland theory that, so far, no indication of normal sweat gland tissue has been found at any age in the breast proper. The characteristic pale epithelium occurs only as a lining to cysts of various sizes. As already mentioned, even the smallest of such pale structures is considerably larger than the non-cystic acinus or duct of the normal mammary lobule, as is shown in Fig. 2, *a*, and usually, though not always, shows evidence of the epithelial proliferation which caused the distension. It is also considerably larger than the normal (*i.e.* non-cystic) sweat gland elements found in the skin. It is apparently only when true sweat glands show cystic enlargement, whether in the skin or in the axilla, that the characteristic eosinophile or pale epithelium is also in evidence. The impression is therefore strengthened that this epithelium, wherever found, is essentially a degenerating, pathological cell type, associated in some way with cyst formation. I return to this point later. Meanwhile, the arguments against the sweat gland origin of pale epithelial structures can be summed up in Nicholson's words,⁵ "I fail entirely to see the smallest grounds for the assumption that they must be caused by arrests of development, faulty states of differentiation or any other kind of congenital malformation." Ewing's opinion about normal inclusion has, in addition, been commented on.

B. Mammary Origin.—If we, therefore, feel justified in rejecting, on this available evidence, the sweat gland theory of origin of these pale structures, we must admit, as already indicated, that they are derived from ordinary mammary tissue. The evidence, both in the literature and from my examination of much breast material, in favour of such a view, seems to me adequate for adopting it. Its main support, in a positive direction, lies in the finding of transitional stages which show the change from ordinary mature mammary epithelium into the pale type. This has been observed by various writers.

Delbet³ notes "one sees often in the same cystic acinus cells with different development. Those in one part of the cyst maintain the normal cubical type of the mammary acinus, while others, in another part, have become idrosadenoid (*i.e.* pale or eosinophile). One type passes into another and one can observe the transition stages." Figs. 7 and 8 at *x* illustrate these. Delbet also mentions, in dendritic epitheliomata (more usually called papillomatous or papillary growths) the presence of vegetations

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covered with these pale cells, as indicating the diversity of cell forms to be met with in the same tumour; this is illustrated in Fig. 9. He is, however, not primarily interested in the origin of any atypical cells found in pathological growth; since these cell types are not found in the normal mamma, he considers it of little use or interest to attempt to identify the cells from which any subsequent malignant development may originate. This is, of course, an opinion with which no histologist can agree, but it does not weaken his argument that pale epithelium is derived from normal mammary cells and that the transition stages can be frequently observed.

Semb¹⁵ finds pale cells proliferating mainly in cystic ducts and has observed pale and normal epithelium in the same duct "merging directly into each other." He agrees with Delbet in finding cysts with papillomatous outgrowths in which the epithelial cells may be of the pale or the ordinary type; he would not agree with Cheatle and Cutler in their view that pale cysts arise essentially from acini. Semb considers that they originate from small and medium-sized ducts, the transition from normal to pale epithelium being usually found at the junction of the normal and cystic parts of the duct, but it may be shown in the cyst itself.

Cheatle and Cutler¹⁴ in describing "cystiphorous desquamative epithelial hyperplasia" and the desquamating acinar cells, consider that "the essential characteristic is their pallor . . . they are described by some authors as 'pale cells.'" Such cells, therefore, represent a desquamative change associated with epithelial overgrowth in previously normal acini; the pallor is, in their opinion, the essential early change. "In the next stage, these pallid cells increase in number to form two or three rows from which columns of cells may spring and project into the lumen." As the condition advances, such acini coalesce and a composite cyst is formed, resulting later in the formation of the large cysts seen in the breast, the "blue-domed cysts" of Bloodgood's description.¹⁶

Keynes,¹⁷ in describing the epithelial changes found in chronic mastitis, gives, as one type of change, "the swelling of cells without very much active proliferation," which may be patchy in distribution. "The cells tend to disintegrate . . . these changes may precede the formation of smooth-walled cysts." The illustration in his text of these swollen cells, forming the partial lining of a duct, is similar to Fig. 10 from

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my own material and shows a condition apparently identical with the pale epithelium under discussion.

Prym,⁸ who considers that pale epithelium develops, in part at least, from mature breast tissue, and indeed predominantly from acinar tissue, thinks the pale change can justifiably be called a metaplasia. He found these pale structures occasionally in otherwise normal breasts. As he thinks that they originate mainly from acini, he states that a necessary condition for the formation of pale epithelium is the existence of acini (Endstücke); a further probable condition, he adds, is that the patient is married and multiparous, which brings his position near to M'Farland's conception of "residual lactation acini." "The majority of these pale structures," Prym states, "first appear in the developed breast as a substitute for acini or alveoli," meaning thereby the secreting glandular tissue.

M'Farland¹⁸ also considers that pale epithelium is derived from normal mammary tissue, but takes up a different position from most of the observers already mentioned, in that he thinks these pale structures are residual (*i.e.* non-involuted) lactation acini. The disappearance of secreting acini after lactation has ceased is, he thinks, an uneven process. He is of the opinion that some acini may escape involution; they then show large cuboidal or cylindrical epithelial cells with the characteristic eosinophile staining. "They accumulate in groups at the periphery, looking like slightly distended ducts . . . later, these residual acini show other changes, of which dilatation is the most important. As they dilate, partition walls may be ruptured, so that a large cavity is formed . . . later, these structures may enlarge to form cysts of considerable size." The size of the cyst depends, he thinks, on the water-absorbing affinity of its contents. "This termination of involution, with the formation of residual lactation acini represented by pale glandular structures, occurs more or less in every lactated breast." A similar picture, met with in virgin breasts, though apparently rarely in M'Farland's experience, he explains by possible secretion during menstruation. I have been unable to find confirmation for these observations on "residual lactation acini." In my material, which includes numerous whole breast sections of cystic conditions at all stages of development in both nulliparous and multiparous subjects, these pale structures are found invariably associated with the formation of cysts, quite irrespective of whether the patient has lactated or not.

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If secretion were associated with menstruation and could account for the presence of pale epithelium, one would expect to find pale structures in at least the majority of normal mammæ, but this does not occur.

Berka,¹⁹ who calls the pale cells "anomalous epithelium," also considers that the pale structures originate from alveoli, and represent incomplete involution after pregnancy. He apparently found them in senile breast tissue only of those who had borne children.

II. The Significance of Pale Epithelium.

If we accept the view that pale epithelium arises from normal mammary tissue, we are faced with questions as to its nature and the bearing of its altered characters on the all-important question of possible malignant development. Here we find ourselves again on controversial ground.

Borst¹ considers that the formation of pale cells indicates "a malignant degeneration," basing this opinion on the marked increase in the size of the cells, and the variations in the shape and size of cell body and nucleus.

Krompecher⁷ considers the proliferative appearances, which may be very striking in the smaller cysts, indicate a "metaplastic regeneration," which can be interpreted as a "pre-cancerous change, since it frequently leads to cancer."

Cheatle and Cutler¹⁴ state, with regard to these pale structures, that they "agree entirely with those authors who regard these truly mammary appearances as being the frequent sites of carcinoma in the breast." "Small papillomata are often seen in the acini . . . they are indications of the passage of the cystiphorous process into the neoplastic stage." They make no mention of the pale papillomata described by Delbet, Semb and others, and to be seen in many of my own sections, since they observe, with regard to the desquamative process, that "when the neoplastic state has supervened, it gives rise to a progeny of cells which are viable, their nuclei are chromatic and their protoplasm stains normally" (*i.e.* is not pale). Figs. 7, 9 and 11 show, however, the persistence of pale epithelium in papillomata. If we follow the argument of Cheatle and Cutler to its logical conclusion, it seems permissible to infer that such papillary growths, which at the neoplastic stage show no pale cells, might have arisen from proliferative activity which failed

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at any stage to show pale cells, and, therefore, would throw no light on the end-result of pale proliferation. Nor need such papillary formations have arisen in acini, for these authors admit "we have never been able to observe a direct passage of invading cells of carcinoma from an acinus. We can only say that it may occur." Does this not suggest the possibility either that (a) the pale cells which originate in "cystiphorous desquamative epithelial hyperplasia" in the acini are essentially not neoplastic in character, or (b) the neoplastic stage of growth must arise in ducts and not in acini, and has no essential connection with the formation of pale epithelium in these latter structures? From my reading of Cheatele's work, it seems difficult to escape from one or other of these conclusions.

M'Farland¹⁸ makes the important point that the epithelial lining cells of pale cysts apparently cannot multiply, an obvious argument against the view that such cells can be the starting point of malignant growth. He thus implies, without expressly stating, that the pale cell is a degenerating cell, which atrophies *pari passu* with the progressive dilatation of the cyst. The end-product is, therefore, a completely atrophic cyst, that is, one denuded of epithelial lining cells, the blue-domed cyst of Bloodgood's description.

Paul²⁰ considers that "this very tall epithelium is apparently of slow growth and innocent nature . . . intra-cystic growth is frequently derived from this long-celled epithelium; it is seen in all stages, from the smallest vegetations to branching dendritic growths, but I have never observed any clear evidence that these long-celled vegetations pass over to a carcinomatous formation."

Von Saar²¹ mentions the fact that pale epithelium is frequently found in benign tumours, and occasionally in the breasts of children; "no direct transformation into carcinoma has ever been confirmed."

Theile²² considers pale cells not a specific kind of cell, but a form of degeneration, distinguished from normal cells by "a greater growth energy and secretory power, but a shorter life duration."

Prym⁸ seems uncertain what pale epithelial proliferation indicates. "Though the proliferative possibilities of pale epithelium cannot be denied, yet much can be said for the view that the formation and proliferation of these cells signify rather marked involution processes in the breast tissue." He

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implies, therefore, as M'Farland does, that the tendency of the pale cell is towards atrophy, if the pale change is not in itself a degenerative process.

Semb¹⁵ observes that "in areas where there is much proliferation of these pale cells, they greatly resemble cancer cells." He does not say that they become cancer cells; where they line an enlarging cyst, he expressly states that the cells become progressively atrophic, until, in the larger cysts, no epithelium is discernible. In chronic mastitis, or, as Semb prefers to call this condition, "fibroadenomatosis mammae," in the male subject, he found no definite cyst formation and no pale epithelium, a finding borne out by examination of the male breast material in my collection. He is, nevertheless, apparently uncertain as to the malignant possibilities of the pale cell. On the examination of a series of 100 cases of fibro-adenomata, he found pale epithelium lining cavities in 14 of these; "it appeared to line small ducts which showed connection with cavities lined with ordinary epithelium." Fig. 12 from my material shows a similar transition in a fibroadenoma. As is well known, fibroadenomata very rarely become cancerous, so rarely indeed that the existence of proved cases is denied altogether by some writers, and Semb therefore concludes that "pale epithelium is not indicative of a malignant change." But elsewhere in his study of the breast, an elaborate monograph which treats in detail much of the pathology of mammary tissue, he speaks of cancer in "fibroadenomatosis" (chronic mastitis) arising from "atypical proliferated pale epithelium." The accompanying illustration in his text, which is not in colour, is, however, suggestive rather of the fatty degenerative changes which produce, in part, the colostrum-like cells met with in many non-malignant conditions of the breast. These colostrum-like cells are frequently found outside the duct walls, and even if epithelial in origin, are in no way indicative of the invasive properties of malignant epithelium, as Cheatele has pointed out. But Semb goes further than this in his estimate of the malignant possibilities of the pale cell; he thinks that even in Paget's disease of the nipple, the proliferating cells in the ducts and on the nipple surface are pale epithelium. I have found no support for this position elsewhere in the literature, nor does my own series of cases of Paget's disease in any way confirm it.

Berka⁶ considers the relation between pale cells and their parent cells, the normal mammary epithelium, to be "some-

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thing intermediate between metaplasia and anaplasia." Their capacity for independent existence does not, however, go on to the usual anaplastic tumour growth, "in fact, tumour growth is somewhat lacking." He observes¹⁹ that "this type of cell resembles atypical elements in large-cell carcinoma without, however, showing malignant growth . . . one interprets them as transition stages to carcinoma, though they are not yet malignant, *even if capable of proliferation.*" (The italics are mine.) He mentions finding pale structures, as Prym does, in otherwise normal breasts, and the impression he leaves is that the proliferated appearances found in these structures may be, in some way, associated with the atrophy of mammary tissue (at and after the menopause) rather than with the likelihood of continued growth activity. The degenerated appearances in the pale cells, very marked in the larger cysts, form, in fact, a difficulty for all who support their neoplastic tendency. To escape this difficulty, Thiele²² speaks of "a degeneration *sui generis*," but Berka, stressing the obvious proliferative appearances, explains the degeneration by considering it an earlier phase than the proliferation, and concludes finally that the pale process must be classified as a special kind of tumour growth. The tendency to progressive activity is, in his opinion, indicated by recurrences in partially removed cystic breasts, and he goes so far as to state that "these changes include most cystic and tumour-forming pictures of the breast." He considers the stages of this deviation from normal tissue to be, consecutively (*a*) a few pale cysts in normal mammary tissue; (*b*) more proliferation in the pale cysts, at the expense of normal tissue; (*c*) more advanced tumour-like character of these cysts, with papillæ and solid outgrowths—the stage of cystadenoma—and (*d*) further proliferation into actual carcinoma. He admits, however, that it is very difficult to say when this last development occurs. The type of carcinoma is an adenocarcinoma with large cells and cysts, and later a scirrhus, when the large proliferating cells get into the dense stroma. In order to adapt themselves to conditions outside the duct, Berka thinks the large "anomalous" cells become smaller and cubical, which agrees with Cheatle's observation that the pale cells lose their essential characteristics when neoplasia supervenes, but not with Ewing's findings, which separate "sweat gland tumours" from other malignant mammary growths by the morphological appearances of the pale cells.

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Ewing's position in this matter is definite and important. As already mentioned, he considers that sweat glands are normally or "nearly constantly" found scattered through the breast, and his opinion with regard to their association with mammary malignancy is best illustrated by some quotations from the third edition of his text-book¹⁰ (1928): "A considerable proportion of mammary cancers arise in the sweat glands of the breast. In my material the proportion is about 25 per cent." "A malignant form of adenocarcinoma involves . . . islands of sweat glands in any part of the breast." "They contribute a large share of the adenocarcinomas." Sweat glands "give rise to tumours which may be difficult to distinguish from true duct carcinomas. The separation is especially difficult between different cases of comedo carcinoma, many of which arise from the sweat glands. The cells of the sweat gland tumours are large and the cytoplasm is opaque and strongly acidophile, while these features tend to persist in extensions and metastases." It is to be noted here that while Ewing considers that the acidophile character and large size of the pale cells persist after malignancy has supervened, Cheatle and Cutler observe, as already mentioned, that the characteristic staining property of the pale cell disappears when the neoplastic stage is manifested, and Berka, that the large, tall cell becomes smaller and cuboidal. Ewing comes nearer Creighton's view when he says "in small atrophic breasts at any age, glandular tissue being deficient, carcinoma usually takes the form of duct cancer of the comedo type, and often affects the sweat glands," for Creighton⁴ stressed the fact that the emergence of malignant growth about the menopausal period is associated with the disappearance of normal mammary tissue and the consequent appearance of pathological changes in the persisting sweat gland structures in the breast, which thus give rise to most of the mammary tumours originating at, or after, this period.

Ewing's observations on the possibility and the frequency of mammary carcinoma arising in sweat glands constitute a formidable argument. There are, nevertheless, a number of difficulties which it does not meet.

(a) Sweat gland carcinoma in the skin is only very occasionally encountered; in this laboratory, where the routine reporting material of the histological department reaches an average of over 3000 cases annually, only one case of sweat gland carcinoma was met with in four and a half years, and even this case was

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doubtful. It is difficult to understand, therefore, why the malignant possibilities of these structures should be so much enhanced when, as it is claimed, they form a more or less normal inclusion in the breast substance.

(b) Ewing notes that "very few cancerous breasts fail to show phases of chronic mastitis in the outlying portions of the parenchyma," and "it appears from the histological evidence that many cancers arising from chronic mastitis . . . are the natural result of steadily increasing overgrowth . . . which affects the normal and adult glandular epithelium." These two statements taken together imply that the great majority of mammary carcinomas arise subsequent to chronic mastitis which affects the normal mammary structures. Do the proliferative changes of chronic mastitis therefore affect also the sweat glands in the breast and to an extent to produce 25 per cent. of all malignant breast tumours?

(c) Ewing illustrates an adenoma of axillary sweat glands, "an occasional source of mammary carcinoma," but neither in his text-book nor elsewhere in the literature, if we omit the photograph in Semb's monograph already referred to, have I found an illustration which shows, with any conviction, that the pale cells are a source of malignant proliferation and subsequent invasion. Fully developed "sweat gland carcinomata" are illustrated, both in the ducts and infiltrating the breast tissues; the proof of their origin from pale epithelium in these cases is based on "the large size and opaque, acidophile character of the cells," which enables "the separation of the sweat gland tumours of the breast to be accomplished with considerable certainty on morphological grounds" (Ewing). But the examination of over 600 cases of malignant breast tumours, many of which show the pre-malignant, transitional and actually cancerous and invasive stages, has provided little, if any, evidence that the morphological character which a malignant cell will assume can be foretold by, or resembles its pre-malignant forerunner. One of the most striking histological features in mammary carcinoma is the great variety of cell-type which the malignant cell shows, and its usual marked deviation from its normal and even hyperplastic pre-malignant morphology. Berka, as already mentioned,¹⁹ finds that the pale cells resemble the cells of large cell carcinoma, without exhibiting malignant characteristics; Theile,²² von Saar,²¹ Kuru²³ and others point out that no intermediate steps between pale

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cells and carcinoma cells can be found. Deaver and M'Farland²⁴ note that pale cells are never found invading the breast tissue even when the surrounding basement membrane is difficult to define, and they lay stress on the point that actual transition from a pale cell to a malignant cell has not been observed. Nicholson⁵ says "mammary carcinomata of this type have been explained on the assumption that these (*i.e.* sweat) glands, being more prone to become blastomatous than normally situated tissues, are responsible for their formation . . . is it not far more probable that they (the pale structures) are, in most cases at all events, secondary to, and caused by, the atrophy and involution that are physiological at the period of life when chronic mastitis is most common? These are essentially senile changes."

The views regarding the nature and possibilities of pale epithelium may thus be summed up, roughly, into two main groups:—

- (a) The view that pale epithelium indicates a proliferative change, with a more or less definite possibility of later malignant development (*e.g.* Krompecher, Borst, Ewing, Cheatele and Cutler, Creighton and, possibly, Semb, Berka, etc.).
- (b) The view that pale epithelium indicates a proliferative change with later, and progressive, degeneration (*e.g.* von Saar, Theile, Nicholson, Deaver and M'Farland, Bloodgood and, possibly, Prym, Keynes, etc.).

III. Analysis of Material Examined.

The mammary sections examined in this study have included—in addition to normal breast material at all stages of development, maturity and involution:—

- (a) 120 cases of malignant tumour, selective only in the sense that those which did not definitely show the site of malignant origin were rejected. The detailed examination of cases—all cut in whole breast sections and at different planes of the mamma—was limited to 120, as this was considered an adequate number from which to draw conclusions regarding the possibility of malignant development from pale epithelium.

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- (b) 60 cases of benign tumour, the majority in whole breast sections.
- (c) 60 cases of pathological breast conditions, other than malignant and benign tumours; these were also in large sections and consisted, mainly, of the developmental stages of chronic mastitis with cyst formation, but also included pregnancy, lactation and post-lactation conditions.

In addition to this material in 700 whole breast sections, numerous small breast sections have been examined from my own material and from the routine reporting material of the laboratory. The sections are stained with hæmatoxylin and eosin, and with van Gieson's stain.

IV. Findings and Discussion.

My own findings in regard to the questions raised in this brief survey of some of the literature on pale epithelium have already been indicated, in part, in the preceding pages. They can now be set down more consecutively.

I have been, as yet, unable to find evidence in this material for any association of pale epithelium in the breast substance with sweat gland tissue. This does not, of course, touch on the question of the genetic relationship of sweat gland and mammary structures; the paths of development in the embryo may diverge so early that no conclusion can be drawn from the appearances of the tissues at a more differentiated stage. But the weight of evidence from this histological investigation, supported by my study of the literature, inclines me to the view that pale epithelium in the breast is not to be identified at any stage whatever with sweat gland tissue. Its occurrence in the mammary substance is far too frequent for any supposition of accidental inclusion as a developmental anomaly, for it is hardly an exaggeration to say that pale structures are to be expected in practically every pathological and cystic breast condition, whether malignant or not. They were found in 116 out of the 120 malignant breasts, and in every one of 48 non-malignant cystic conditions, examined in detail in large sections. Such frequency negatives any theory of developmental anomaly.

The progressive atrophy in the enlarging cyst, which I consider sets in after the appearance of the pale change, is

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against the view that the change implies a metaplasia or metaplastic regeneration. Metaplasia is not an atrophic change, but implies growth activity in a new direction, by the formation of cells which recall an earlier stage of development. It seems to me, that, in spite of the frequently obvious proliferative appearances in the pale structures, the onset of the pale change is post-proliferative and an evidence of a checked and receding epithelial activity.

The third position in the sweat gland theory, that of the normal or "almost constant" presence of true sweat gland structures in the *corpus mammae*, has also not been substantiated in my findings. When these pale structures are found in what is apparently normal tissue, at any age, they are evidence of cystic changes associated with epithelial proliferation and later degeneration and desquamation. None of my material from normal developing breasts shows the presence of pale structures apart from these rare cystic formations. These are, however, of frequent occurrence in older tissue, which has undergone the involution changes associated with glandular hyperplasia and subsequent atrophy, and here pale epithelium is found invariably in the various stages of cyst formation. I can note, therefore, in summary that, so far, I have found no ground for supporting any theory of the sweat gland origin of pale epithelium in the breast.

The presence of what is interpreted as pale epithelium in other organs and tissues of the body is additional evidence against its association in any way with actual sweat gland structures in the breast, and, if the interpretation is admitted, it forms a conclusive argument against any essential connection of pale epithelium with sweat gland tissue. Pale glandular structures have been observed in the uterus, the ovary, the prostate and the kidney, all of which are sites associated with possible cyst formation. The finding of pale epithelium in these organs is interpreted as confirmation of the non-specific character of the pale change. This matter cannot be dwelt on further here, except to mention that attention has been drawn to the similarity of proliferative and degenerative changes with cyst formation met with in the breast and prostate by Theile,²² by Cheatele and Wale,²⁵ by Walker²⁶ and others. The pale change as I have seen it in uterus and prostate is illustrated in Figs. 13 and 14.

Though no support has been found in my material for any

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version of the sweat gland theory of origin for this cell type, I find very definite evidence to confirm the view that pale structures are derived from normal mammary tissue. That they can originate from duct or from acinus seems proved from the material examined, some of which is illustrated here. I am unable to draw as sharp a dividing line as Cheatle does between the "cystiphorous desquamative epithelial hyperplasia" as it occurs in these two structures. Groups of pale structures in relation to a more or less normal duct indicate almost certainly an acinar origin, while in other cases the duct alone may be affected. It may be mentioned here that the term acinus is used in the ordinary acceptation of the word as indicating one of the "end-pieces" of which the resting lobule is composed. No view is expressed as to its secretory function or otherwise. A large solitary cyst, lined by very degenerate pale cells, may imply later development from such a group of pale acini by their progressive dilatation and the formation of a confluent cyst by rupture of their walls, but it does not necessarily rule out the possibility of primary pale degeneration in a duct, which I have observed as an early and partial change in fibroadenomata, as in Fig. 12, *b*, and in both smaller and larger ducts in the cystic mamma, as in Figs. 7 and 10. These drawings show, therefore, the origin of pale cells in both acini and ducts, but the actual site of origin is a question secondary in importance to the nature of the change and its consequences.

Wide variation in the size, shape and arrangement of pale cells can be seen in any cystic breast tissue; some of these are illustrated in detail in Fig. 15 and in other drawings in this paper. The essential characteristic in all these pictures is the eosinophile or pale cytoplasm. The pale change, in my opinion, supervenes on a more or less proliferative condition in the glandular structures, though Fig. 10 suggests that, in ducts at least, it may be a primary degeneration with little preceding epithelial activity. In the acini, this cell activity is usually very marked. The transition from normal to pale cells shows elongation and swelling of the cells, which produces a markedly larger, taller, paler epithelium than the ordinary mammary type (Figs. 2 and 15, *a* to *c*). Apart from rare, apparent mitoses (Fig. 15, *f* and *g*, at *x*), which will be referred to later, I have seen little if any evidence of pale cells themselves increasing in number. If examined before obvious degenerative changes have set in, they appear intact and active

looking, with clear homogeneous cytoplasm, defined cell-outline and well-stained nucleus (Fig. 15, *f*, at *y*), but in all cases where the cysts are enlarging, the swollen condition of the cell in the early stages, and later, the smaller, poorly-staining nucleus in a flattened cell, the increasingly granular appearance of the cytoplasm, the desquamation and disintegration of cells in the cyst lumen, all indicate progressive atrophy (Fig. 15, *h*, *i*. to *v*).

What is apparently an early transition stage from the normal acidophile to the degenerating eosinophile type of cell with small cyst formation, has only rarely been observed in my sections unaccompanied by more advanced dilatation, a finding which has a possible explanation in the fact that such an early phase has no clinical counterpart to make the breast condition suspect. This early stage may show only swelling of the inner lining cells, which retain their cylindrical shape and elongated nuclei (*e.g.* in Figs. 10 and 2, *c*, at *x*); much more frequently, however, when examined microscopically, the swelling of the cytoplasm and consequent hypertrophy of the cell has involved an apparent shrinking and rounding of the nucleus, even though the cell-body still retains its exaggerated columnar shape (Fig. 15, *b*, *c* and *d*). At this stage, only one cell layer is usually evident, and cellular débris, isolated nuclei and coagulum are to be seen lying in the enlarging cyst lumen. With progressive dilatation of the cyst and presumably increasing intra-cystic pressure, the lining cells are gradually flattened out, until, finally, no epithelium is discernible. This is the completely atrophic, permanently quiescent cyst, and it may reach very considerable dimensions.

The formation of pale epithelium in certain infective conditions of the breast strengthens the position that the pale change is essentially degenerative in character. An infective condition, whether acute, as seen in a lactation abscess, or more chronic, as in a tuberculous lesion, in general destroys the mammary glandular tissue; but where degenerating areas beyond the infective foci can be examined, pale epithelium may be observed, in association with giant cells, granulation tissue, etc. Some material examined also suggests that the presence of pale epithelium may indicate an infection, without any diagnostic histological evidence of this in the breast itself, as in material examined from a married patient of twenty years, with suspected tuberculosis, where the breast tissue showed no tubercles or other signs of the lesion, but numerous minute

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cysts, with the pale change evident in hypertrophic lobules and in small dilating ducts. Advanced fatty changes indicating degeneration in the duct epithelium were also to be seen. Deaver and M'Farland have also found pale epithelium in tuberculous conditions in the breast.

It seems justifiable to assume that all cases of pale cell formation in cysts have been preceded by some degree of epithelial proliferation. This is very obvious when the lining cells are heaped up in masses (Figs. 7, 8 and 15 at *d*), or form pale papillary processes (Figs. 9 and 11), or have almost filled the duct lumen with what is sometimes called a "laciform" type of cell increase (Fig. 16). All these forms of proliferation are frequently seen in the smaller cysts. As a cyst enlarges, with progressive desquamation and lysis of the pale cells, those remaining attached to the wall may form a continuous, fairly intact layer which gives little evidence of previous cellular overgrowth, but the size of the cyst itself implies an earlier hyperplasia as well as hypertrophy of its lining cells.

All observers seem agreed about the proliferative appearances associated with pale epithelium, and this has led to the conception of its progressive growth and possible malignancy, but many are convinced, as I am, that, in spite of this, a degenerative process is at work which ends in quiescence and the formation of atrophic cysts. I have, however, found as yet no support in the literature for the conception to which I have been led from my own observations, that the pale change supervenes on a proliferative state of the normal epithelium. As already noted, there is no evidence that the pale cells themselves multiply; the pale change appears to be a post-proliferative degeneration which inhibits an earlier cell activity, and leads, after progressive cell destruction and glandular dilatation, to quiescent, atrophic cyst formation. This position is the only one which seems to explain the histological appearances seen in my material and illustrated to some extent in these pages.

These forms of epithelial proliferation, which in this view are antecedent, not subsequent to the pale change, seem a definite indication of the remarkable extent of possible cellular increase in mammary structures which may yet be inhibited by the supervention of degenerative changes. This touches on the larger question of the extent of cellular overgrowth which may be considered a more or less normal process at various stages of

physiological breast activity and retrogression. This matter is not relevant for discussion here, as the histological changes to be found, for example, during menopausal involution of the breast, have been made the subject of a more extensive study in collaboration with Professor Lorrain Smith, but the general trend of these findings, as already published in recent reports of the British Empire Cancer Campaign, can be noted here. Examination of much tissue shows that involution of the breast is not a mere atrophy of glandular structure coincident with subsidence of ovarian function; mammary tissue shares the instability evident in the body generally during this period of endocrine upset, and presents not a uniform picture, but one which varies greatly in different breasts. In contrast with post-lactational involution, menopausal involution seems essentially, in its initial stages, a hyperplastic process, though this may not always be clinically evident. At all stages of activity in the mamma, there are both constructive and destructive processes at work in the ducts and lobules, a cellular increase followed by cellular atrophy. In involution, the initial cell increase should pass finally into atrophy of glandular structure and permanent quiescence. In the majority of cases this does happen; in the relatively few in which malignant tumours develop at this period, excessive cell increase, associated with continued and possibly incomplete cell destruction, seems to lead to loss of control of the proliferating cell. The borderline between normal and pathological epithelial activity, especially in the breast before and during menopausal involution, is difficult to define and has been the subject of much discussion in the literature, but my histological material provides undeniable proof that marked degrees of cell overgrowth in the breast can be checked, and produce finally quiescent pictures, when the degenerative change in the proliferated cells is of the pale type. Cheatle has pointed out that it is not possible to foretell the eventual outcome of epithelial hyperplasia in the breast, an opinion which has general confirmation in much clinical and histological evidence; my own observations suggest, however, that where pale changes can be observed in the proliferated epithelium, further activity has been checked at least in that area, quite apart from what may be happening in other parts of the breast. Clinical evidence supports this position in many cases reported in the literature, for example by Bloodgood,²⁷ who emphasises the benign

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character of "the blue-domed cyst," the end-stage of the dilating pale structure. It may also explain the finding of Berka and many others, that malignancy can develop later in breasts partially resected for a cystic condition, for progressive atrophy in pale cysts throws no light on the outcome of other types of epithelium proliferation, which do not, like pale epithelium, necessarily tend to atrophy and quiescence of the mammary tissue. Two cases recently seen from the routine reporting material in this laboratory may be mentioned here. A breast was removed because of a tumour in the nipple, which had been present for twenty years. Sections showed extensive pale degeneration of papillary growths in the large ducts, without any indication of a malignant change. In the other case, which raises many difficult questions, the patient aged 60, gave a history of thirty years sanguineous discharge from the nipple, with rapid growth of a breast tumour during the preceding few months. A small area of malignant infiltration was found, and some small periductal lymphatic channels were permeated with malignant cells. All stages in the evolution of the malignant cell from the hyperplastic duct cell could be observed. The non-malignant areas showed advanced atrophy of the mammary tissue, and both there and in the malignant field, proliferated and degenerated pale cysts were present, the cells of which were in no way associated with the development of the malignant growth.

I am unable to say anything with regard to the chemical nature of this degenerative change from the normal to the pale cell. Semb found that staining reactions for fat, mucin and glycogen were all negative; Keynes also found no indication of a fatty change. I have noticed as an almost invariable finding the absence of cell infiltrations in the stroma surrounding pale structures, in marked contrast to the cell accumulations near glandular tissue which shows fatty changes, as in colostrum cell formation.

The large size attained by atrophic pale cysts suggests that dilatation has been produced, not only by the growth and subsequent desquamation and lysis of proliferated cells, but, in addition, by the inflow of tissue fluids through a duct wall no longer lined by viable cells. Borst²⁸ lays stress on "transudation" as a cause of progressive dilatation in cysts, when the initial epithelial proliferation has become a desquamating, degenerating process. Dreyfuss⁹ notes that this increase in

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size cannot be ascribed to proper secretion, which implies the functional activity of living cells, since the cells lining an enlarging cyst are desquamating and dying. Though the early distension is no doubt the result of the proliferation, in my view, of normal cells which later become pale, as is seen in the smaller cysts, it is difficult to understand how progressive dilatation can be associated with progressive cell atrophy, unless we admit the possibility of some such extra-glandular fluid inflow as suggested here. I have found no evidence of stenosis associated with post-inflammatory fibrosis round these cysts or the associated ducts, a condition claimed by many observers to be the starting point of dilatation; in contrast to other forms of degenerative change in mammary epithelium, it is, as already mentioned, remarkable that the pale change is accompanied by little or no stroma cell activity or cell accumulations.

One or two other points noted in the literature with regard to the morphology of pale structures may be mentioned here.

The presence under the pale epithelium of what is interpreted by some observers as a muscle layer or "myo-epithelium" has been brought forward by them as a strong argument in favour of the origin of these pale structures from sweat glands, where such "muscle cells" are held to be more in evidence. Krompecher for example, illustrates in detail this muscle layer in what he calls sweat gland cysts of the breast, and lays stress on its appearance in both the proliferating and, as he claims, the malignant stages of pale cell activity.⁷ My own study of the detailed cytology of mammary tissue is incomplete and I am therefore unable to confirm or deny the muscle nature of this subepithelial layer by any specific test, but in material from older patients, similar elongated cells with spindle-shaped nuclei have been frequently observed round involuting, non-cystic mammary structures, and provisionally associated with the increased fibrous tissue content of the thickening basement membrane. Dreyfuss laid stress on the hypertrophy of the basement membrane as the initial step in cyst formation and apparently denied the presence of this special muscle layer. These fibres, whether entirely connective tissue, or in part muscle and elastic tissue, are, in older breasts, often observed at right angles to the duct wall, instead of in the ordinary parallel position. Cheatle enumerates the structures forming the wall of mammary glandular tissue as being, from

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the lumen outwards, epithelium, an unstriped muscle layer, the subepithelial connective tissue, and, round the ducts only, the elastica and another layer of unstriped muscle. If this morphology be accepted, the presence of muscle cells would not, in itself, therefore, imply any connection of pale structures in the breast with actual sweat gland tissue. Examination of my material suggests that pale degeneration in cysts in the breast and in actual sweat glands is associated with initial swelling of all the glandular wall constituents, the cell-body, the nucleus, the basement membrane and this possible "muscle layer," and it is only when a section passes tangentially through the cyst wall that these "muscle cells" are made so prominent. In Fig. 15 at *e* and *k*, the nuclei at *m* may indicate these cells. Careful search with the oil immersion lens has failed to demonstrate their presence in the majority of pale cystic formations; Krompecher himself admits that they are not always to be found.

Another similar accident of sectioning may explain the appearances called "mosaic" or "pavement epithelium" by several German writers. This epithelial arrangement is illustrated in Fig. 15 at *k*. As it shows always an eosinophile staining and is found only in association with the more usual types of pale epithelium in cysts, as Krompecher and Pryn note, it seems unnecessary to seek for a further explanation of its derivation.

The finding of occasional mitotic appearances in the pale cells raises no real difficulty in accepting the view of their retrogressive character. The anaphase stage has not been met with and the prophase stage may be indicative only of karyorrhesis, but, even if demonstrable, actual cell division may be explained by the fact that mitosis can occur in a dying cell, and is an "agonal mitosis." In speaking of the radiation treatment of skin cancers, Murdoch²⁰ describes "a wave of atypical mitoses," which seems to be an unavoidable sequel to the first stage of treatment in which the number of mitoses decreases. Continuing the treatment cannot shorten this phase of atypical mitosis; "it is followed by total or sub-total mitotic arrest." A later stage of treatment shows the appearance of "cellular monstrosities." These findings in degenerating and dying cells in the skin offer a possible explanation of the very rare mitoses and occasional "cellular monstrosities" to be seen in pale structures in the breast, and

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illustrated in Fig. 15, *f* and *g* at *x*, and *a* and *c*. They support the position that such appearances are compatible with the early stages of a process evident in the pale cells, which is essentially degenerative and destructive in its nature.

A difficult question is raised by a consideration of the erratic distribution of pale structures in the breast. Fig. 17 shows cyst formation in three stages, in the same breast area and at the same low-power magnification. In *c*, at *x*, some of the glandular structures show colostrum-like cells, which are, in part at least, probably indicative of a fatty epithelial degeneration; others, at *y*, show pale degeneration going on to small atrophic cyst formation. The earlier proliferative and transition stages of the latter type and the size of the pale structures in comparison with more or less normal mammary tissue, are well brought out in this area. It is difficult to understand why different parts of the same terminal glandular group show different types of degenerative change. The localisation and limitation of pathological change is a mystery in many organs; it seems a particularly difficult problem in the breast.

The argument against any malignant tendency on the part of the pale cells rests, therefore, on the following findings in my material:

(*a*) No intermediate stages between the pale and the malignant cell have been observed; (*b*) no malignant invasion, definitely associated with pale cell proliferation in a glandular structure, has been found; (*c*) even when the developed malignant cell is large and eosinophile and therefore might suggest origin from pale epithelium, its evolution through the hyperplastic stages of normal mammary cells has been observed in all cases where the breast tissue examined shows the origin of the malignant focus; it is a very frequent finding that the malignant cell is markedly different in morphology from its non-malignant ancestor; (*d*) pale epithelium in other organs and tissues has been found associated with degeneration and cyst formation, and not with progressive activity and eventual malignancy.

V. Summary.

(1) Pale epithelium in the breast, which some observers call "sweat gland tissue," is derived, apparently in all cases, from normal mammary glandular tissue and has no demonstrable connection with actual sweat gland structures.

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(2) Structures lined by pale epithelium are not found in normal, non-cystic breast tissue; where they do occur, they are cystic formations, to be attributed to some excessive antecedent epithelial proliferation, followed by degenerative changes.

(3) This epithelial proliferation with subsequent degeneration may be found in various conditions of mammary activity and at different ages, but is predominantly associated with glandular involution of the menopausal period, when cystic conditions of the breast are most in evidence.

(4) The pale change is regarded as post-proliferative, *i.e.* it indicates a degeneration which supervenes on the earlier epithelial activity of normal cells and checks it. The question, therefore, of the malignant possibilities of the pale cell does not need consideration, if this view can be accepted.

(5) This view of the essentially degenerative character of pale epithelium finds much clinical support in the long-maintained benign course of those cystic breast conditions which histologically show widespread pale changes.

(6) The material examined (700 large breast sections and numerous small ones) shows the presence of pale epithelium in practically every state of breast tissue associated with cyst formation, *e.g.* cystic mastitis, cystic benign tumours and malignant growths associated with cysts. Pale cysts may also occur in breasts otherwise apparently normal, where they indicate an earlier excessive epithelial cell activity which has passed into quiescence.

(7) Of the 120 cases of malignant tumour examined in detail in whole breast sections, 116 showed the presence of pale epithelium in addition to the malignant tissue, but in no single case was the origin of the carcinoma to be attributed to the progressive proliferation of the pale cell. No pale cells were found in the remaining four cases. Even when the malignant tissue, because of its large eosinophile cells, suggested a similarity to the pale cells, in every instance the transition to the malignant cell type could be traced from normal mammary epithelium lining a large or small duct, the non-malignant proliferative stage of which showed no indication of the pale change. No case of "acinar carcinoma" was observed in this series of malignant growths.

(8) The view that pale epithelium in the breast has no connection with actual sweat glands, nor has any malignant

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tendency, but is essentially a type of epithelial degeneration associated with cyst formation, is strengthened by the fact that it has been observed in other organs of the body, such as ovary, uterus, prostate and kidney, where glandular activity, followed by epithelial degeneration and cyst formation, is of frequent occurrence.

VI. Conclusions.

1. "Pale epithelium" in the breast is not sweat gland epithelium, but is derived from normal mammary tissue.

2. Evidence for the existence of sweat gland carcinoma of the breast has not been found.

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DESCRIPTION OF PLATES.

PLATE I.

- FIG. 1.—Glandular tissue with eosinophile epithelium (x), in contrast to other mammary structures (y).
FIG. 3.—Photograph of a section through a whole breast, actual size; the cysts lined by eosinophile epithelium are outlined.

PLATE II.

- FIG. 2.—(a) and (b) Groups of eosinophile glandular structures (x), showing contrast to other mammary tissue (y).
(c) Eosinophile structure under higher magnification.

PLATE III.

- FIG. 4.—Sweat glands in the skin, in an eight months' foetus.
FIG. 5.—Developing mammary tissue in an eight months' foetus, same tissue and same magnification as in Fig. 4.
FIG. 6.—Sweat glands in the skin, showing cystic formations with pale epithelium (x). Note the associated cystic duct (d) and (y) normal sweat glands and ducts.
(x') higher magnification of one of the pale structures.

PLATE IV.

- FIG. 7.—Mammary structures with proliferated epithelium, showing transition from normal to pale epithelium (x). Note also colostrum-like cells in the duct (y).
FIG. 8.—Transitions from ordinary to pale epithelium (x).
FIG. 9.—(a) A small papillomatous tumour in the nipple, actual size.
(b) The type of papillomatous outgrowths in this tumour, showing pale epithelial cells.

PLATE V.

- FIG. 10.—Partial pale change in a duct, affecting only one of its smaller branches.
FIG. 11.—One of a large group of pale structures, showing the eosinophile cells in papillary outgrowths.
FIG. 16.—Part of a group of acini, showing various stages of degeneration after a "laciform" type of proliferation.

PLATE VI.

- FIG. 12.—Pale epithelium in a fibroadenoma.
(a) The tumour, actual size.
(b) Transition from normal to pale epithelium in a duct.
(c) Small cyst in the centre of the tumour, lined with pale cells.
FIG. 13.—Endometrium with cystic glands lined with pale cells; in the centre, a normal gland.
FIG. 14.—Tissue from prostate, showing degenerative pale epithelium and cyst formation, with papillary outgrowths and desquamation.

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PLATE VII.

FIG. 15.—Types of pale epithelium under higher magnification.

- (a) Variation in the size of nuclei, and desquamation.
- (b) and (c) Exaggerated columnar type of cell.
- (d) Localised proliferation with pale change and desquamation.
- (e) Variation in the size of cell and nucleus; possible "muscle cell" nuclei (m).
- (f) Apparent mitosis in pale cell (x); regular columnar cell lining (y).
- (g) Mitosis in pale cell (x).
- (h) (i) to (v), progressive flattening and atrophy of cells lining a cyst.
- (k) "Mosaic epithelium," with "muscle cells" (m) suggesting tangential sectioning of a pale cyst.

PLATE VIII.

FIG. 17.—Cyst formation in three stages, in the same tissue and at the same low-power magnification.

- (a) Proliferation of ordinary (acidophile) mammary epithelium.
- (b) Early desquamation with small cyst formation.
- (c) Later stage of same, with terminal duct and lobules showing colostrum-cell formation (x) and transition to pale epithelium (y).

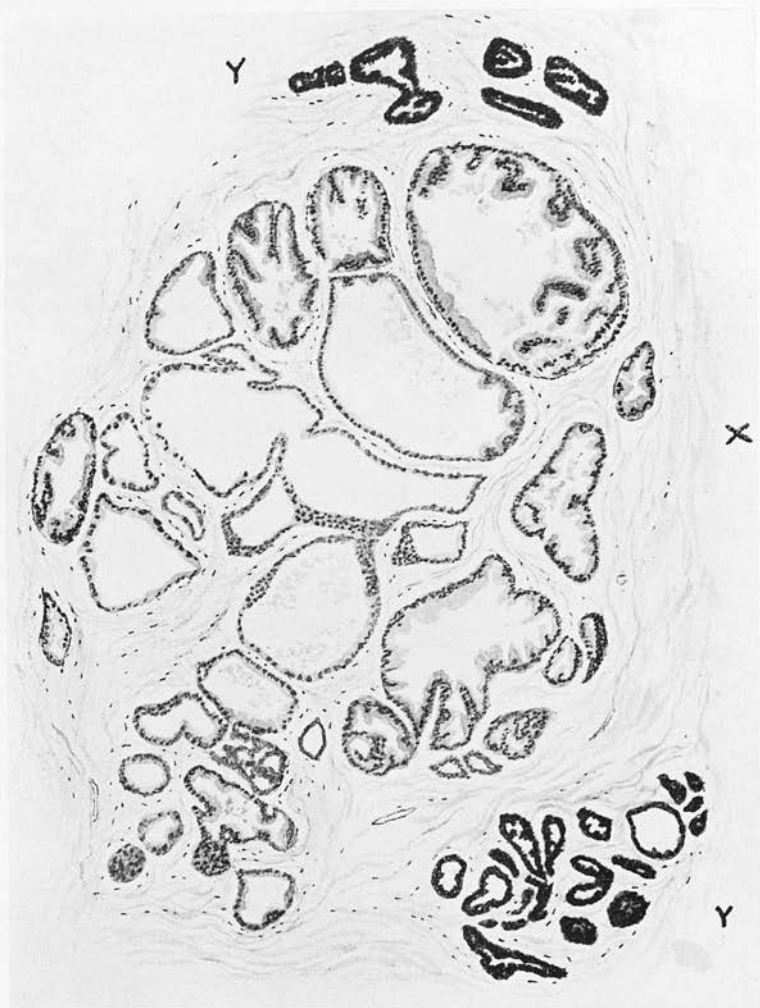


FIG. 1.

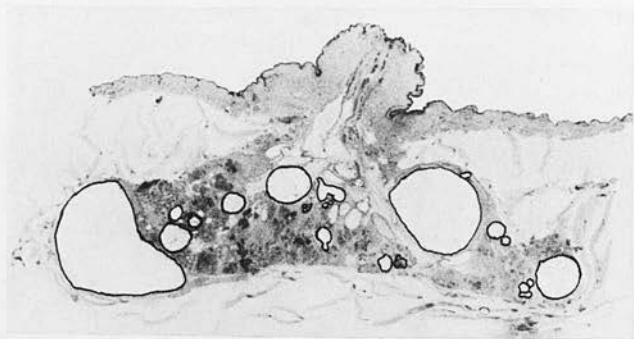


FIG. 3.

Glandular tissue in the breast, with eosinophile epithelium.

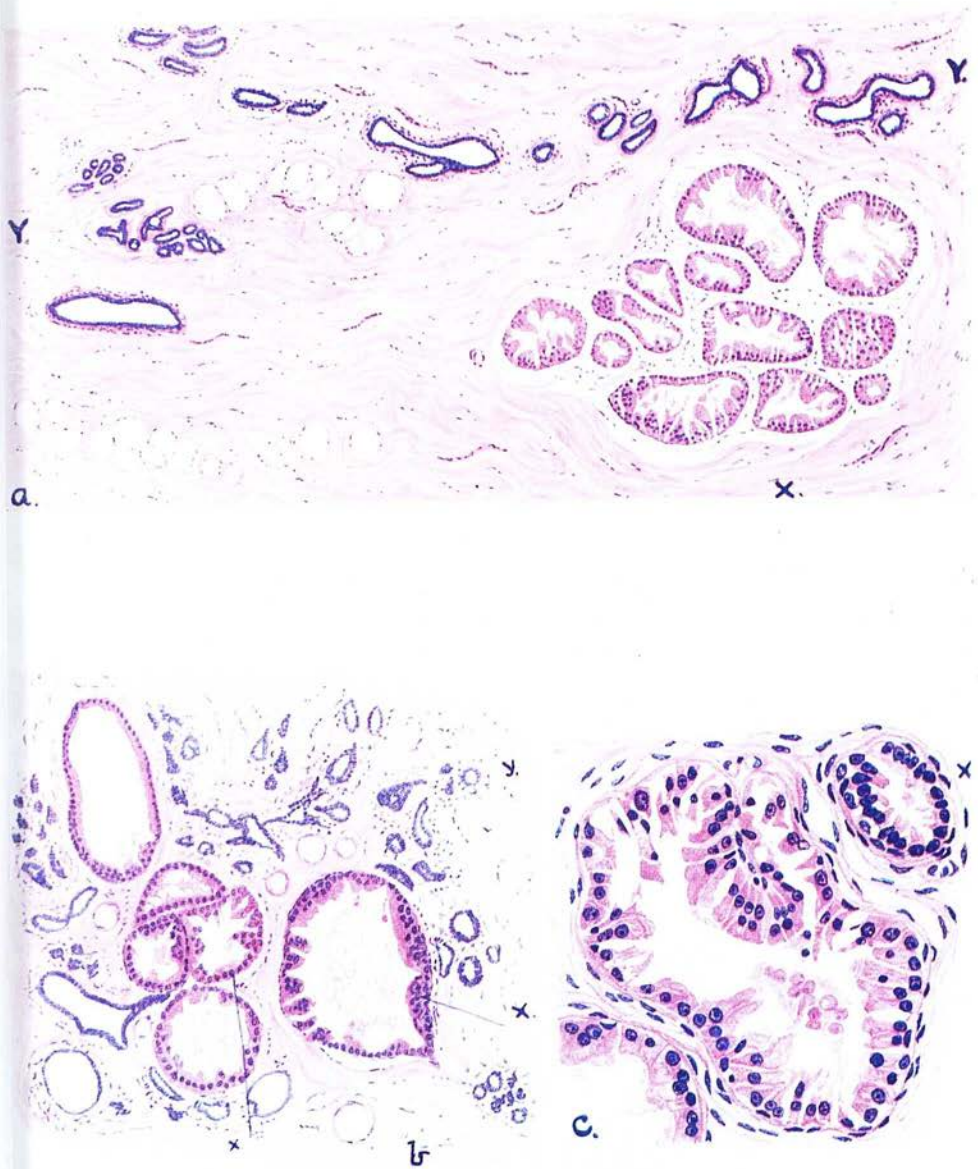


FIG. 2.—Glandular tissue in the breast, with eosinophile epithelium.

a and *b*, low power; *c*, high power.

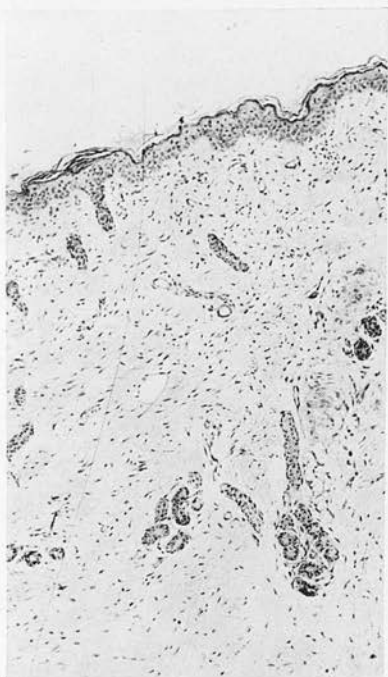


FIG. 4.—Sweat gland tissue in an 8-months' fetus.

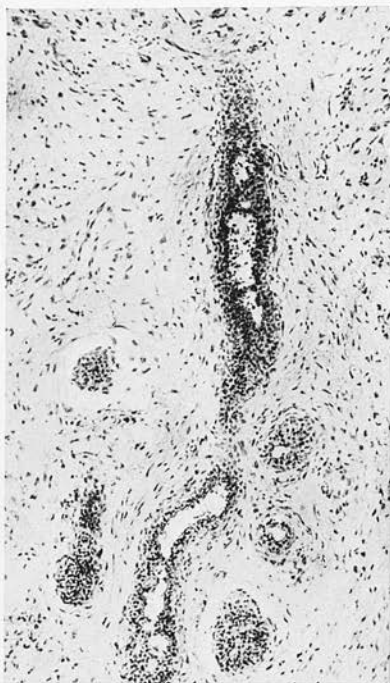


FIG. 5.—Developing mammary ducts in an 8-months' fetus.

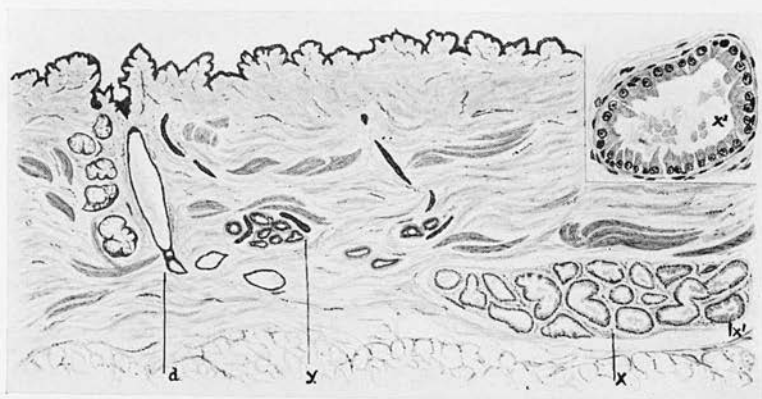


FIG. 6.—Cystic sweat glands in the skin, lined with pale epithelium.

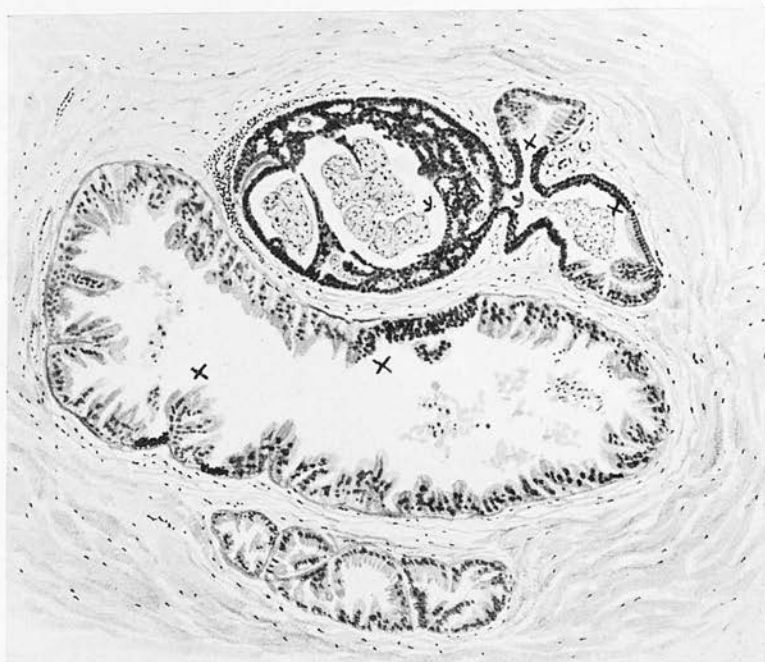


FIG. 7.—Transition from normal to pale epithelium in mammary tissue.



FIG. 8.—Transition to pale epithelium in mammary tissue.

FIG. 9.—Papillary growth in nipple with pale epithelium.



FIG. 10.—Partial pale change in a duct.

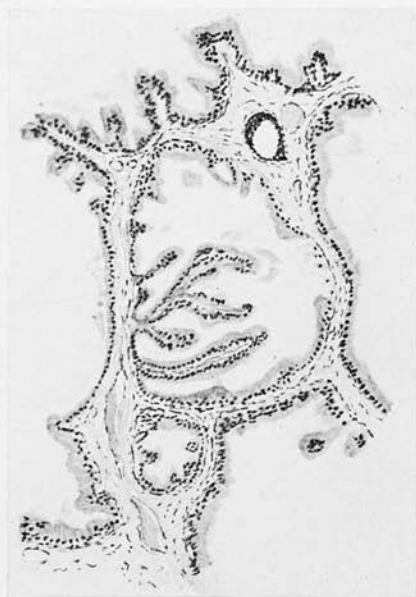


FIG. 11.—Papillary outgrowths with pale epithelium.

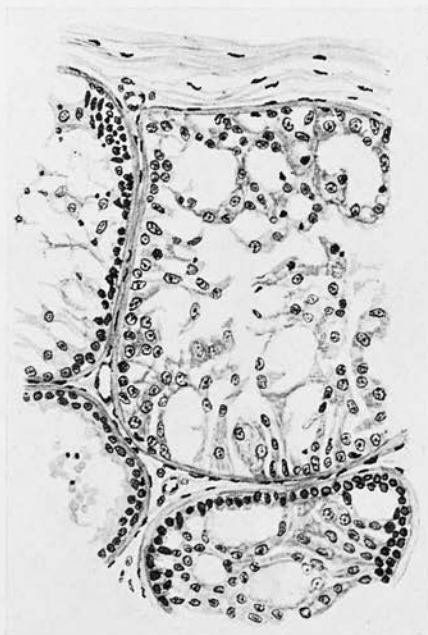


FIG. 16.—Pale cells in a "laciform" type of proliferation.

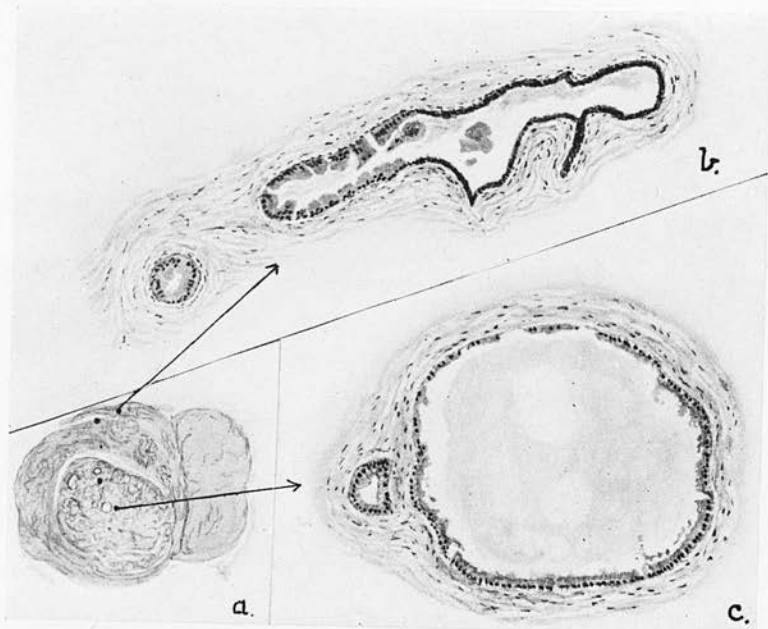


FIG. 12.—Fibroadenoma with pale epithelium.

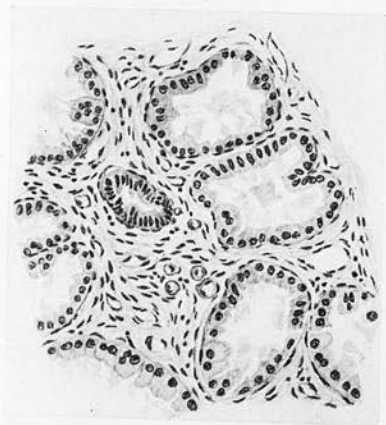


FIG. 13.—Tissue from endometrium, showing pale epithelium.

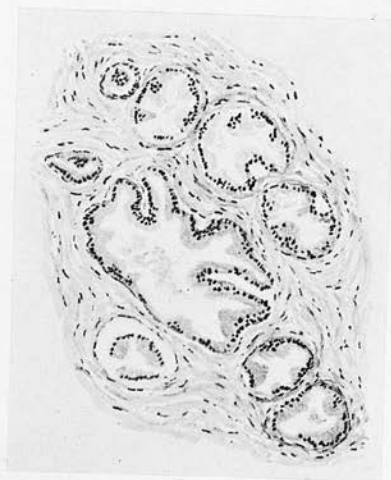


FIG. 14.—Tissue from prostate, with pale epithelium.

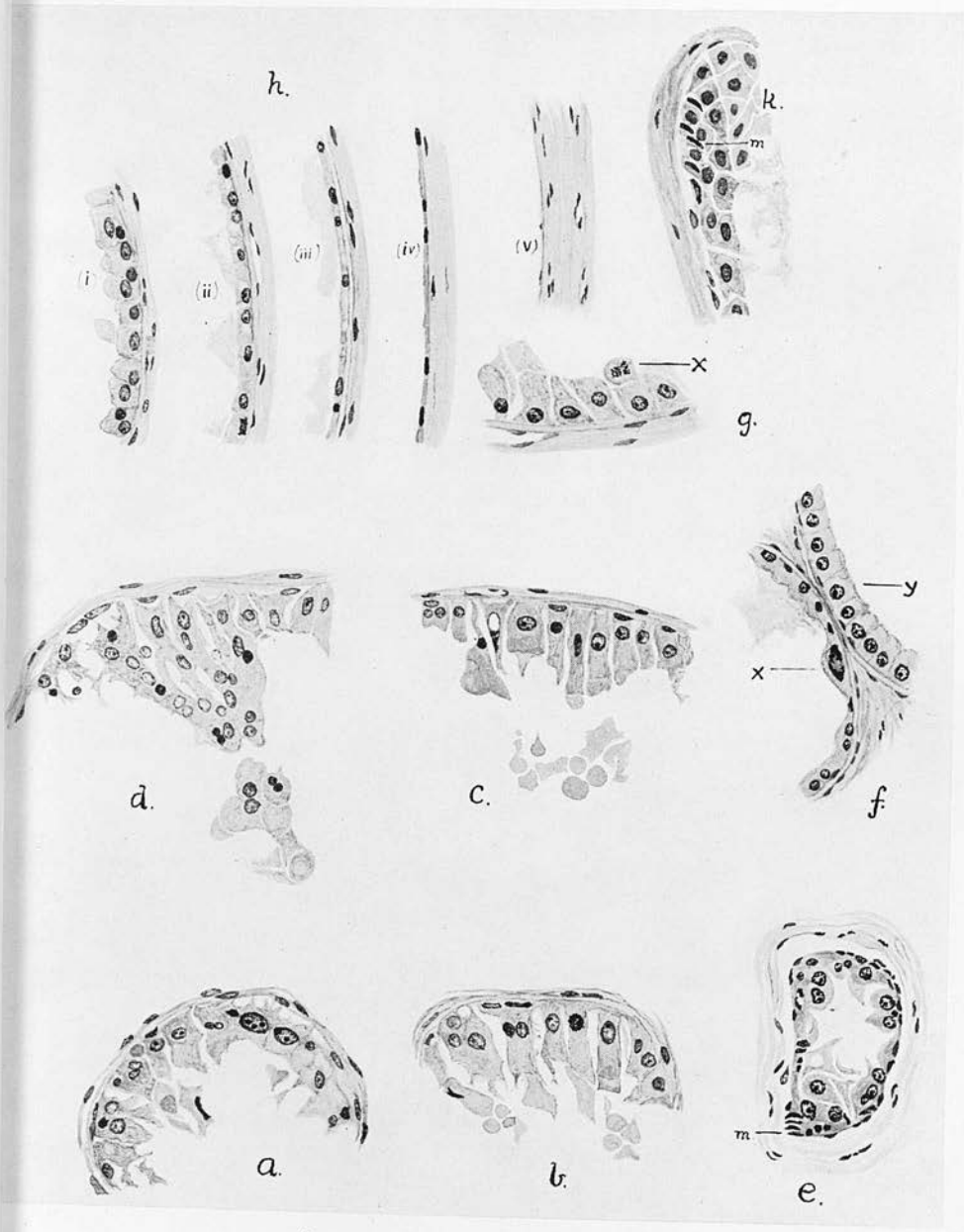


FIG. 15.—Types of pale epithelium.

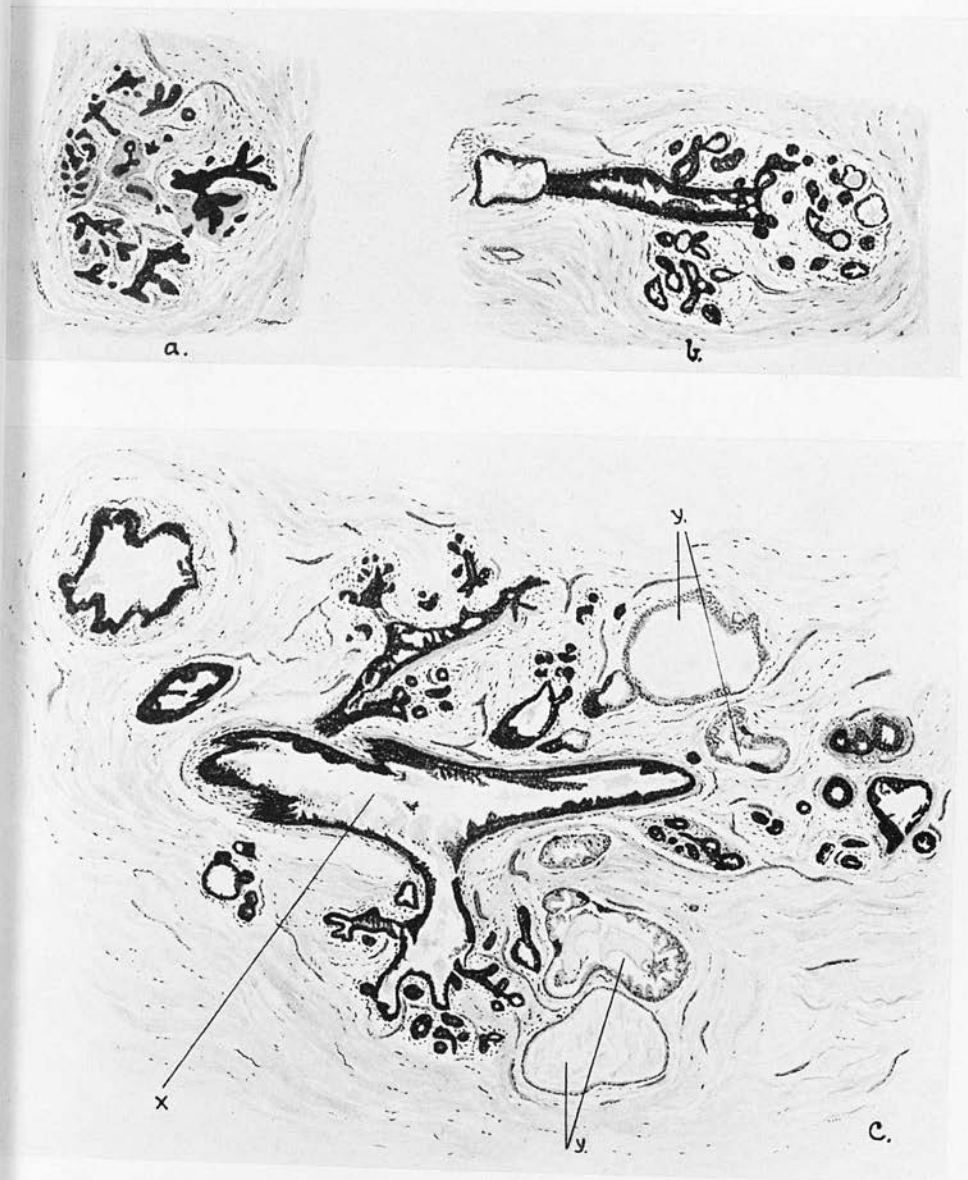


FIG. 17.—Cyst formation in three stages.

THE MENOPAUSAL AGE AND MAMMARY CARCINOMA

BY

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THE MENOPAUSAL AGE AND MAMMARY CARCINOMA

MUCH experimental work has been done in an attempt to define the relation of normal mammary growth and functional activity to the influence of ovarian and other growth factors. In the human subject, histological and clinical evidence show this interdependence at all stages of the mammary life-cycle, from the initial formation of the organ before birth, through the growth activity of puberty, pregnancy, and lactation, and at the period when atrophy of glandular structure is associated with the subsidence of the reproductive function. But when abnormal growth or tumour formation, and especially carcinoma of the breast, is in question, curiously little attempt has apparently been made to correlate such pathological activity in the mamma with disordered function of the growth stimuli which produce and maintain its normal condition. Most experimental work has been an effort to establish some connexion between tumour growth and more or less extraneous factors, such as inflammatory and irritative processes, stasis of secretory or other products, and like conditions.

It is, of course, obvious that much difficulty lies in the way of estimating such correlation in the human subject, but it seems possible that more progress might be made in elucidating and defining the factors which lead to the development of tumours in the breast, if these growths were regarded, not merely as surgical emergencies needing appropriate local treatment, but as manifestations of a wider derangement in the organism. If this were so, the pathologist and the statistician might be provided with data which would assist in histological interpretation, and which would go towards building up simple but important physiological generalisations on the interrelations of the commencement, continuance, and cessation of activity of glandular organs. It would be helpful in the attainment of this object to have on record the marriage state, the number of children, if any, whether they were nursed, any further details of the lactation history, and the length of time

which had elapsed since the last lactation. These latter questions have an obvious bearing on the possibility of retention of secretion in the glandular tissue, and the part this may play in the production of benign or malignant growths. Even more helpful would be information with regard to gynæcological function and, if the patient is older, the age of the menopause and any disturbance associated with it. The absence of information with regard to these last questions is almost general, and is the more surprising when it is remembered that all statistics of the age range of malignant development in the breast associate the emergence of mammary carcinoma, in the great majority of cases, with the menopausal or post-menopausal period.

AN INVESTIGATION OF AGE-INCIDENCE.

During a study of normal mammary histology, in association with the late Prof. Lorrain Smith, the idea of trying to connect more definitely the menopausal period with pathological growth in the mamma suggested an investigation into a number of histories which might provide some more exact information regarding the age range of the menopause in women. The collection of these statistical data had in view the determination of (1) the frequency distribution of the menopausal ages, and (2) the correspondence of this with the ages at which mammary cancer makes its appearance. In the latter case, the age-period is known to be more or less coincident with that of the menopause. There is, however, in the first place, insufficient knowledge of what the age at the menopause may be, and in the second place, it would be of some interest to show how far cancer in an organ such as the mamma, with its close hormonal connexion with ovarian and uterine activity, runs parallel in regard to age-incidence with that of the menopause.

The investigation was carried out on the surgical side of a women's hospital, where gynæcological data are taken as a routine part of the patient's history. The age of the menopause was therefore available in almost all cases where the period had been completed. The conditions for which patients had entered hospital included the usual wide range of surgical lesions, with a preponderance of gynæcological disorders. A series of 300 histories of patients past the menopause was studied, but 56 cases of

intermenstrual hæmorrhage and other uterine disturbances which made the time of the menopause uncertain have been excluded. This left 244 cases, a small number of the total available, but one considered sufficient for a preliminary statistical survey and for comparison with a series of malignant breast cases, which numbered 343.

The figures for the two series are as follows: those belonging to the first series of 244 cases, in which the year of the menopause was under examination, are entered in the second column (Mnp.); those of the series of 343 malignant breast cases, giving age at time of operation, are entered in the third column (Mlg.).

Age.	Mnp.	Mlg.	Age.	Mnp.	Mlg.	Age.	Mnp.	Mlg.	Age.	Mnp.	Mlg.
23	0	1	39	4	10	55	1	7	71	0	0
24	0	0	40	14	12	56	1	6	72	0	6
25	0	1	41	7	6	57	0	5	73	0	5
26	0	0	42	7	9	58	0	12	74	0	4
27	0	0	43	7	14	59	1	7	75	0	1
28	0	1	44	14	7	60	0	14	76	0	5
29	0	0	45	20	10	61	0	10	77	0	1
30	0	2	46	13	12	62	0	7	78	0	1
31	1	2	47	16	12	63	0	8	79	0	0
32	0	3	48	24	19	64	0	9	80	0	1
33	0	1	49	23	13	65	0	9	81	0	0
34	0	0	50	52	30	66	0	3	82	0	2
35	1	8	51	10	8	67	0	1	83	0	0
36	2	5	52	10	7	68	0	4	84	0	1
37	2	5	53	7	4	69	0	2	85	0	0
38	2	6	54	5	7	70	0	6	86	0	1

The graphs of these figures are here illustrated, the numbers being grouped in two-year periods; thus the age-period extending from the completion of the thirtieth year of age to the completion of the thirty-second year is called on the graph 31 years. However grouped—in two-year, three-year, or five-year periods—the maximum incidence, both of the completed menopause and of the emergence of malignancy in the breast, lies in the five-year period, 48 to 52 years inclusive, with the peaks close together and on the same ordinate. The wide range of the menopause—29 years—is to be noted.

WIDE RANGE OF THE MENOPAUSE.

Several facts emerge from a study of the histories which provided the menopausal figures.

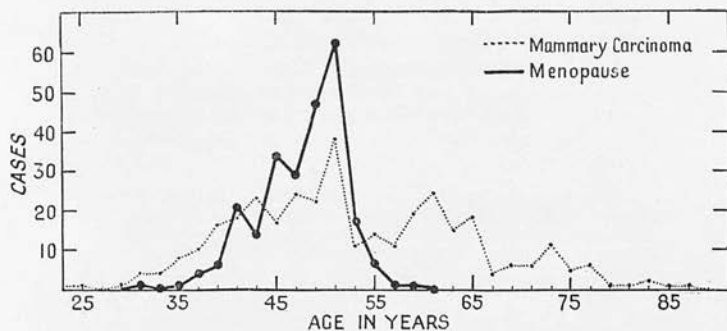
1. The usual period given for the completion of the menopause is between 40 and 50 years, with the maximum incidence between 45 and 48 years, but a

wider range of variation in the age—from 30 to 59 years—is brought out by these figures. This result suggests that, in the absence of detailed data, the conclusions to be drawn regarding the histological appearances in the breast, the relation of cancer to involution at the menopause and so on, should be strictly qualified. The actual age of a patient may be less accurate than the age of the menopause, as an index of mammary atrophy. It is frequently stated in the literature, for example, that cystic disease of the breast occurs, in the majority of cases, at too early an age to be associated with menopausal disturbance, but in the light of these figures such a statement has little validity unless menopausal data are also available.

2. The earliest age in the series at which the menopause was completed is 31 years. This patient, aged 56 came to hospital with intestinal carcinoma. She had two children, the younger aged 25. Since the birth of this child, when the patient was aged 31, she had never menstruated again. The birth was normal, and as she was otherwise quite well, she thought it unnecessary to seek advice. I have come across a number of references in the literature to the occurrence of the menopause before 35 years; Bloodgood¹ mentions a case, also at 31 years, in a nullipara, and associates such early atrophy with absence of pregnancy and lactation. The patient with the menopause at 59 years, the latest in the series under review, came into hospital for a prolapse of 12 years' duration. She had had ten children, and a miscarriage when she was 54 years old. An extraordinary case of prolongation of menstrual life, reported recently by Andrew,² may be mentioned here. One of his patients, an old lady of 80 years of age, "first started to menstruate at the age of 12. She is married, and has had eleven living children, three stillborn, and four miscarriages. Her last was born when she was 46 years of age. Since then she has been absolutely regular . . . up to about five years ago." The periods were still quite regular (at the age of 80) though diminishing in duration.

3. The menstrual irregularity which precedes the completion of the menopause in the series extends from a few months to five years; from one to three years is not unusual. This is not in accord with the observation frequently met with in the literature that the climacteric in women, in contrast with the

similar period in men, supervenes more or less rapidly. Walker,³ for example, states that "in the case of woman, the ovaries pass from full activity to complete cessation of function in the course of a few months; in man, the process of genital extinction may be spread over several years." The duration of this menstrual irregularity associated with subsidence of ovarian activity suggests that the process of involution in the breast may also, in certain cases, be uneven, variable, and protracted. This possible instability or "physiological unrest"⁴ may have a bearing on mammary pathology, especially when it is remembered that the majority of cases of carcinoma emerge at the same age-period as that



The age-incidence of mammary carcinoma and the menopause.

of the completed menopause. It would be interesting to have a frequency distribution of the duration of the menopause.

4. It is often stated that the menopause is earlier if lactation hypertrophy has not taken place; various generalisations are also made regarding the association of pathological growth in the breast with such conditions as the absence of pregnancy, the absence of lactation or its curtailment, and the rapidity of successive pregnancies; but it appears from the histories in this small series of 244 cases that such statements need more investigation before they can be accepted. So far, no obvious relation is revealed by these cases between (a) the number of pregnancies and the age of the menopause; (b) the absence of pregnancy and an early menopause; (c) the age of puberty and the age of the

menopause; and (d) the interval between the last pregnancy and the age of the menopause. The establishment or denial of any correlation between these data needs the examination of a larger series of cases, and these, it is hoped, will be available for a later investigation.

CONCLUSION.

In this short study I have endeavoured to make a simple survey of the duration of the menopause, and have set up in parallel the frequency distributions of the menopause and the age-incidence of cancer of the breast. I may be permitted to conclude from my figures that—

(1) The age-distribution of the menopause, as shown in this series of cases, has a longer range and frequency than is commonly allowed.

(2) The figures representing the age-distributions of the menopause and the incidence of cancer of the breast are not inconsistent with the hypothesis, suggested also by other considerations, that a correlation exists.

My acknowledgments are due to the British Empire Cancer Campaign, with whose assistance I am engaged on a general investigation on mammary carcinoma, and to the honorary surgical staff of the Bruntsfield Hospital for Women and Children, Edinburgh, for access to their case records.

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Carcinoma in the Mammary Lobule and its Origin

BY

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(From the Research Laboratory of the Royal College of Physicians, Edinburgh)



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Carcinoma in the Mammary Lobule and its Origin

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CARCINOMA IN THE MAMMARY LOBULE AND ITS ORIGIN.

By E. K. DAWSON

(From the Research Laboratory of the Royal College of Physicians, Edinburgh.)

- I. Introduction. II. Definition of Terms: Lobule, ductule, acinus; adenosis, epitheliosis. III. The Site of Malignant Cell Origin. IV. Acinar Carcinoma. V. Ductule Carcinoma. VI. Summary.

I. Introduction.—One of the difficult problems in a histological study of cancerous growth in the breast is an analysis of the advanced malignant picture. It appears to be still the case, unfortunately, that the majority of patients with breast lesions are first seen at a stage when malignant growth has extended considerably beyond the site of origin, and has, to a large extent, destroyed or obscured the normal mammary structure. This finding, as well as the varied picture which even normal breast tissue may present before malignant development occurs, may explain, to some extent, the difficulty of morphological analysis. It seems also to lie behind the present unsatisfactory classification of breast tumours and the numerous terms in use in mammary pathology, descriptive of so-called types of carcinoma in the breast. Almost every aspect of the study of malignant mammary growth requires some scheme of classification, and an effort to arrive at a satisfactory division of tumour types is therefore a matter of practical importance and not merely of academic interest. Prognosis and the grading of malignancy demand a knowledge of the type of growth in question, and the late results of treatment are comparable in relation to the nature of the primary growth as well as to the stage of extension. An estimate of the time factor in malignancy suggests, indeed, that these two considerations are closely related.

Ewing considers that any significant knowledge of the etiology, the prognosis, and the value of treatment of mammary

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tumours is dependent on a fuller knowledge of their anatomical structure and histogenesis. This statement amplifies the view of Borst, that the most helpful basis of tumour classification is a combination of histogenesis and the morphological picture presented at the time of examination. It suggests that analysis of the histological picture exhibited by malignant epithelial mammary tumour at any stage should be based more definitely on the normal structure of the breast and on the early stages of malignant cell proliferation.

This paper is a contribution to such analysis. It attempts to relate tumour in the breast to normal mammary structure by defining the early stages of neoplastic proliferation in the lobule. Though it deals with one group of breast tumours only, variously called acinar, acinous, or acinal carcinoma, it involves a definition of mammary structure as part of the treatment of the subject.

II. Definition of Terms.—One is met at the very outset by a number of questions which indicate how fundamental is the lack of definition in mammary pathology. Do the terms acinar, acinous, and acinal carcinoma, as found in the literature, describe the same histological appearance? If so, do they describe a malignant growth which arises from acini or one which morphologically resembles acini? When the malignant growth is observed in acini, is it possible to distinguish a primary from a secondary acinar carcinoma, in other words, is the growth one which has originated in, or spread to acini?

Attention to terminology is necessary before any of these questions can be discussed.

The epithelial tissue of the breast, if we exclude the overlying skin and the epidermoid lining of the main ducts at their junction with the skin, consists of ducts of varying size and the glandular structures of the lobules. There is considerable variation in the amount and morphology of this glandular tissue in different breasts, but an examination of normal material from the foetal stage to maturity suggests that the following is a usual type of structure. The dichotomy evident in the larger ducts is replaced deeper in the *corpus mammae* by a more complex division into smaller ducts, and when the terminal duct level is reached, the lobule is formed by the sprouting of tube-like processes grouped round its distal extremity (*cf.* diagrams *a* and *b* in the text). These tube-like structures forming a lobule are variously called acini, alveoli,

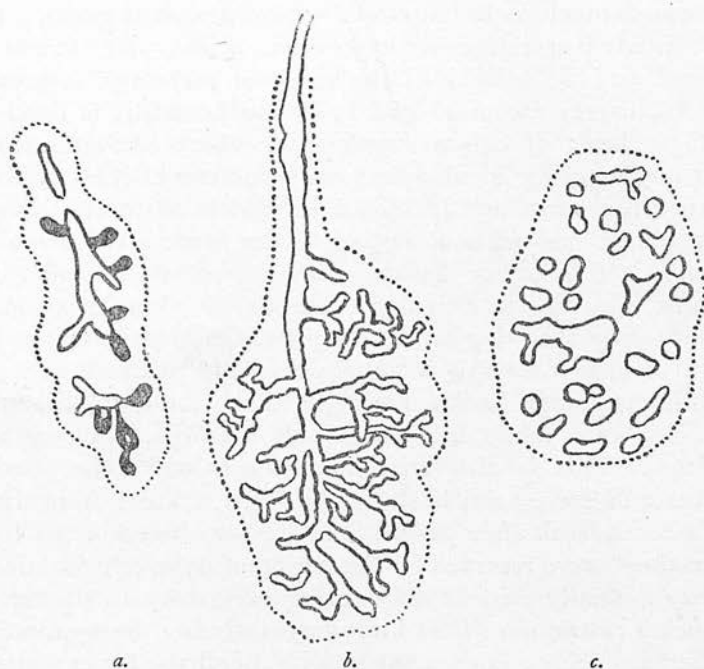
Carcinoma in the Mammary Lobule

tubes, tubules, or ductules in the literature. They form the "end-pieces" (Endstücke) of the glandular tissue in the quiescent (non-secreting) breast. During pregnancy, they increase greatly in number, and towards the end of the period, differentiate for the function of milk secretion. Actual secretion is not initiated, however, until after parturition; it continues normally during lactation, and when this ceases, the differentiated structures involute and disappear, leaving the original lobular framework much as in the virgin or non-pregnant gland. The differentiated secreting structures are acini. An acinus in general may be defined as the terminal secretory outgrowth of a tubular or racemose gland; in the breast, it is lined by a single layer of cubical epithelium, which distinguishes it from any large or small glandular structure of the quiescent organ. The term acinus should be restricted to this, but it is in general use without regard to the functional (secretory) activity it implies, or on the possible assumption that the mamma, like the intestinal mucosa or the thyroid gland, is a continually secreting tissue. My own observations have led me to believe that this assumption is not justified, and my material supports Loeb's findings¹ that secreting structures are, as a rule, found in women only during pregnancy and lactation. This is also Dieckmann's opinion.² The specific character of these acini is shown in Fig. 1, Plate I, from tissue at the tenth week after parturition. It were better if the term "secretion" were reserved for the period of definitely functional activity normally evident only during pregnancy and lactation, for such a restriction would limit very desirably the application of the term acinus, in contrast to its general use for any phase, at any age, of mammary activity. I am therefore unwilling to accept the term acinus for the "end-piece" of the lobule found at other phases of mammary life, though to reject it involves one in great difficulties, because of its accepted place in the literature. Alveolus is also unsatisfactory, since it is used indiscriminately either for a secreting structure or simply for a gland-like structure without reference to function. Tube, tubule, and ductule are all possible terms for the same structures, the end-pieces of the quiescent lobule and *ductule* is perhaps the preferable one. It is this term which I have adopted.

Diagrams built up from sections at different levels of the same lobule show that the ductules, as thus defined, arise as lateral sprouts from a considerable length of the terminal

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segment of the small (intralobular or terminal) ducts and these sprouts, in turn, form other short tube-like segments. By such lateral budding, lobules of varying size are gradually formed, a growth process which, in Dieckmann's opinion (*loc. cit.*), begins at puberty and continues until the "adult lobule" of the mature gland is produced. My own study of normal developing mammary tissue supports Dieckmann's findings, the material showing, as adolescence advances, larger and more



a. Developing lobule
in girl of 13.

DIAGRAM I.
b. "Adult" lobule in
woman of 52.
(Cf. Fig. 4, Plate II. at x.)

c. "Adult" lobule in
woman of 34.

complex lobular groupings. The ductules forming the lobules at this stage are lined by two-layer epithelium; the characteristic structure of the acinus, as already mentioned, is the single-layer lining.

This progressive growth of the mammary lobule is shown in diagrams *a* and *b*. Diagram *a* is from tissue of a girl of 13, and illustrates the early stages of ductule formation, with most of the lateral sprouts short and not yet canalised; diagram *b*, from the adult tissue seen in Fig. 4, Plate II., is built up from

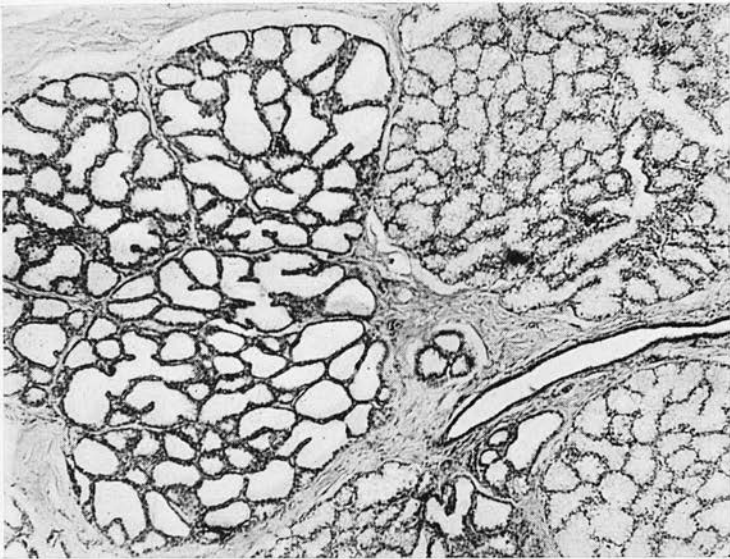


FIG. 1.—Acini at the tenth week of lactation. ($\times 30$.)

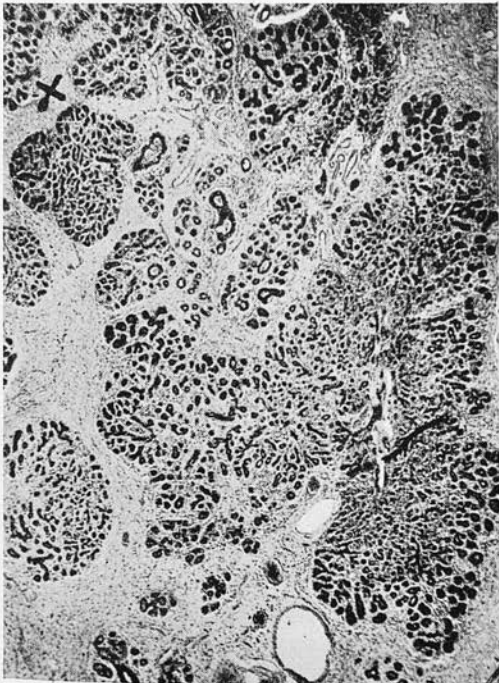


FIG. 2.—“Adenosis.” ($\times 40$.)



FIG. 3.—“Epitheliosis.” ($\times 40$.)

Carcinoma in the Mammary Lobule

a number of sections of the lobule *x*, in which the connections of the ductules with the terminal duct could be traced in almost every case. The actual microscopical appearance of a lobule depends on the plane of the section; in diagrams *a* and *b*, the sections have been parallel to, and in part coincident with the length of the duct, but it often happens that a section misses much of the duct and cuts most of the ductules at right angles, giving a picture such as that shown in diagram *c*. The ductules then appear as isolated, more or less rounded, epithelial structures in the loose lobular stroma. The limit of this loose connective tissue is indicated by a dotted line in the diagrams. The amount of terminal dilatation of the ductules varies considerably in the quiescent breast. Very little dilatation is evident in the lobules from which these three diagrams were drawn, and ductules are often best described in Dieckmann's phrase as "tubular end-pieces," which defines well their morphological and developmental aspects.

The examination of many lobules, at different levels of sectioning, in quiescent and active breasts, suggests that increase in the size of the lobule is produced always by the type of epithelial activity which shows the formation of lateral sprouts, as outlined above. Increase in the actual number of lobules seems to be produced by branching of the smaller ducts proximal to the terminal lobule; each branch then forms one or more lobules.

One hesitates before suggesting an addition to the already overburdened terminology of pathology, but there is apparently no term in use which exactly describes this growth process, by which the size and the number of lobules are increased in both physiological and pathological conditions. Adenomatosis has a connotation beyond that of increase of glandular tissue and implies the beginning of tumour formation; it is therefore inapplicable to the physiological states. Hyperplasia is ambiguous, since it includes another form of epithelial increase in the lobule; this second form shows proliferation of cells within the ductules, without necessary increase in the actual number of ductules. It is frequently difficult to interpret the exact meaning attached to "lobular hyperplasia" in the literature, since the two types of epithelial activity are covered by the term, but they appear to be different in kind and each to need a distinguishing term. They are illustrated in diagrams *d* and *f*, and in Figs. 2 and 3, Plate I.

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For the former type, Colonel Harvey suggests the term *adenosis*, on the analogy of melanosis, acanthosis, etc., and this word is both descriptive and accurate, indicating, as it does, an increase of glandular tissue without suggestion of tumour formation, and thus including in its scope both physiological increase, such as occurs during pregnancy, and pathological increase, evident at other periods and not obviously associated with normal proliferative stimuli. For the second type of epithelial activity, the increase of cells inside the glandular

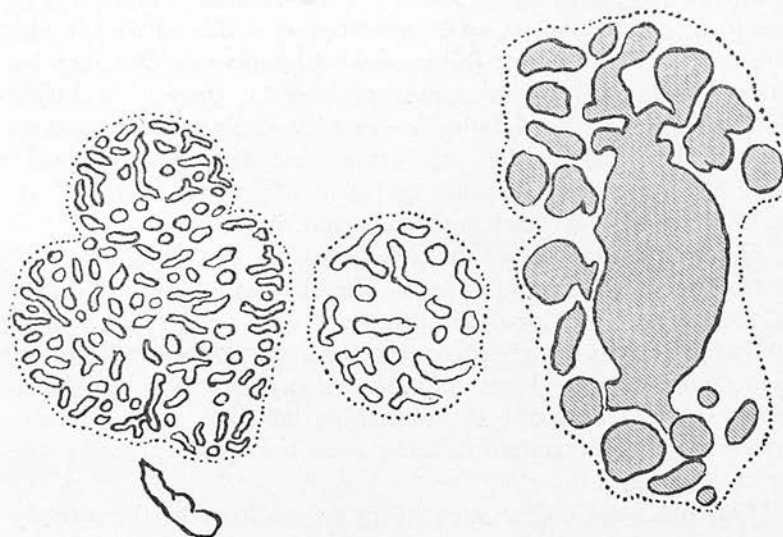


DIAGRAM 2.

d. "Adenosis."
(Cf. Fig. 2 at x.)

e. "Normal" lobule.

f. "Epitheliosis."
(Cf. Fig. 3.)

structures without necessary increase in the actual number of duct or lobular elements, the analogous term *epitheliosis* appears equally suitable. Epitheliosis is met with in a variety of forms, as an increase in the number of lining cell layers, or the formation of cellular buds or papillary outgrowths in the lumen.

That adenosis may develop into adenomatosis, a diffuse or localised tumour-like glandular overgrowth, is evident and of comparatively frequent occurrence in its pathological condition; a further stage is seen in the more or less circumscribed adenoma. As Adami said,³ "there is gradation of growth activity in glandular hyperplasia, adenomatosis and adenoma,

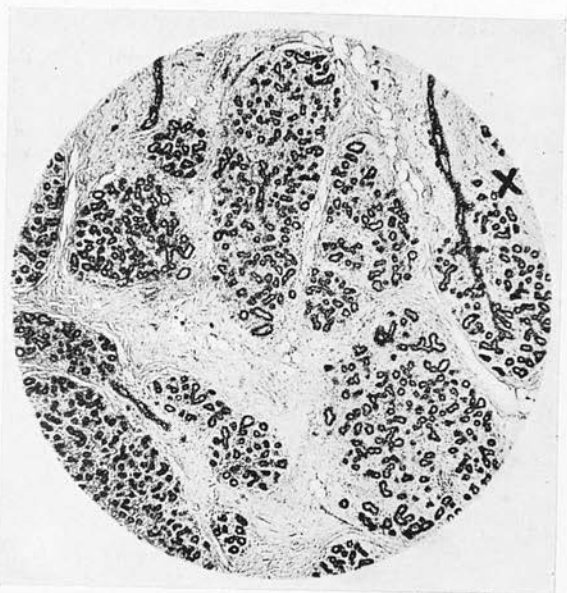


FIG. 4.—“Adenosis,” woman aged 52. ($\times 40$.)



FIG. 5.—Malignant lobule, cut parallel to long axis of terminal duct. ($\times 30$.)

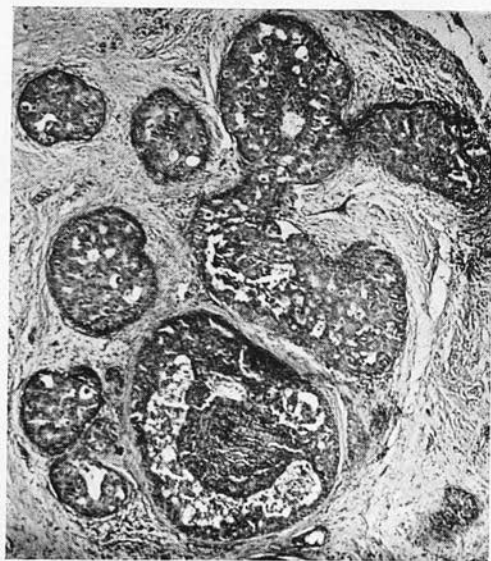


FIG. 6.—Malignant lobule, cut at right angle to terminal duct. ($\times 40$.)

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and the dividing lines are not easily placed." In the breast, stroma activity accompanies epithelial increase in almost all cases, so that fibro-adenomatosis (*cf.* Fig. 17) and fibro-adenoma become more accurately descriptive terms.

I have perhaps dwelt overlong on the type of proliferation observed in the expanding lobule and here termed adenosis, but it is important that it be constantly borne in mind in discussing the origin of malignant growth in the smaller glandular structures, owing to the confusion arising from the loose use of terms such as acinar, acinous or alveolar carcinoma for tumours which, in many cases, have apparently no connection with malignant epithelial proliferation within the lobule. When malignant growth arises in the small duct of the lobule, the ductules are, as in normal tissue, necessarily connected with each other and with the duct, in the early stages of neoplastic activity. This is shown in the malignant lobule of Fig. 5, Plate II., in which the section has cut the terminal duct parallel to its long axis (*cf.* diagram *b* in text). The apparent isolation of malignant ductules, as in Fig. 6, Plate II., which shows the structures cut at right angles (*cf.* diagram *c*) is obviously a matter of the plane of section. When actual loss of connection between duct and ductule does occur, it implies that malignant growth has reached a stage when the normal boundaries of the glandular tissue have been crossed and detached cancerous cells are invading the surrounding stroma, with the formation of acinus-like structures or rounded cell-groups. These are not, however, ductules, although they resemble them on section. They are what Cheatele calls "secondary deposits in the breast,"⁴ and if "the primary tumour," that is to say, the malignant growth in the duct and ductules, is no longer recognisable as such, their origin might have been from the glandular tissue at any level. It must not be assumed, however, that transgression of the normal boundaries necessarily results in the formation of completely isolated cell-groups in the surrounding stroma, though for earlier observers, such as Virchow, this appearance was the evidence and the criterion of actual malignancy. Hauser⁵ and Petersen⁶ showed, however, that the appearance of "actually detached alveoli" was due to an accident of sectioning which failed to demonstrate their connection with the structure or tissue of origin. Malignant spread outside normal boundaries is usually in the form of long branching cell-columns before detachment and independent

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proliferation is observed. Such detachment is naturally more likely to occur early when the malignant cells find their way into a moving stream like the lymph or blood.

Before discussing the site of malignant cell origin, it will be helpful at this point to repeat our definitions of mammary structures. A *ductule* is a tube-like outgrowth from a terminal duct, forming the "end-piece" of the glandular tissue in the quiescent (non-secreting) mamma. An *acinus* is the secreting element, lined by a single layer of epithelium, and normally present only during pregnancy and lactation. A *lobule* is a grouping of the terminal glandular structures of the breast and it may be quiescent or secreting. The quiescent form is composed of ductules, the secreting form of acini.

III. The Site of Malignant Cell Origin. If we exclude the squamous or transitional epithelium which lines the exits of the main ducts on the nipple, malignant epithelial growth in the breast must arise at some level between this exit and the lobule. Actually, carcinoma may arise at any level of this glandular tissue; it may be observed simultaneously in large and small ducts and in the lobules, and in such cases, only an examination of the very early stages of proliferation could have thrown light on the actual level of malignant cell origin.

The hyperplastic stages of epithelial activity before malignancy emerges are necessarily restricted to the inside of the duct or ductule, but the early stages of actual cancerous growth must also be looked for here. The invasion and transgression of the basement membrane is objective evidence of an acquired malignant character, but it would be difficult to maintain that only after egress does a cell become malignant. The cell is found outside the glandular structures because it is already malignant. The study of much malignant mammary material inclines me to believe that carcinoma of the breast is histologically recognisable, in the majority of cases, before actual invasion occurs. *The acquisition of the cancerous nature is associated with marked and definite changes in cell morphology*, and in most cases, little difference can be observed between the intra-duct and the extra-duct malignant cells, though the latter may show more exaggerated deviations from the non-malignant cell type, especially when they are found in the lymph or blood stream. The pre-cancerous condition is a non-cancerous condition. We do not need, in the majority of breast cases, the added fact of the transgression of normal boundaries to

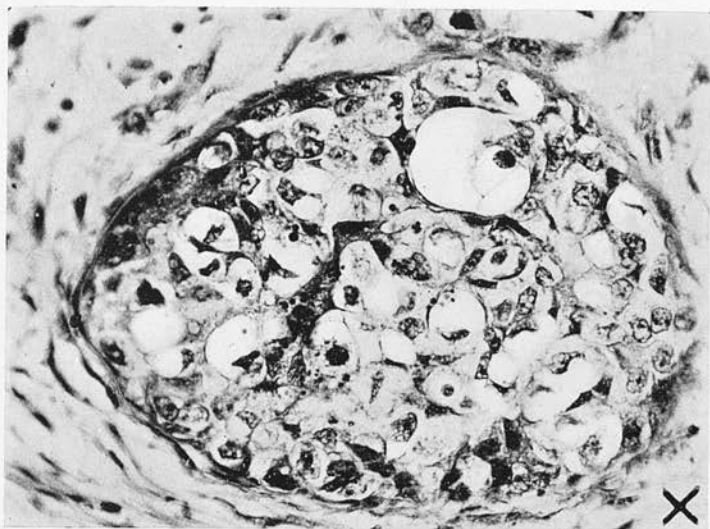


FIG. 7.—Malignant ductule from tissue of Fig. 5. ($\times 350$.)

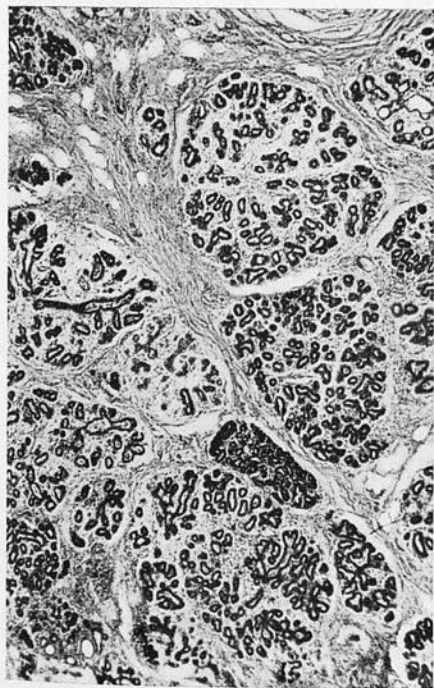


FIG. 8.—Normal adenosis at the tenth week of pregnancy. ($\times 40$.)

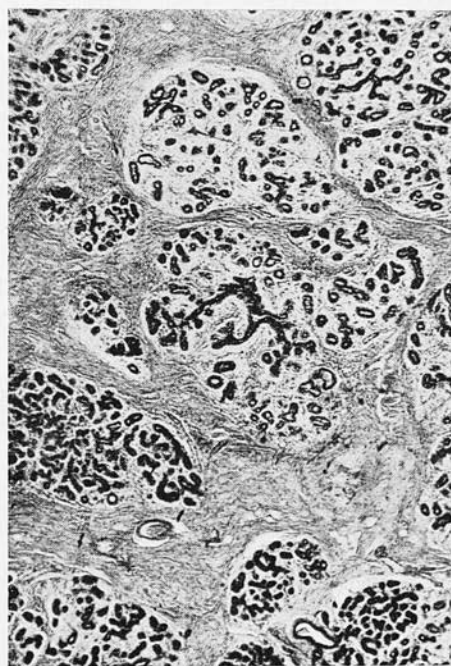


FIG. 9.—Pathological adenosis, in an unmarried patient, aged 49. ($\times 40$.)

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establish the definitely malignant change in the glandular cells, and the acceptance of this fact justifies the use of the terms duct and ductule carcinoma for a growth which not only originates in duct or lobule, but which, at the stage examined, is still largely confined to them. Actual invasion may indeed be late and subsequent to considerable filling of the glandular lumina with malignant cells, as shown in Figs. 5 and 6. This type of growth is called by Muir⁷ intra-duct cancer, and is well seen in the carcinoma sometimes associated with Paget's disease of the nipple, from a case of which Fig. 6 is taken. Ewing⁸ describes this type of growth as "diffuse duct cancer," in which there is widespread extension inside the ducts before any invasion is evident. Very little invasion could be found in the sections from which Fig. 5 was taken, though the cell type illustrated at much higher magnification in Fig. 7, Plate III., leaves no doubt that the proliferation was fully malignant. Fraser⁹ divides the spread of mammary carcinoma into two stages, an intra-mural and an extra-mural spread, both being considered definitely cancerous. Cheatele, as already mentioned, calls the intra-mural stage "the primary tumour," the extra-mural stage, "secondary deposits in the breast." According to many other writers, however, such as MacCarty¹⁰ and Semb,¹¹ these "secondary deposits" in the surrounding breast tissue alone supply the objective evidence of definitely malignant growth.

If, however, we accept the position that malignancy is recognisable in its early stages inside the glandular structures, all carcinoma of the breast must be initially duct or ductule or acinar carcinoma or a combination of these.

IV. Acinar Carcinoma.—I have not yet found evidence in the literature of the possibility of malignant growth arising in actual acini, the secreting mammary structures. On theoretical grounds, one would hardly expect to find progressive vegetative growth arising in tissue so differentiated for function that it does not normally survive beyond the period which called for its formation, but gradually disappears after the cessation of lactation. Cornil, it is true, describes a type of malignant tumour in which there is "an extensive multiplication of acini," with the formation of a tissue "somewhat resembling the lactating breast."¹² Ewing, however, as will be noted later, considers that these "small alveolar tumours," traced by Cornil and others to an origin in acini, are derived

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chiefly from duct epithelium, though Ewing includes the group as a possible form of "acinar carcinoma." I gather, however, that, in speaking of "acinar carcinoma," Ewing himself is using the term in its ordinary connotation of the end-piece of the non-secreting lobule, and that no restriction of the term to the secreting structure is implied. In other words, Ewing's "acinar carcinoma" is ductule carcinoma, in our terminology here. This interpretation is supported by the views of various other writers. Berka,¹³ who calls acini alveoli or Endbläschen, notes that "they appear in pregnancy, persist in lactation, and disappear again after lactation." He emphasises the finding that "no tumours or pathological formations are in any way like them." Gruber¹⁴ describes in detail a mammary carcinoma in a patient who died shortly after child-birth. He examined both breasts, and found in the cancerous one that both large and small ducts had become solid with malignant proliferation of their lining cells; there was a little secreting tissue outside the tumour mass, but it was being destroyed by the spread of the malignant cells. A detailed examination of six malignant mammary tumours removed during pregnancy and lactation has provided me with no evidence that cancerous growth is in any way associated with proliferative activity in acini formed during these periods. These tumours were all duct cancers, and the growth, as it spread both within and around the glandular tissue, was destroying the acini, as in Gruber's case. My present findings therefore exclude the possibility of malignant tumour arising in acini.

There remain the duct and the ductule as initial sites of malignant proliferation, which means that all carcinoma of the breast must be, in the early stages, either duct or ductule carcinoma, or a combination of the two types. Both are necessarily *glandular carcinoma*, since we include in glandular tissue all the epithelial structures in the *corpus mammae*. There seems little justification for the additional term "adenocarcinoma," which by derivation means glandular carcinoma, and even less necessity for "malignant adenoma," if our endeavour is to use terms of more exact connotation and eliminate the redundant in mammary terminology. The omission of both terms, and especially of adenocarcinoma, may seem unnecessarily drastic, since they are frequently used in describing breast tumours, and yet the literature does not provide any uniform interpretation of either, but only a limited and special meaning which varies with

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different writers. The term adenocarcinoma is generally used as an indication of a supposed stage of differentiation and of a degree of maturity, and such growths are therefore considered to be tumours of limited malignancy, but when applied to mammary growths, this opinion does not seem to be founded on any description of the origin, anatomy, or morphology of the tumour so described. Ewing defines adenocarcinoma *in general* as "a partially developed form of carcinoma," which "may become fully malignant," thus suggesting a restriction of the term to the pre-cancerous or pre-invasive stage of pathological proliferation, but adenocarcinoma *of the breast* is, in his classification, a definitely carcinomatous tumour arising in cystic ducts. Other writers include in adenocarcinoma tumours composed of "hollow tubes," or of "large or small alveoli," or of "nests of cells," without any indication whether the cells are still in ducts or ductules, or are proliferating in the stroma, or even spreading in the lymphatic channels. I am unable from these various descriptions to find any exact morphological or histogenetic meaning of the term; I would suggest that its use makes for ambiguity and its rejection from mammary terminology entails no real loss.

Our terms would now seem sufficiently defined for a discussion of ductule carcinoma, if lobule, acinus, and ductule are understood as described and illustrated here, and if adenosis and epitheliosis are accepted as terms descriptive respectively of physiological or pathological increase of glandular structures, and an increase of intraglandular epithelium. Except in quotation from the literature, I shall avoid the terms adenocarcinoma and malignant adenoma. I have already mentioned that a restriction of the term acinus to the secreting structures of pregnancy and lactation involves one in difficulties with the literature, but now that my terms are defined, I think it will create less confusion if I use acinus and ductule in this strict sense, and not, as they are ordinarily employed, without reference to their secretory or non-secretory character. In order to make quotation from the literature available, I shall therefore translate into the terminology adopted here, without comment.

V. Ductule Carcinoma.—Ewing (*loc. cit.*) bases his classification of malignant epithelial mammary tumours on the anatomical division between duct and ductule. His scheme includes three groups: (a) adenocarcinoma, arising from cystic ducts, or from sweat glands; (b) duct carcinoma, arising from ducts, but many

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also from sweat glands; and (*c*) ductule carcinoma, arising from ductules. If we avoid the term adenocarcinoma, as suggested above, and omit the possibility of intrinsic malignant breast tumours arising from sweat glands, a subject treated in an earlier study in this *Journal*,¹⁵ Ewing's classification comes to be:—

- A. Tumours arising from ducts: 1. from cystic ducts;
2. from non-cystic ducts.
- B. Tumours arising from ductules.

This is a logical classification based on histogenesis; it divides the varied forms into two main groups, and places types such as scirrhus, mucoid (colloid), etc., into subdivisions.

If a duct carcinoma is a carcinoma arising in a duct and still confined mainly to it, ductule carcinoma should mean malignant growth arising in ductules, but the latter definition lacks the exactness of the former, since two types of primary activity are possible in the ductules, and both are included under the term in the literature. These types are, by our definition—

1. A cellular proliferation within the ductules, which subsequently undergoes malignant transformation without necessary increase in the actual number of ductules, that is, epitheliosis without necessary adenosis, and
2. An increase in the number of ductules, producing an excess of lobular tissue, variously called lobular hypertrophy, adenomatous hypertrophy, or "chronic lobular or glandular mastitis," which becomes disorderly and eventually malignant, that is, a malignant adenosis without necessary epitheliosis.

The difference between these two types of epithelial activity seems, as already noted, to be one in kind as well as in morphology, though it is often obscured by both conditions being included in the term hyperplasia. It has been shown in diagrams *f* and *d*, and in Figs. 3 (epitheliosis) and 2 (adenosis). Adenosis would appear to be the normal reaction of the mammary gland to a proliferative stimulus, though it may become pathological by its irregular growth and time of occurrence; the new tissue produced, however, though excessive in amount, still conforms to the physiological pattern. This is brought out by a comparison of Figs. 4, 8, and 9.

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Normal adenosis, as exhibited at the tenth week of pregnancy, is shown in Fig. 8, Plate III.; in Fig. 9 there is an almost identical picture of adenosis which is pathological, in an unmarried patient of 49 years. Fig. 4, Plate II., is from another case of pathological adenosis in a patient of 52 years; Fig. 10 in the text shows the whole breast section of this case with the area of adenosis marked. It may be noted in passing that in both these cases of lobular overgrowth a radical operation was performed for a "suspicious lump" in the

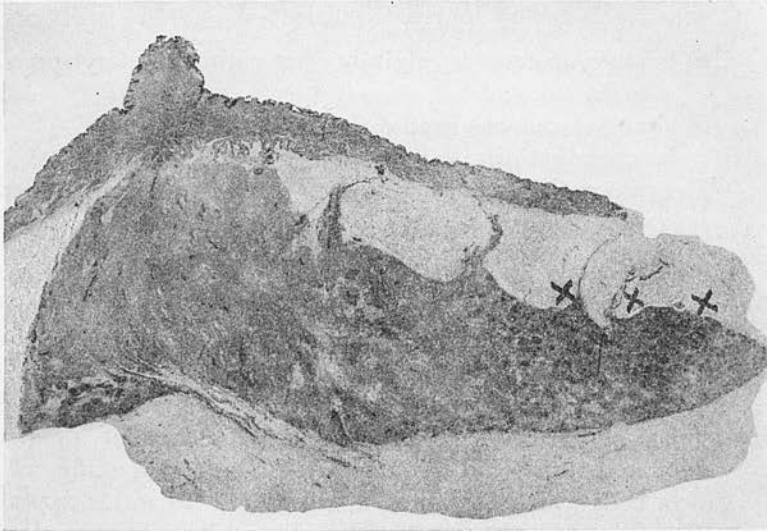


FIG. 10.—Pathological adenosis (at X) in a patient aged 52.
(Cf Fig. 4, Plate II., from same tissue.)

breast, but no pathological activity apart from this adenosis was evident in whole breast sections, when examined microscopically. Bloodgood has written much about these tumours, considered by him clinically "border-line" cases.¹⁶

Epitheliosis is essentially a different condition; it is an increase of epithelium which does not form new glandular tissue of physiological pattern, but which fills up and distends existing glandular structures. Dieckmann (*loc. cit.*) calls adenosis an "everted or physiological type of growth," and epitheliosis an "inverted type which resembles pathological forms."

These two types of epithelial activity in the lobule need

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more detailed consideration, in view of the possibility that either may become the starting-point of malignant growth.

1. Epithelial proliferation within ductules, or ductule-epitheliosis, as a possible origin of ductule carcinoma.

Opinions differ whether a primary epithelial cell activity within the ductules can occur in the absence of a similar process in the associated intralobular duct. I am here considering only the association of duct and ductule, without prejudice to the question of the number and site of primary malignant foci in the breast.

There are in theory four possibilities:—

- (a) primary cancerous origin in duct with secondary spread to ductules;
- (b) simultaneous origin in duct and ductule;
- (c) independent origin in duct and ductule, and
- (d) primary origin in ductule with spread to the associated duct.

(a) *Primary Malignant Development in the Small, Terminal Intralobular Duct* is of frequent occurrence—I am inclined to consider it *the most frequent origin of mammary carcinoma*—and the process may or may not involve the ductules secondarily. In speaking of secondary involvement, I do not distinguish here between extension of the tumour process from duct to ductule, and replacement of normal ductule cells by cancer cells which originate in the duct. It would appear that both methods of spread are possible. The likelihood of spread depends apparently on the age of the mammary tissue, or, to be more exact, on the degree of menopausal involution of the smaller glandular structures. It is sometimes forgotten that when malignant growth emerges in the breast, the lobules are, in the majority of cases, already atrophic; many have disappeared, others are collapsed and show hyaline-ringed ductules and dense surrounding fibrous tissue. That these involutionary changes offer some sort of a barrier to the spread from the duct of malignant cells to the ductules seems demonstrated by the frequency with which direct invasion into the stroma is observed from smaller or larger ducts without involvement of the lobular elements. In younger subjects, where the lobule is still active, spread to ductules from malignant foci in ducts is more obviously possible (*cf.* Figs. 3 and 5); it may be initially “a path of least resistance”

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for the cancer cells, but even in these cases, it is surprising how much more frequently the cancer cells are observed invading directly through the duct wall, without evident growth along the duct to the still patent ductules.

(b) *Simultaneous Malignant Origin in Duct and Ductules.*—Cheatle speaks of malignancy arising in terminal ducts and ductules, which might suggest a simultaneous origin, but he notes that though he has seen many early carcinomata arising in terminal ducts and ductules, he has never yet detected a primary growth situated only in ductules. In his work with Cutler,¹⁷ he also states that they have never been able to observe a direct passage of invading cells of carcinoma from a ductule. (I may mention again that Cheatle uses "acinus" where I have quoted "ductule" in these passages; I shall continue to use the stricter terminology in similar references.) Cheatle's findings suggest that the presence of malignant cells observed in duct and ductules is evidence of spread from duct to ductule, rather than of simultaneous origin in both structures. Semb (*loc. cit.*) mentions a case examined by him, in which ductule origin was suggested, but he could not exclude the possibility that malignancy began in the duct and spread to the ductules, so that he is uncertain of the existence of true primary ductule carcinoma, or of simultaneous origin.

(c) *Independent Origin in Duct and Ductules.*—This possibility is maintained by Ingleby,¹⁸ who considers that an independent and even morphologically different type of carcinoma may arise in duct and ductules. Her interpretation of the malignant picture on which this assumption is based rests largely on the acceptance of Rosenberg's position¹⁹ in regard to the influence of the menstrual cycle on mammary structure. I have not been able to find evidence in my material to support Rosenberg's opinion that the ductules disappear in the intermenstrum, nor have I observed what Ingleby interprets as the cyclic influence on actual or developing malignant mammary growth. The failure to find malignant cells in ductules only, or direct invasion from ductules, seems strong evidence that carcinoma is a secondary, rather than a primary, development in these structures.

(d) *Primary Origin in Ductules with spread to Ducts.*—The findings noted against the likelihood of simultaneous or independent malignant origin in duct and ductules are *a fortiori* against this possibility, and need not be repeated.

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This course of malignant development and spread raises interesting questions of structural and functional differences between duct and ductule. In Loeb's opinion (*loc. cit.*), there is a gradation of metabolism, structure and function between them, though the transition is not abrupt; various other writers have pointed out a difference indicated by the arrangement of the surrounding elastic tissue. Maximow's experiments²⁰ with normal mammary tissue grown in culture media support this position by indicating a quantitative difference in cell activity in duct and lobule. He found that even in the ductules of early pregnancy, the growth changes are less active than in duct epithelium, though until they are fully differentiated to form acini, they can, to some extent, show the same type of structural changes and proliferation. Maximow noted, however, that when the ductule proliferates, the surrounding connective tissue is not penetrated, in contrast to the "cancer-like behaviour" of the duct epithelium. The cell changes, he found, begin always in the ducts and gradually spread along the inside of these structures, until, in some cases, they finally extend even into the ductules. This seems to me strong evidence in favour of the duct rather than the ductule being the site of initial cellular activity. In the great majority of breast tumours, even at an age when the ductules are active, malignant growth apparently arises in the smaller ducts rather than in the ductules, and though these latter may be secondarily involved, invasion, when it occurs, is from the duct and not from the terminal structures. This observation indeed strongly suggests the possibility that *the duct is always the primary site of malignant proliferation* and the ductule involvement always secondary. It would explain the simultaneous appearance of cancer cells in duct and ductule as well as the failure to observe any primary growths in ductules only or direct invasion from ductules. In all the cases of early carcinoma which I have examined in detail in large and small sections, malignant proliferation, when both duct and ductule are involved, appears more advanced and of longer duration in duct than in ductule (see Figs. 3, 5, and 6). There is no obvious inherent reason why malignant invasion should not occur from a ductule if carcinoma arise simultaneously in both glandular structures, but my observations support Cheate's opinion that it rarely if ever happens. The nearest I have seen to it is the vague and somewhat broken outline of the basement membrane in the ductule shown in Fig. 7, at

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the area marked x. I am not altogether prepared to deny that this structure might be a duct, since its connections in the lobule could not be traced, but examination of the lobule in question supports its ductule nature. Ewing does not mention a primary epitheliosis in ductules giving rise to carcinoma in these structures. When malignancy is associated with ductule proliferation, it arises, in his opinion, in the other type of lobular hyperplasia, that is, in adenosis.

These findings argue against a primary origin of malignant growth in ductules. In the examination of over 600 malignant breast tumours, many in the early stages of growth, when the site of malignant origin was still recognisable, I have found no instance of a primary ductule carcinoma. It would seem probable that ductule carcinoma arising from epitheliosis is always secondary to proliferation of cancer cells in the terminal duct, and is an evidence of spread.

2. The second type of ductule activity is shown in an increase in the number of ductules, an adenosis. Can this produce a disorderly growth which eventually becomes malignant?

This is a type of glandular proliferation which, as far as my acquaintance with the literature extends, seems to have been little dealt with as a source of malignant growth in the breast. Ewing alone seems to have considered in detail the possibility of carcinoma arising from an excess of lobular tissue. In his opinion, there is a small group of malignant mammary tumours which may be separated from the duct carcinomata and which are derived from ductule epithelium. They may show no evidence of duct involvement at all, and are thus primary ductule carcinomata. Ewing considers that ductule carcinoma in this restricted sense may develop in three conditions: (i) in the malignant transformation of fibro-adenoma; (ii) in rare cases of "alveolar carcinoma," called "primary acinar carcinoma"; and (iii) as a type of fibrocarcinoma. The origin and early stages of malignant growth in these three conditions are not illustrated in his text-book, but as far as I am able to interpret the descriptions, these tumours arise subsequent to an actual increase in the amount of lobular tissue, that is, from adenosis, and I feel justified in placing them in this second group of ductule carcinoma. They need further examination.

(i) *Ductule Carcinoma arising from Fibro-adenoma.*—Ewing mentions cases described by Billroth and other writers of

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"diffuse adenomatous hypertrophy" which is said to have terminated in carcinoma of the breast, but the details given are hardly sufficient for recognition of the histological type of growth in question. Ewing himself notes that "specific and detailed reports are rare." The co-existence of carcinoma and fibro-adenoma does not necessarily throw light on the origin of the malignant development; of his own cases, Ewing mentions that the structure suggests a ductule origin, but in some, both duct and ductule seem to have been involved. *I have not yet found described and illustrated in the literature any undoubted case of malignant epithelial growth arising in a fibro-adenoma in an otherwise unaffected breast*, nor does any of the large number of these benign tumours examined by me suggest the likelihood of epithelial malignant transformation. Semb found no sign of cancer in the examination of 100 cases of fibro-adenoma, some with multiple tumours in the same breast. He also dismisses the diffuse form, fibro-adenomatosis without cyst formation, as a possible source of malignant growth. Fibro-adenoma may arise at any period of mammary life; it is not infrequently associated with the earlier ages, when cancerous development is exceedingly rare. Cheatle describes "mazoplasia" as an almost physiological condition, with an increased number of "acini," and associates it at various ages with the possible formation of fibro-adenomata, but he has been unable to trace any microscopical indication of a transformation of mazoplasia into malignant tumour. *If malignant growth arise in a fibro-adenoma, it is of sarcomatous type*. From a study of the few sarcomata in my material, I am inclined to think that these tumours in the breast originate as fibro-adenomata in which stroma proliferation has become uncontrolled, though at the time of removal the epithelial elements have been partly or wholly destroyed. A fibro-adenoma may, of course, show malignant epithelial growth if invaded from foci elsewhere in the breast, or possibly by sharing in the effects of proliferative stimuli evident in the mammary area outside its limits. I have material showing the invasion type, but none of the other.

(ii) "*Alveolar Carcinoma*" or "*Primary Acinar Carcinoma*."—In this group, Ewing includes "tumours of a peculiar and specific histology which is rarely observed"; they are met with in two forms, one in which "the structure presents a very large number of extremely small cell-groups or acini lined by small atypical epithelium," and the other, a form described by Cornil,

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and already referred to, in which there is "an extensive multiplication of acini in rather well-defined lobules . . . with a disordered growth which may extend beyond the lobules, the structure somewhat resembling the lactating breast." No signs of proliferation of duct epithelium were observed in these tumours. I have retained the term acinus in this quotation, as I am unable to rule out the possibility that actual secreting structures are implied in this description. The description of these two forms implies that in this group of "acinar carcinoma" malignancy arises from adenosis, an irregular increase in the number of "acini," which shows on section numerous small cell-groups either with or without a lumen, and with the lobular arrangement lost or retained. There is no mention of cellular proliferation—epitheliosis—with malignant transformation inside the individual "acini." Though he includes such tumours among "primary acinar carcinoma," Ewing considers that "the majority of these small alveolar tumours, although their development has been traced to acinar epithelium by Cornil and others, are forms of duct cancer and are derived chiefly from the ducts, while the acini are subsequently invaded and contribute only secondarily to the neoplasm." This opinion suggests that even in this case, the structures referred to are really ductules, and not true acini.

I have not yet been able to trace the origin of malignant growth in the breast tumours which I have examined to either of these forms of ductule or acinar activity. The former description, of a large number of small cell-groups lined by small atypical epithelium, might include the morphological type of malignant growth shown in Figs. 11 and 12. These illustrations are from the tumour seen in large section in Fig. 13, in the text, from a patient aged 63. The lobular structures and the mammary tissue in general showed marked atrophy; an infiltrating scirrhus growth had invaded the dermis and tacked down the skin at the outer margin of the breast. Fig. 11, from an area of this malignant invasion of the dermis at some distance from the nipple, shows ductule- or acinus-like formations, but the epithelial cell-groups cannot be ductules in this position; still less can they be acini, at this age. They are evidence of malignant infiltration or "secondary deposits" in the skin. This is confirmed by a similar arrangement of cancer cells in an axillary gland from this patient, illustrated in Fig. 12. Neither have I observed any malignant growth which conforms

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to the second type, described by Cornil, of a structure resembling the lactating breast. The specific structure of acini, the secreting elements of mammary tissue, has already been referred to and illustrated. This tissue disappears after lactation ceases, though isolated areas of incomplete involution may persist for a considerable time. In malignant tumour associated with

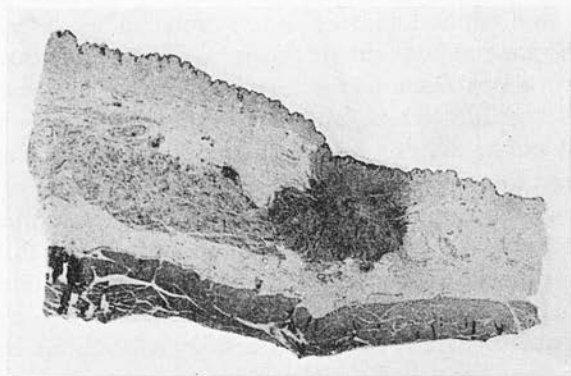


FIG. 13.—Large section, showing malignant invasion of dermis at outer margin of breast. (Cf. Figs. 11 and 12, Plate IV.)

pregnancy or lactation, there is no suggestion that the cancerous growth originated in adenosis or resembled it morphologically. Growth in the lobule would appear to be finally checked by the differentiation of the "end-pieces" into secreting structures, since these have not been observed to bud off other acini, in either normal or pathological tissue.

(iii) *Fibrocarcinoma*.—In this form Ewing describes the ductules about the unaltered larger or smaller ducts as increased in number and breaking up into many small groups of atypical cells which are compressed into narrow rows, giving rise to some cases of "primary scirrhus cancer." Malignancy is thus here also associated with adenosis. The actual stage at which malignant characters emerge is not indicated, though elsewhere in his text-book Ewing suggests that the isolation of epithelial cells may in itself be a condition entering into the causation of malignant development. The difficulty of assigning an origin to cancerous growth examined when much invasive spread has occurred is illustrated in Figs. 14 and 15, from the same malignant breast. Fig. 14 shows an acinus-like malignant infiltration of the looser tissue of the dermis, Fig. 15 a more



FIG. 11.—Acinus-like malignant growth in dermis. ($\times 40$.)

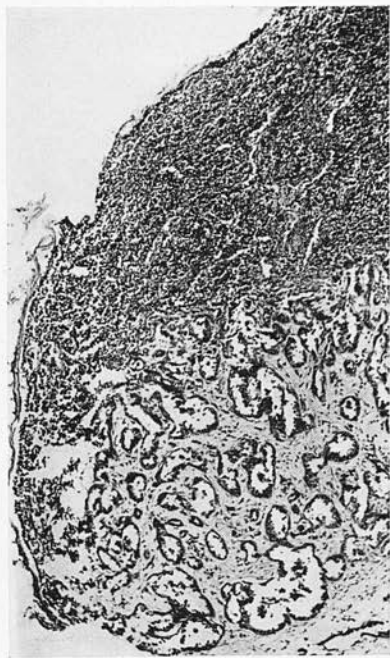


FIG. 12.—Similar malignant spread in axillary gland, same case as Fig. 11. ($\times 40$.)

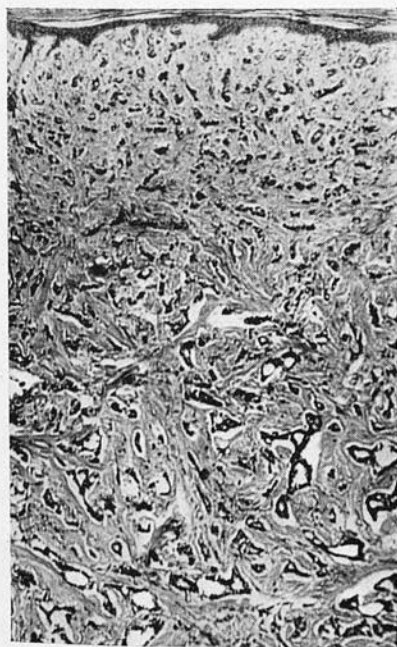


FIG. 14.—"Glandular" type of malignant spread in dermis. ($\times 40$.)

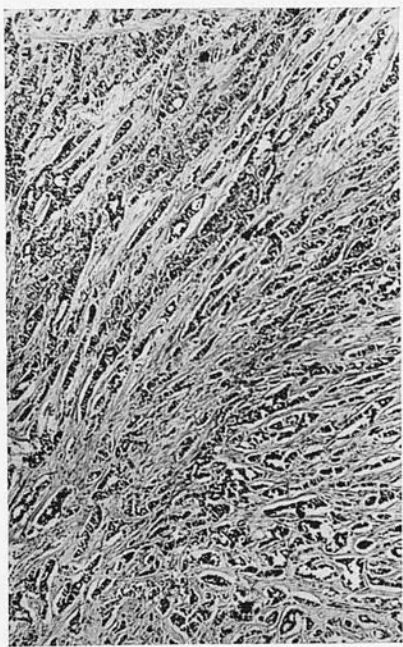


FIG. 15.—Malignant spread deeper in breast, same tissue as in Fig. 14. ($\times 40$.)

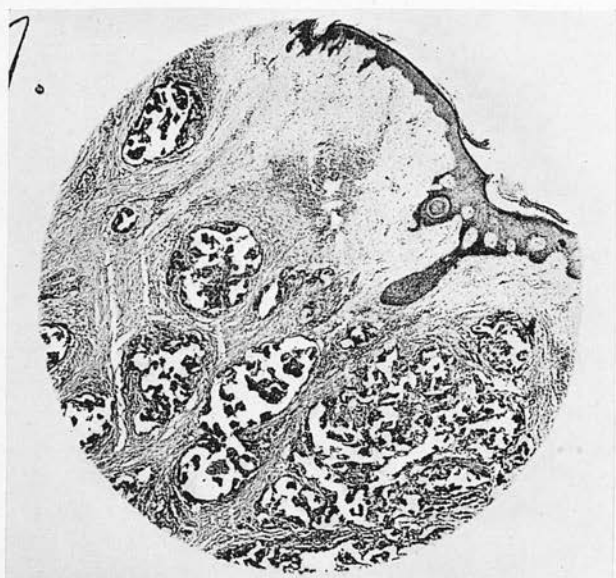


FIG. 16.—Gland-like malignant spread in dermis. ($\times 50$.)

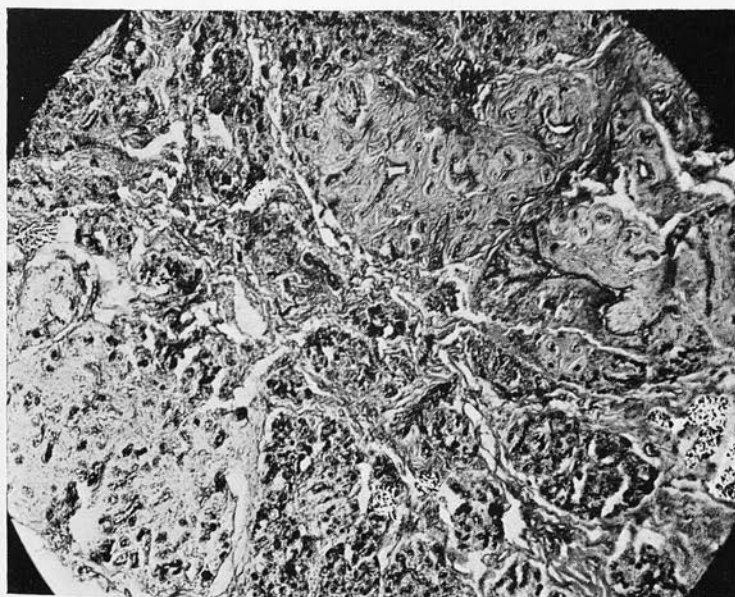


FIG. 17.—Fibro-adenomatosis, patient of 42 years. ($\times 30$.)

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usual cell arrangement in a scirrhous tumour, in the denser tissues deep in the breast. Even if we accept the possibility of primary ductule carcinoma, no assumption regarding the origin of malignant growth could be based on morphological structure as shown in Figs. 11, 12, and 14. The condition of the stroma in which the cancer is spreading seems to be an important factor in determining the arrangement and mode of spread of the malignant cells. An acinus-like arrangement is not necessarily an index of "differentiation," as is frequently assumed; it may be evidence of looser stroma rather than of lesser degrees of malignancy.

An important point arises from an analysis of these three types of ductule or possibly acinar carcinoma. In all of them, malignancy is supposed to be associated with, and originate from, an increase in the number of lobular elements, an adenosis, described as a "diffuse adenomatous hypertrophy," "an extensive multiplication of acini" (or ductules) or the formation of "a structure resembling the lactating breast." When other observers, apart from Cheatle, speak of "acinar or acinous carcinoma," though they attribute these growths to an origin in "acini" or ductules, the many types in their "acinar" group suggest that they are including tumours which are acinus-like in morphology rather than actually acinar or ductule in origin, and therefore not necessarily within our definitions of acinar or ductule carcinoma. Such tumours have been referred to in Figs. 11 and 14; another type of gland-like arrangement of malignant cells in a spreading growth is shown in Fig. 16, Plate V., from another area of cancerous invasion of the skin at some distance from the nipple. Few if any of these writers suggest, as Ewing does, that malignancy may arise in an adenosis evident in lobular hyperplasia. The general opinion is indeed against such an origin. Adenosis therefore needs further consideration.

As already noted, adenosis may be physiological or pathological.

(1) *Physiological Adenosis*.—Glandular increase is evidence of normal mammary activity at certain periods, such as at puberty and during pregnancy.

(a) It is seen *at puberty* and during adolescence, when new glandular tissue is being formed by the gradual building up of larger lobules. Physiological adenosis at this period cannot strictly be called overgrowth, but it may show exaggerations which are difficult to explain or classify, since the microscopical

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picture is so little different from the rest of the normal developing structure. These formations are usually placed in the second stage of the gradation seen in adenositis, adenomatosis and adenoma, but, as already mentioned, the dividing lines are not easily drawn. Even localised areas of overgrowth which become clinically palpable at this period as adenoma may, on histological examination, show glandular tissue almost indistinguishable from the remaining mamma. Berka (*loc. cit.*) has reported a number of such cases, and other observers, like Bloodgood²¹ and Trinca,²² note that such "tumours" may disappear without treatment; they thus indicate "neoplasia" only in the literal sense of "new growth," with little that is distinctively pathological in structure. The important point for our argument here, without entering into the question of how or why adenomatous areas develop in the puberal breast, is the extreme rarity of carcinoma at this period of life and the justifiable assumption that adenositis in itself has little if any association with malignant development.

(b) The breast *during pregnancy* gives a much more striking picture of lobular overgrowth; the glandular increase is gradual (*cf.* Fig. 8, Plate III., for tissue at the tenth week of pregnancy), but it becomes so profuse that when the newly-formed structures dilate with the onset of secretion, almost the entire microscopical field may be occupied by the differentiated acini, as in Fig. 1. This lobular overgrowth is obviously and essentially physiological in type. In the cases examined and already referred to, of malignant growth emerging during pregnancy or lactation, there was no indication that the origin of the pathological condition was in any way associated with the lobular activity, that is, with adenositis. All these tumours were duct cancers, with later invasion of the stroma and the lymphatic channels. Greig,²³ in describing a case of puberal mammary hypertrophy, mentions that a similar condition of glandular and fibrous overgrowth may be initiated by pregnancy. The reported cases are very rare, at either period, and when they occur, rapid growth has been followed by defective blood supply, with infection and the risk of sloughing and septicæmia, but there is no indication of the possibility of malignant epithelial transformation.

This formation of new mammary tissue, evident as larger and more numerous lobules, which is a characteristic phase of growth between puberty and adult life, and in a much greater degree, during pregnancy, is essentially physiological. It may occasionally be excessive in amount and unequal

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in distribution, to an extent which almost passes into the pathological; but the type of proliferation is, in my opinion, essentially physiological and different in kind from the epithelial activity which may lead to malignant growth.

(2) *Pathological Adenosis*.—Lobular overgrowth may be considered pathological when it occurs without obvious relation to the normal growth periods of the mamma, or when, during these periods, it is excessive beyond physiological demands, or so marked at any period that it becomes clinically recognisable as diffuse mammary enlargement, or a localised palpable "thickening" in the breast substance, or, more rarely, as a definite nodule. It is, as already pointed out, difficult to distinguish histologically between normal development and the lesser degrees of excessive lobular increase, as mammary tissue, even at the same age and under apparently similar conditions, varies widely in the amount of glandular structure it contains. Abnormal lobular increase which becomes clinically evident may occur at any age, and frequently produces a clinical picture difficult to diagnose. Semb (*loc. cit.*) places pathological adenosis as the first stage of what he terms fibro-adenomatosis cystica mammæ, more generally called "chronic mastitis," occurring on an average at about 33 years, in his series of cases. This condition in the adult gland has received various names; it is described as "chronic lobular mastitis" or "chronic glandular mastitis," though neither term is acceptable, owing to the ambiguity associated with the conception "chronic mastitis." Cheate's term mazoplasia apparently covers the same histological appearance, as mazoplasia is described as "an almost physiological condition," with an increase in the number of "acini," indicating that the breast is more active than it should be, instead of being completely at rest. Pathological adenosis indicates the formation of new glandular tissue in the absence of normal demand; it is not necessarily accompanied by epitheliosis, though this type of proliferation may be present in some of the glandular structures and lead by degenerative changes to cyst formation, or by progressive epithelial activity, to actual carcinoma. When the connective tissue is active with adenosis, either at the earlier ages or at the later periods, areas of fibro-adenomatosis or definite fibro-adenoma may be produced. An early and a later stage of fibro-adenomatosis is shown in some areas of Figs. 9 and 17 respectively. These formations eventually become hyaline and quiescent, if not removed on

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suspicion at an earlier stage of activity. Fig. 17 is from breast tissue removed by radical operation, because of a hard, defined area, in a patient of 42, whose other breast was malignant three years previously.

Adenosis, as a pathological condition, may thus lead to benign tumour, either in a diffuse or localised form, but I am unable to find evidence, apart from Ewing's descriptions of "acinar carcinoma," that adenosis in the breast may give rise to malignant growth. In other organs and tissues of the body, "simple adenomatous structures, adenocarcinomatous areas, and pure carcinomatous infiltration" are regarded as progressive stages of abnormal growth, but carcinoma in the breast would appear to be always the end stage of a pathological process which shows itself as epithelial proliferation—epitheliosis—within glandular structures, without necessary adenosis. Not that all such intraglandular proliferation necessarily becomes malignant, since desquamation, degeneration, and lysis of the epithelial cells may occur even after considerable filling of the lumina, but if malignant growth does emerge, the study of much breast material has indicated the probability that, in all cases, its origin can be traced to epitheliosis and not to adenosis. This epitheliosis, moreover, would appear to be primary in the duct rather than in the ductule, so that when malignant transformation occurs, the lobular elements may become malignant by secondary spread from the duct, and not as the result of primary malignant cell origin in the ductules themselves. This primary growth in the duct may originate at one or several foci of neoplasia at any level of the glandular tissue, but there is a marked preference for the smaller ducts. I have found no evidence at all that malignant growth either originates in the secreting elements, the acini, or involves them secondarily, except to destroy them.

The acceptance of these conclusions means the elimination of both acinar and ductule carcinoma from a scheme of classification based on histogenesis, for it designates all carcinoma of the mamma as primarily *duct carcinoma*.

This may be considered an extreme and unjustifiable simplification, when the varied appearance of cancerous breasts is remembered, but the bewildering number of "types" of malignant growth would seem to be due to the varieties and vagaries of physiological activity or inactivity in the mamma, which distort the tissue background against which malignant

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tumour develops and spreads, rather than to the site and complexity of tumour origin. Unless the growth is so advanced and destructive that anatomical landmarks have been obliterated or destroyed, it should be possible, in the majority of cases, to build up a general picture of the progressive stages of hyperplasia, neoplasia, and actual malignancy on a basis of the anatomy of the tissue, by comparing these different stages in different tumours. Ewing, in speaking of the cancerous breast, considers that "not until the anatomical structure and histogenesis of these tumours is more fully understood can any significant knowledge be obtained of their etiology, prognosis, and the value of treatment." The basis of such an anatomical analysis would seem to be the recognition of the site of malignant cell origin. I would record as my main conclusion in this discussion, that all malignant tumours of the breast are, in their initial stages, duct carcinoma, and never either acinus or ductule carcinoma. If this thesis can be accepted, we have a possible index to a clearer analysis of the malignant mammary picture and a suggested starting-point for a simplified classification of malignant epithelial mammary growths.

VI. Summary.—1. A more exact connotation of the terms applied to mammary structures is discussed, and definitions of *lobule*, *ductule*, and *acinus* are elaborated.

2. Justification is brought forward for the restriction of the term *acinus* to the secreting structures normally produced only in pregnancy and lactation; for the lobular structures of non-secreting tissue, the term *ductule* (*acinus*, *alveolus*, or *tubule* in the literature) is suggested.

3. Two types of epithelial proliferation in the lobule are described, and distinguished by the terms *adenosis* and *epitheliosis*.

4. These proliferative conditions, *adenosis* and *epitheliosis*, are discussed in relation to the origin of malignant mammary tumour, with special reference to Ewing's "acinar carcinoma." It would appear that cancerous proliferation in the breast is associated always with *epitheliosis*, and not with *adenosis*.

5. Examination of much tumour material suggests that malignant *epitheliosis* has its primary site always in the ducts, and, in the majority of cases, in the terminal, intralobular ducts. Involvement of the ductules is not primary but secondary, and is evidence of extension of the cancerous process. No participation in the tumour process by acini has been observed; they are apparently destroyed by the spread of malignant cells.

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Conclusion.—It is suggested that all carcinoma of the breast is, in its initial stages, duct carcinoma.

It is a pleasure to acknowledge my continued indebtedness to the Laboratory Committee of the Royal College of Physicians for the facilities afforded my work. I owe a special debt of gratitude to Colonel Harvey, Histologist to the Laboratory, for much helpful criticism and interest.

My acknowledgments are also due to the British Empire Cancer Campaign, with whose assistance I have been engaged on a general investigation of mammary tumours, and to the Carnegie Trust for the Universities, for help towards defraying the cost of illustrations. The photographs for these, with two exceptions, have been made with much care by Mr Watson and Mr Hamilton, of the Laboratory staff.

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Prognosis in Mammary Carcinoma

IN RELATION TO GRADING AND TREATMENT

BY

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Physicians, Edinburgh)*



PROGNOSIS IN MAMMARY CARCINOMA IN RELATION TO GRADING AND TREATMENT.

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*(From the Research Laboratory of the Royal College of
Physicians, Edinburgh.)*

- I. Prognosis in Relation to Grading. II. Difficulties raised by Early or Grade I. Tumours. III. Biopsy and other Diagnostic Procedures. IV. Methods of Histological Grading in Mammary Cancer. V. Consideration of Some Histological Appearances—(a) Differentiation and Anaplasia; (b) Fibrosis; (c) Lymphocytic Cell Infiltration. VI. The Anatomy (Topography) rather than the Cytology of the Tumour as the Basis of Histological Grading. VII. The Correlation of Clinical and Histological Grading—(a) Grade I. Tumours; (b) Grade II. Tumours; (c) Grade III. Tumours. VIII. Prognosis in Relation to Treatment.—A. Surgical Methods—(a) Radical Operation; (b) Endothermy. B. Treatment by Irradiation—(a) Radium; (b) Combination of Radium and Surgery; (c) Roentgen Rays. IX. The Choice of Treatment—(a) Doubtful and Early Cases; (b) More Advanced Cases; (c) Late Cases; (d) Local Recurrences; (e) Distant Metastases. X. Summary.

Foreword.—The following study contains, in substance, a paper given to the Edinburgh Medico-Chirurgical Society in May 1933. The work is based, in part, on a series of nearly a thousand mammary tumours, many cut in whole-breast sections, which has provided the material for previous investigations by one of us, and in part, on the more recent material now available from the Tumour Service follow-up departments of the Royal Infirmary and the Edinburgh Hospital for Women and Children. These departments have been organised since 1930, and we are grateful for the opportunity thus given of studying mammary cancers in relation to clinical and histological findings, treatment, and end-results. This correlated study is only in its beginnings, and some of the suggestions put forward in the following pages are necessarily

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of a tentative character and need much further detailed investigation. This is more especially the case with the histological observations, which have indicated that assessment of the malignancy of a mammary cancer for prognosis demands the consideration of many complex factors.

Our acknowledgments are due to the Laboratory Committee of the Royal College of Physicians for the facilities afforded our work, and to the surgeons in Edinburgh, Bradford, and Dunfermline, who have kindly supplied us with clinical details and follow-up notes on their cases. We owe a special debt of gratitude to Colonel Harvey, Histologist to the Laboratory, for much helpful criticism and interest. The photographs were prepared by Mr Watson, of the Laboratory staff, and Mr Pettigrew, of the University Surgery Department, to both of whom we tender our thanks.

The generous help given by the Carnegie Trust for the Universities towards the cost of reproducing the plates has made adequate illustration possible.

Prognosis, in the literal sense of "knowing beforehand" the outcome of a pathological condition, is perhaps more difficult in mammary cancer than in many forms of malignant disease, and it may be questioned how far it is possible to foretell with any reasonable accuracy the end-results in these cases.

Though the attitude of the medical profession to mammary cancer is in general a pessimistic one, it may be claimed that no problem in surgery or pathology has been more diligently studied, and no surgical operation has a more reasoned technique based on microscopical findings. Why is it then that the literature of end-results indicates that prognosis, during the last twenty years at least, shows little improvement? We need only compare the data furnished by the first statistics on breast cancer, those from Billroth's clinic in 1878,¹ showing an operative mortality of 23 per cent. and a mere 4.7 per cent. three-year survivals, with results obtained in general to-day, to realise that great progress has been made since his time, but, though recent advances make us hopeful that further improvement is now possible, with the adoption of newer methods of treatment, we must admit that at present progress is slow, if not actually at a standstill. In view of the fact that survival figures still show, in cases treated by surgery alone, only one patient alive out of three, five years after operation, it is

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desirable to consider why this is so and whether improvement can be hastened.

Many attempts have been made to estimate prognosis in mammary carcinoma, based on the evaluation of clinical and histological data, but, stated in the broadest way, it is obvious that cure, or the prolongation of life, depends on the possibility of the removal or killing or blocking of the malignant cells, and this in turn is directly dependent on the stage the growth has reached when the patient presents herself for treatment. Complex and difficult as the question of treatment is, one fact stands out clearly; if the disease is treated while it is still early and confined to the breast, the proportion of cases alive and well ten years later will be at least 70 per cent., while of the cases which already showed further spread, only some 5 per cent. will remain. Apart from the choice and efficacy of treatment, a reasonable basis for prognosis is therefore the findings which indicate the stage of growth. If the stage of malignant growth is early, prognosis should be favourable; if the stage is advanced, prognosis is unfavourable, whatever other factors are evaluated. Where then is the dividing line beyond which a bad prognosis must be given?

I. Prognosis in Relation to Grading.

All statistics indicate that this line lies between the cases in which the axillary lymph nodes* are free from invasion and those in which they are already invaded at the time of treatment. If the nodes are invaded, the growth is relatively advanced and the outlook unfavourable, whatever the other circumstances of the particular case. Survival figures, for example those of the Leeds investigation in the Ministry of Health Reports,² bring out the fact that the percentage of survivors, treated in the early stage of growth before the axilla is invaded, is not only much higher than in any other stage, but, where the ten-year figures are available, they show that this percentage remains almost constant up to that period; in the more advanced stages, however, while a not inconsiderable percentage survives three years, a smaller number survive five years, and only an occasional case after ten years.

* We use "lymph nodes" rather than "lymph glands," to avoid confusion with the glandular tissue of the breast.

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Early cases, that is, those where malignant growth is limited to the breast and axillary lymph nodes not yet involved, are classified as Grade I. tumours; more advanced cases are variously subdivided. The National Radium follow-up scheme places cases with invasion of axillary nodes in Grade II., and those with further dissemination, *e.g.* into other lymph nodes or pectoral muscles or with ulceration of the skin, in Grade III.; for distant metastases, into lungs, bones, etc., a Grade IV. would seem advisable. Lane-Clayton's scheme³ is similar, but is modified by the fact that it is based on collected case-records taken a number of years previously. The cases are divided into three main groups: Grade I., axillary nodes not invaded; Grade II., axillary nodes involved, but nothing to indicate further spread of the disease; Grade III., disease extending to some tissue outside the breast itself other than axillary nodes. Lane-Clayton subdivides the cases in Grades I. and II. according to whether a pathological report on the lymph nodes is available or not; those where the absence or presence of malignant cells in the nodes has been confirmed by histological examination are classed IP and IIP; those where clinical findings only had to be relied on are classed as IC and IIC. Other schemes, such as Steintal's⁴ and Schmitz's,⁵ are more detailed, but we have found them difficult to use, because they are apparently based on the assumption that the disease extends from the site of origin to other structures such as skin, deep tissues, etc., in a definite order, which is not always the case. All such grading schemes, however, emphasise the dividing line between the cases in which the nodes are involved and those in which they are not, even when other findings, such as the age of the patient, the size, duration and type of the growth, its situation in the mamma, the association of pregnancy or lactation, are also taken into consideration as important data in prognosis.

The acceptance of this dividing line between early and later stages of growth, *i.e.* between Grade I. tumours and the more advanced grades, to indicate the extent of malignant spread as a criterion of prognosis, involves the adoption of a method of grading based upon it, and the registration of the clinical stage of growth when the patient is examined. It is necessary to emphasise the importance of this grading as an essential basis for any deductions regarding prognosis, as well as for any estimate of the value of treatment. If end-results are obtained by adding all cases together, as is frequently done in published

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figures, they are misleading in giving both an unduly unfavourable result for early cases, and a too favourable one for advanced cases. This is obvious when an over-all survival rate of 35 per cent. at five years includes, as in the Leeds figures already referred to, 91 per cent. survival for Grade I. and 15 per cent. for Grade III. The more general adoption in mammary case records of a grading of malignant tumours on some accepted basis such as the National Radium Commission's scheme would provide a large body of data for comparison and analysis. The error in clinical grading associated with the presence or absence of enlargement of axillary lymph nodes can be eliminated, in the great majority of cases, by histological examination.

Why is prognosis so favourable in Grade I. cases and so definitely unfavourable in all others? It would seem to be not merely a question of the invasion of axillary nodes, otherwise careful removal of the axillary contents should make end-results in Grade II. cases, where apparently the nodes are the only area invaded beyond the breast itself, almost as favourable as in Grade I., but this is not the case, since results in Grade II. approximate to those in Grade III. There is indeed considerable evidence to the effect that, if the malignant cells have once passed beyond the actual mammary area, the axillary nodes are not the only site of possible involvement, though they are probably the first and the most easily detectable in the great majority of cases. Numerous reports of cases show that, in the more advanced grades, though treatment by operation or irradiation is so effective that the primary tumour is successfully removed and later recurrence is not found in the scar or surrounding parts, yet there is frequently a fatal issue from more distant metastases.⁶ The explanation of the wide divergence in end-results between Grade I. tumours and the more advanced growths may lie here, invasion of lymph nodes indicating not merely extension of malignant cells from breast to axilla, but being also an index that, in the majority of cases, the disease is already beyond effective attack. Eggers,⁷ for example, finds that with the radical operation and meticulous care in dealing with the axilla, recurrence in the mammary area or chest wall or axilla is and, in his opinion, should be very rare, but he notes that his survival rates are no better than those from other clinics. His patients die from more distant metastases, not from local recurrence. These metastases, as he points out, must have been carried from the primary growth

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before or during operation ; if before, the tragedy has already happened, hastened possibly by frequent handling by the patient herself or in the clinic before treatment ; if during operation, the likelihood of the danger might have been lessened by various precautions, to be mentioned later. Sampson Handley⁸ explains these more distant metastases by distinguishing between spread by embolic invasion of the axillary lymph nodes, "a route of dissemination which has attracted undue attention because it is patent to clinical observation," and spread by "permeation of the fascial lymphatic plexus which lies upon the great pectoral muscle . . . and gives the disease access ultimately to the whole of the parietal tissues," as well as to the chain of internal mammary nodes lying behind the costal cartilages, beyond the range of operative removal.

These considerations make the outlook for all cases of mammary cancer, other than early ones, appear very gloomy. It is true that in any individual case, special features and circumstances may modify prognosis, but it is difficult to escape from the conviction that improvement in the outlook of other than early cases must be brought about by improvement in methods of treatment, rather than by a more adequate consideration of other data. We deal with treatment later in this paper, so we may now consider these earlier cases, where prognosis is surprisingly hopeful if diagnosis is accurate. It may, of course, be contended that this early group forms a very small proportion of all cases coming for treatment, and this is unfortunately true. Lynham⁹ estimates that 75 to 95 per cent. of all malignant mammary cases show spread beyond the actual breast when first examined ; MacCarty¹⁰ mentions that of the operable cases at the Mayo Clinic, 62 per cent. have invaded axillary nodes, while 30 to 50 per cent. are inoperable and hopeless when first seen. With education of the public, however, numbers in the early group should increase, and the diagnostic and other problems involved in their treatment would then become more urgent.

At present, we have no data which suggest that any-form of treatment other than radical operation can give results comparable with those which early or Grade I. cases show by this method, *i.e.* at least 70 per cent. five-year survival (see tables). On the other hand, it must be admitted that results in the more advanced grades suggest that operation, unaided by other means, has only in a minimum of cases justified itself, if eradica-

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tion of the disease were aimed at. In these cases, the possibility of better prognosis would seem to demand the better adaptation, if not indeed the entire readjustment of therapy to the conditions of advanced malignant growth.

II. Difficulties raised by Early or Grade I. Tumours.

Early cases of mammary carcinoma raise a number of difficult problems which need further light thrown on them. This is the group where diagnosis is often difficult, where histological examination is most necessary, and where present figures show that a favourable eventual outcome depends upon an operative treatment considerably more extensive than the clinical condition indicates. It is, however, apparently demanded if the patient is to benefit from treatment at this early stage of the disease, since the five- and ten-year survival figures, so favourable at this early stage, are those of cases with radical operation. Survival figures for early cases treated by irradiation, or by a combination of surgery and irradiation, are, as yet, numerically insufficient for comparative consideration, and the weight of evidence is, at present, definitely against any lasting benefit accruing from limited operation in Grade I. cases. It is this fact which is largely responsible for the problem of dealing with breast cancer in its early stage.

Early cancer in the breast is not easily detected. The growth in most cases shows no text-book signs, for these are all indicative of considerable spread in the tissues, and yet, if the growth is malignant, extensive removal is advisable. Every means of confirming or denying the presence of malignancy at this stage must therefore be weighed.

III. Biopsy and other Diagnostic Procedures.

Various means have been advocated to aid diagnosis when clinical appearances are indefinite, such as biopsy before or during operation, the examination of frozen sections, and the two-stage operation. There is much divergence of opinion regarding the utility or advisability of these procedures, and they need more detailed consideration than is possible here. Biopsy and the two-stage operation are generally condemned, as likely to endanger the patient's chances of ultimate benefit from treatment. Many references to biopsy in the literature,

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however, argue otherwise. Reimann,¹¹ Anschütz,¹² Boss,¹³ Hoffman,¹⁴ Epstein and Fedorejeff,¹⁵ among others, maintain that complications following biopsy are exceptional and that acceleration of tumour growth has not been observed, when necessary precautions are taken. Biopsy prior to operation is, in many clinics, an accepted diagnostic procedure in dealing with growths in other sites, such as the skin, and it may be justified as an aid to diagnosis in mammary tumours if the method of performing it is such as to minimise the likelihood of disseminating malignant cells. But altogether apart from its possible danger, the utility of biopsy may be questionable when it requires a decisive histological report on a small piece of tissue which may not be pathognomonic or may not even contain the suspected area of growth. This difficulty is brought out in the whole-breast sections shown in Figs. 1 to 4, Plate I. In Fig. 1, the area *a* shows only a slight degree of glandular hyperplasia or adenosis ("chronic glandular mastitis"), *b* shows a duct carcinoma prior to infiltration, and *c*, small scattered foci of scirrhus surrounding malignant ducts; clinically, there was a suspicious generalised enlargement and hardness of the breast tissue, under a thick layer of fat. Fig. 2 shows cancer cell infiltration of the tissues in the two-ringed areas, also in a fatty breast, with non-malignant activity in the other zones; though the condition was definitely malignant clinically, biopsy in this case, as in the previous one, might have missed removal of a cancer area. Fig. 3, a malignant tumour in a young patient, illustrates an almost generalised neoplastic activity ("carcinosis"), with malignant infiltration of the connective tissues and invasion of the lymphatics in the areas marked. Clinically, the breast showed generalised enlargement, but there was no fixation, nipple retraction, or other sign to suggest the extent or site of the cancerous development. Fig. 4 shows a type of malignant tumour unusual in our experience; there are minute multiple foci of scirrhus growth at the areas marked in the upper half of the section, the lower part showing only atrophic, hyaline changes with a few small cysts.

Where an early malignant development is feared, and, as frequently happens, is only vaguely localised and unilateral, simple amputation of the breast would appear justified as a minimum protection to the patient. A careful examination of the gross pathology of the tissue will then solve the problem of diagnosis in a large proportion of cases. If there is still

SECTIONS SHOWING DIFFICULTIES ASSOCIATED WITH BIOPSY MATERIAL.

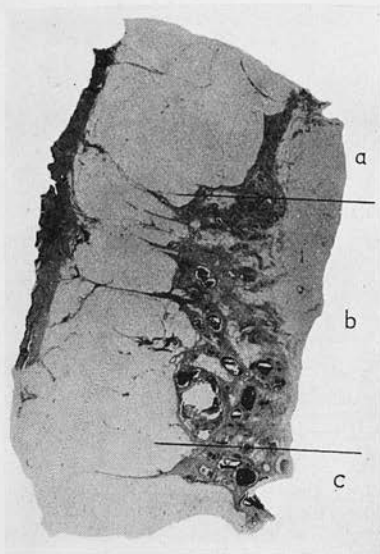


FIG. 1.—Tumour with three types of neoplastic proliferation:—(a) glandular hyperplasia or "adenosis"; (b) duct cancer; (c) scirrhous infiltration round malignant ducts.

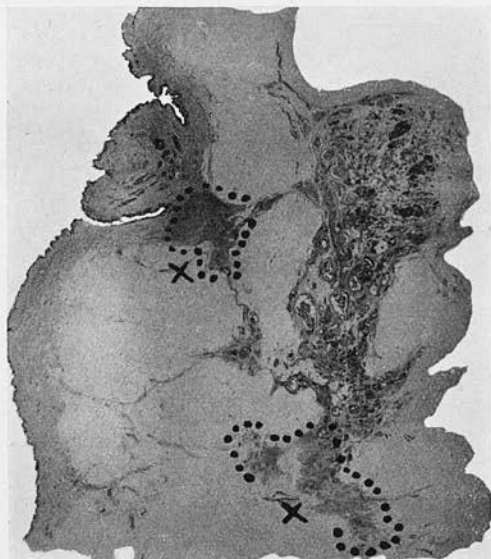


FIG. 2.—Tumour with limited areas of malignant infiltration (ringed); rest of section shows glandular hyperplasia and non-malignant cystic ducts.

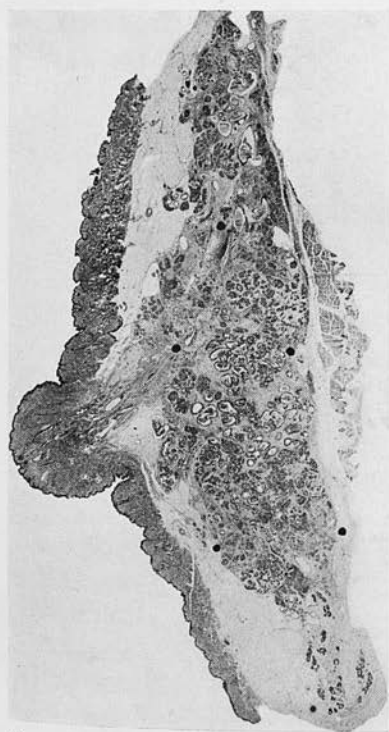


FIG. 3.—Multiple areas of malignant invasion ("carcinosis") in a young patient with generalised mammary enlargement.

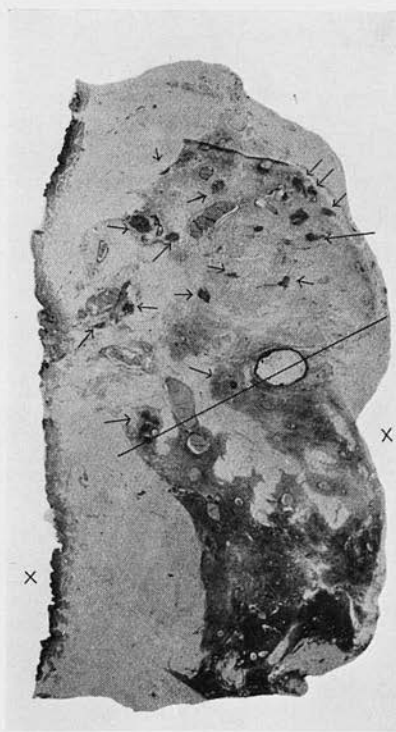


FIG. 4.—Multiple small areas of malignant infiltration; lower half of section (x-x) shows quiescent non-malignant area, with small cysts and much hyalinisation.

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uncertainty, additional help may be forthcoming by the immediate preparation of a frozen section; if this is positive for malignancy, the radical operation can be at once proceeded with, but a negative report is less conclusive, as it suffers from much the same fallacies as those associated with biopsy and leaves the surgeon without definite guidance. Is it advisable at this stage to close the wound and defer further interference until a report on permanent sections of the excised breast is available? If it confirm the presence of carcinoma, the radical operation can still be carried out, without much loss of time. There is much opinion against the advisability of this two-stage operation. Bloodgood states that experience at Johns Hopkins Hospital showed that all the patients so treated were dead within three years, but a small number of cases reported in the Ministry of Health investigations^{2, 3} shows a lower mortality than with one-stage radical removal, and MacLean¹⁶ mentions nine cases living fifteen to twenty-five years after such treatment. The almost routine performance of the radical operation for actual or suspected mammary cancer has perhaps obscured the fact, emphasised by Greenwood,¹⁷ that a cancer, at so early a stage as to defy careful examination before or during amputation of the breast, "will gain little further deadliness by the postponement of the radical operation for the few days necessary to establish a sure diagnosis by pathological examination."

It would seem that either the radical operation must be done for every suspicious mammary tumour, and thus the risk of extensive removal of non-malignant growths faced, or one of the aids to diagnosis, such as biopsy, frozen sections, or the two-stage operation, must be utilised. That the problem presented by these early cases has not been solved is indicated by the wide error limit in clinical diagnosis given by figures in the literature. In the pre-operative diagnosis of 2100 breast tumours at the Mayo Clinic, as reported by MacCarty,¹⁸ a doubtful diagnosis was made in 21.5 per cent, and, of these, the diagnosis of cancer was incorrect in 37.2 per cent. Fischer's figures at the Rostock Clinic¹⁹ are very similar.

IV. Methods of Histological Grading in Mammary Cancer.

Many workers have explored the possibility of estimating prognosis in mammary cancer by a consideration of histological data rather than, or in addition to, the clinical aspects of the

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growth. But it is a curious fact that, though all end-results indicate that the stage of extension of malignant growth is the basic factor in prognosis, methods of histological grading of malignancy described in the literature appear to take insufficient account of this aspect of tumour growth. These methods are based on the varied morphology of the malignant cell, or on the resemblance of malignant tissue to normal mammary glandular architecture, or on appearances in the tumour bed, such as fibrosis, round cell infiltration, etc., interpreted as evidence of resistance to the growth.

There have been many workers in this field, and the methods of histological grading are numerous and in some cases very detailed. Leroux and Perrot,²⁰ MacCarty,²¹ Reimann,²² Greenough,²³ Patey and Scarff²⁴ have considered for prognosis such appearances as cell or tissue differentiation, cell and nuclear inequalities, hyperchromatism, mitosis, and, in the tumour bed, hyalinisation, lymphocytic cell accumulation, etc., in assessing the degree of malignancy. Taylor²⁵ makes a preliminary grading on a general impression of the degree of deviation from the normal, and then, several weeks later, re-examines the sections, and grades them on a basis of several factors thought to be particularly indicative of tissue differentiation, with arbitrary values assigned to such points as general architecture, cell-type, etc. He found a third examination of the sections necessary with an indecisive 11 per cent. of his cases. Another method is that of Schmitz and Hueper,⁵ which has received a wide publicity in the last few years in America. These workers base prognosis on a consideration of twenty factors, with a maximum of eighty points, which compose "the histological malignogram." They claim that with practice the value of this malignancy index can be worked out in about twenty minutes; they admit, however, that "one may find a histological Grade IV. in a clinical Grade I," because, in their opinion, "an index based on histological structure represents the *potential* rather than the *actual* malignancy of the growth." Their final conclusion is, indeed, that prognosis depends mainly on the efficacy and type of treatment, which is dictated by the clinical findings. Lee and Stubenbord²⁶ support this position, attributing "the failure of histological grading to provide a correct prognosis" to the fact that different histological pictures, indicating different degrees of malignancy, may be found in various parts of the same tumour (*cf.* Fig. 7). Patey and Scarff

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note²⁴ that their cases show a uniformly good result, whatever the grade of malignancy, if the lymph nodes are not invaded, and a uniformly bad result in advanced cases, whatever the histological picture may be.

The usefulness for prognosis of methods of histological grading based on cytological appearances in mammary cancer may therefore be questioned, for, as Stout points out,²⁷ the various factors, favourable or unfavourable, tend to modify one another's value in any particular case. Moreover, the validity of some of the underlying assumptions in these grading schemes is not yet generally accepted. This is brought out by a brief consideration of one or two of the factors assessed in them, such as differentiation and anaplasia, fibrosis, and lymphocytic cell infiltration.

V. Consideration of some Histological Appearances.

(a) *Differentiation and Anaplasia.*—Differentiation, a conception derived from von Hansemann's views of cell specificity and anaplasia, is interpreted by many observers as evidence of lessened malignant activity. It is a biological truism that differentiation for function and reproductive activity are mutually antagonistic. Differentiation for function requires time; time means slowness of reproductive activity, hence differentiation means slowness of growth, or even absence of growth. Nowhere is this better demonstrated than in normal mammary tissue, where the *fully* differentiated cell, that is, the functioning unit of the lactating acinus, not only shows little if any evidence of division, but is so highly specialised that it does not survive lactation, the functional period for which it is produced. But differentiation in this sense is not observed in malignant mammary growths. Berka pointed out many years ago²⁸ that no cancer tissue in the breast in any way resembles lactating cells, and the question has been recently discussed by one of us.²⁹ But when the earlier stages of mammary development, from nipple epithelium to normal duct and lobule structure, are also regarded as stages of differentiation, it is difficult to understand what many writers mean by differentiation in mammary carcinoma, as a factor which modifies malignancy. Some identify it with "adenomatous arrangement," as Greenough does,²³ or "acinous structure," that is, a tissue differentiation by which the malignant growth attempts to approximate to

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normal mammary architecture. As far as we can interpret this idea, it is illustrated in the sections shown in Figs. 5 and 6, Plate II.

Fig. 5 is taken from a malignant growth in a patient aged 53, who when first seen was thin, sallow, and fatigued, with Hb 70 per cent. and a red cell count reduced to $3\frac{3}{4}$ millions. The growth was too advanced for complete removal, the breast being replaced by a tumour 5 by 4 inches in size, with discoloured, fluctuating zones and an ulcerated area some distance from the nipple. The axillary lymph nodes were palpably enlarged. Microscopically, there was extensive malignant infiltration of the whole mammary area, as well as invasion of the axillary nodes and surrounding fat. Histologically, the cancer tissue in the plane of section is of a "differentiated" type, forming "hollow acini," but clinically the growth was a Grade III. tumour, with a highly unfavourable prognosis, borne out by the patient's death two and a half years later. Fig. 6 illustrates another type of malignant growth interpreted as evidence of differentiation, with the formation of "solid alveoli"; these in other parts, cut longitudinally, appeared as "tubules" of malignant cells, regarded by Patey and Scarff²⁴ as an index of low malignancy. Clinically, however, this was also a Grade III. tumour, with deep fixation and invasion and some destruction of the great pectoral muscle.

Other workers use the term differentiation in mammary tumours in the sense of cell differentiation, that is, the formation of malignant cells which resemble normal mammary cells, as MacCarty does,²¹ but our examination of a large series of carcinomata in whole-breast sections has shown that, with the acquisition of malignant characters, the mammary cell in almost all cases differs from its non-malignant ancestor. In any case, it would seem obvious that malignant tissue architecture rather than cell morphology would be more reliable as a test for differentiation. Other writers, again, consider differentiation in relation to the so-called functional or secretory activity of the malignant cells, as Delbet does³⁰; he associates the more benign, slow-growing breast tumours with the "secretion" of mucus, but, in our opinion, mucoid degeneration seems a more reasonable explanation of the limited activity in these tumours. Where mucin is found in considerable quantity, the growth is frequently called a "colloid cancer," a tumour type associated with slow extension, but mucoid degeneration may be very limited and only detectable microscopically in small scattered areas which have apparently no inhibitory effect on the spread of malignant cells elsewhere in the growth.

SECTIONS SHOWING "DIFFERENTIATION" AND "ANAPLASIA," IN MALIGNANT MAMMARY TUMOURS.

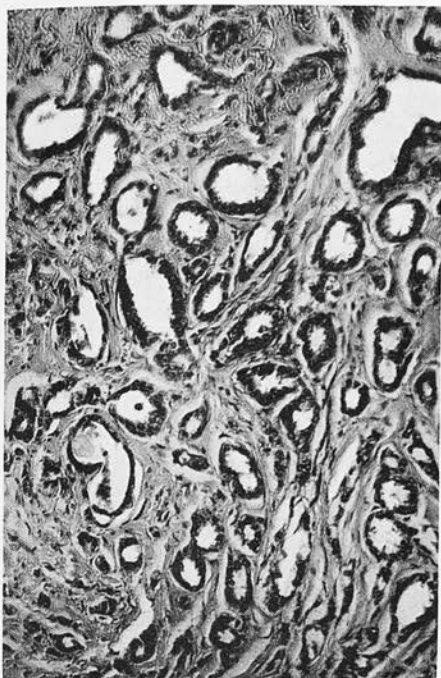


FIG. 5.—"Adenomatous structure" in a Grade III. tumour, with extensive invasion of chest wall and axillary tissue.

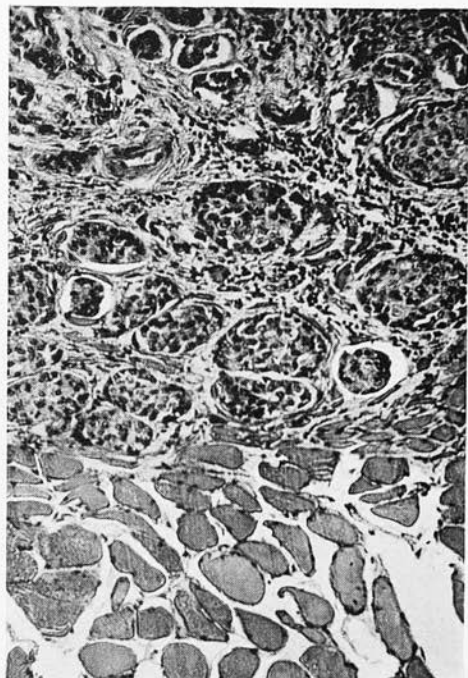


FIG. 6.—"Solid alveoli" or "tubules" in a Grade III. tumour invading and destroying deep muscle.

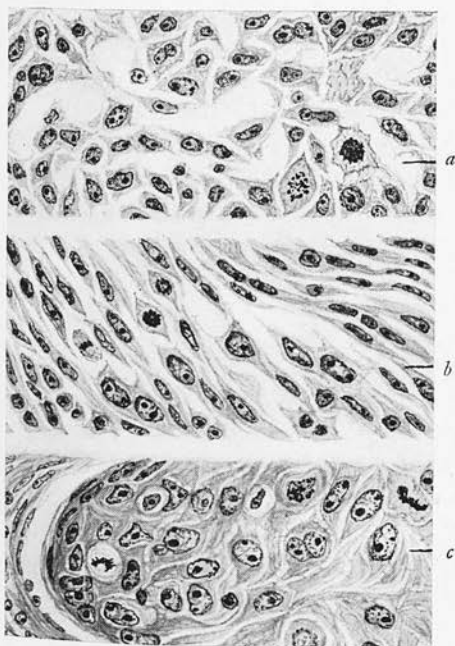


FIG. 7.—Three types of "anaplasia" in the same tumour, a papillary adenocarcinoma.



FIG. 8.—Squamous carcinoma of the breast, showing intercellular bridges and some keratin formation.

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The reverse of differentiation is anaplasia, a condition evident when cells tend to exhibit and maintain an earlier stage of development. If we are logical, this condition in mammary tissue would seem indicated by the emergence of cells suggesting the primitive squamous epithelium of the nipple *anlage*, but this is rather the phenomenon of metaplasia. The formation of squamous or squamoid cells in mammary growths, both benign and malignant, needs further study, but available statistics show that squamous carcinoma is one of the most malignant, if one of the rarest, types of growth in the breast, and the few examples in our material support this finding.

One of these is illustrated in Fig. 8, a malignant tumour in a married patient of 47 years; it had been noticed less than four months, was not defined in outline but radiated into the breast tissue in all directions, with some fixation to the skin. Greatly enlarged, hard lymph nodes were palpable in the axilla. Whole-breast sections showed extensive infiltration and replacement of the mammary tissues by a squamous carcinoma, and invasion of the axilla by a similar type of growth.

Tumours of this type which we have examined do not support Delbet's opinion³⁰ that such growths are less malignant forms than the average because the squamous change is an attempt at differentiation. Anaplasia in a marked degree is usually associated with numerous mitoses and other evidence of rapid, atypical proliferation of malignant cells, such as inequalities in size and shape of cell and nucleus, but when a tumour shows great varieties of histological structure, as sometimes happens, it may be difficult to decide which is the anaplastic cell. This is shown in Fig. 7, which illustrates tissue from three different areas of a papillary adeno-carcinoma, all of which showed numerous mitoses, though there is obvious diversity of cell type. We have observed highly malignant cells, with numerous mitoses and polymorphism, proliferating apparently entirely within cystic ducts, with no evidence of invasion of lymph nodes, that is, forming tumours still at an early or Grade I. stage, a finding which supports Hueper's observation⁵ that a clinical Grade I. growth may be associated with a cytological Grade III. or IV. There is, however, nothing inconsistent in this. Cell type may thus prove of little help in prognosis, and tissue type, in many growths, seems to depend as much on the character of the mammary tissue and tumour

bed before cancer develops as on any inherent tendency of the malignant cells to "differentiate." We have found it difficult to obtain an exact idea of the sense in which the term differentiation is used when applied to malignant mammary tumours; *our studies, so far, do not indicate the bearing of differentiation, as usually interpreted, on prognosis in mammary cancer.*

(b) *Fibrosis*.—Fibrosis and lymphocytic cell accumulation are associated, by many observers, as evidence of stroma reactions which tend to restrain malignant growth and are thus included as favourable factors in schemes of histological grading. Does fibrosis thus interpreted mean an active process, a fibroblastic proliferation which, as some contend, strangles cancer cells? If this were so, even admitting the possible divergence of interpretation of "scirrhus" as a clinical and histological term, scirrhus cancer should be of modified malignancy, but end-results in the literature do not support this view; they suggest that scirrhus is the most malignant form. Perry³¹ found, for example, that only half the cases with scirrhus survived as long as the encephaloid group; Meier, at Arau,¹ found no scirrhus cases free from recurrence three years after operation, compared with 50 per cent. free in a group which included encephaloid, adeno-carcinoma and colloid growths. It is true that the scirrhus tumour most frequently found in elderly subjects is slow-growing and relatively benign, but we would suggest that malignant growth, in these cases, may often be checked, not by active fibrosis, but by the hindrance to cancer extension encountered in a tissue already fibrosed, largely hyaline and avascular, as normally found in the involuted mamma. Such a tissue is shown in Fig. 10, Plate III, where a remarkable absence of fibroblastic activity at the advancing malignant edge is illustrated.

The patient, aged 49, had passed the menopause, her only child being 21 years old. She was first seen about a year before operation, complaining of slight mammary discomfort; no abnormality could be detected, and re-examination six months later revealed nothing to suggest surgical interference. Instead of remaining under observation as advised, the patient allowed another six months to elapse, and by then the skin on the affected side was greatly thickened and darkened, suggesting a "cancer en cuirasse." No tumour growth, however, was palpable in breast or axilla and "the radical operation was carried out more on preventive than on clinical grounds." No enlarged nodes were found in the axilla and histological examination of the axillary

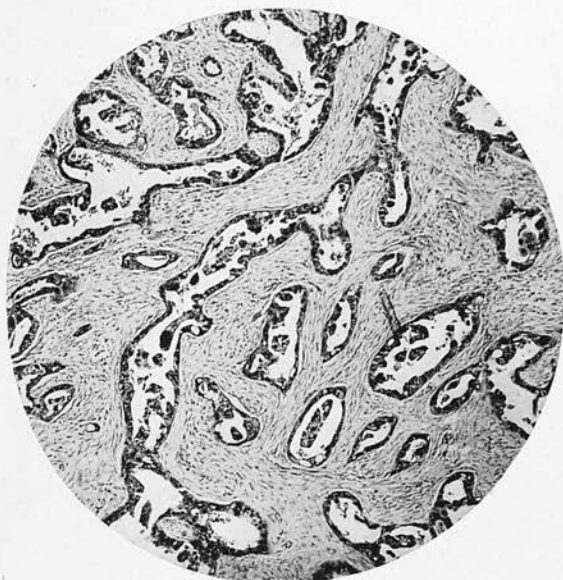


FIG. 9.—Active fibrosis in a rapidly-growing tumour, of highly malignant cell type (mitoses, giant-cells, etc.).

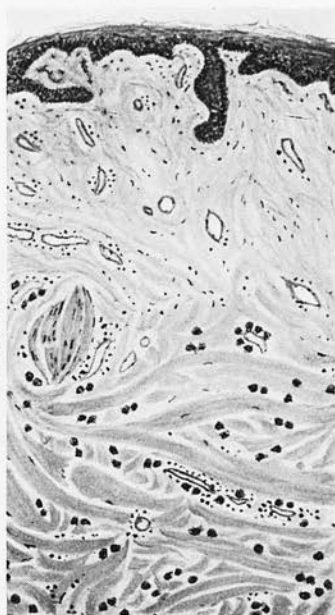


FIG. 10.—Absence of fibroblastic activity at the advancing edge of a clinically slow-growing tumour, without lymph node invasion.



FIG. 11.—Lymphocytic cell infiltration in a tumour removed six weeks after parturition, with a fatal issue six months later: (a) malignant duct with much necrotic material in lumen; (b) another malignant duct with little necrosis; (c) malignant cells filling a periductal lymphatic channel.



FIG. 12.—Lymphocytic cell infiltration associated with extensive lymphatic invasion, suggesting "block" of the lymph drainage of the area: (a) perivascular lymphatic vessel with malignant cells; (b) normal lobules embedded in round cell accumulations, apparently caused by lymph cell extravasation and proliferation.

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tissues revealed no malignant involvement. The entire mammary area showed a seeding of malignant cells as in Fig. 10, but appearances in the infiltrated dermis suggested invasion of capillaries, a finding supported by the later history, as the patient died within four months of leaving hospital from malignant growth within the chest. Invasion of the blood stream alone suggested the unfavourable outlook in this case, for in spite of the absence of fibrosis, growth was slow, the cell type by no means very malignant, the tumour impalpable even at operation and the lymph nodes not invaded. The opposite picture is seen in Fig. 9, where marked fibroblastic activity is associated with the rapid extension of a highly malignant type of growth.

We would suggest that the hard infiltrating tumour, which is clinically a scirrhus cancer, may frequently be associated not with active fibrosis, but with atrophic changes in the mammary tissue, which we construe as indications of age and permanent functional quiescence, and obliteration of many of the lymphatic and blood vessels which in younger cases facilitate malignant cell dissemination. This in itself would explain the slow course of the atrophic scirrhus cancer, without any assumption that delayed growth is due to fibroblastic activity forming a "defence" against malignant extension. Where fibroblastic proliferation is observed, it may be merely a reaction to the trauma of malignant invasion; moreover, a certain degree of stroma proliferation would seem necessary for the propagation of malignant tissue, to provide a framework for the support and nutrition of the invading cells, and such proliferation is often best observed in rapidly-growing malignant areas. *We are therefore inclined to oppose the contention that fibrosis is necessarily a favourable factor in prognosis in mammary cancer.*

(c) *Lymphocytic Cell Infiltration.*—The presence of accumulations of lymphocytic cells in the stroma surrounding malignant growth is also interpreted by many observers as a "defence" or "immunity reaction" which tends to check the progress of malignant cells. There is much evidence for and against this view. Round cell accumulations are characteristic of various non-malignant mammary conditions, such as post-lactation glandular involution and cystic fibro-adenosis ("chronic cystic mastitis"). Round cells may indeed be observed at any period when epithelial tissue in the breast is being destroyed and removed, as they apparently provide a proportion of the phagocytes which deal with epithelial cell debris. Our own findings support the opinion, which is by no means a recent one, and

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which has been expressed, for example by Greenough²³ in relation to breast pathology, that round cell infiltration is probably an expression of a function of the body in response to the presence of degenerated matter rather than the individual's resistance to malignant tumour growth, though a stroma infiltrated with round cells may be a less favourable ground for tumour extension. He notes that round cell infiltration and degenerative phenomena run very parallel, as we have also observed, whether the growth is malignant or benign. Semb³² considers round cells a normal product of post-menopausal mammary involution, the period when malignant tumour in the breast most frequently emerges. *We are inclined to agree with those observers who deny any specific function to the lymphocytes observed in mammary carcinoma; their accumulation apparently represents a response to normal or malignant cell degeneration or necrosis.* This conception would explain their presence in tissues where cancer cells are successfully killed by irradiation, as well as where a transplanted tumour fails to grow in an immune animal. They are frequently also seen in areas which show marked lymphatic vessel invasion by malignant growth, and then they may indicate block of the lymph stream with extravasation and proliferation of the lymph cells. This is shown in Fig. 12, where permeated perivascular lymphatics are seen at the periphery of two normal lobules, the outline of which is almost entirely obscured by round cell infiltration, apparently caused by block of the lymph drainage of the area. Round cell accumulation associated with marked epithelial cell degeneration is seen in Fig. 11, which shows tissue from a malignant growth which began to grow very rapidly after childbirth. Radical excision was performed six weeks after confinement, but the tumour proved fatal within six months. There was marked lymphocytic cell infiltration throughout the breast tissue, associated with malignant and non-malignant ducts filled with fatty debris, malignant cell permeation of the lymph channels and advanced involvement of the axillary nodes.

It would seem that further study of normal mammary tissue, as a background against which malignant growth originates and spreads, and of what Greenwood³³ aptly calls "the oscillations of physiological life within the bounds of normality," with the variations which occur with growth, function and the retrogression of declining years, is necessary before any position

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can be taken up regarding the significance of these histological appearances in estimating prognosis.

It has already been mentioned that some of those who have attempted to grade malignancy on a histological basis are driven to the conclusion that prognosis seems to depend less on the cytology of the growth than on clinical findings, and especially on the stage it has reached when the patient is treated. Healy and Cutler³⁴ find that, in uterine cancer, the cures obtained in early and borderline cases are proportionately high, regardless of the cell type of the growth. In advanced cases, they state that prognosis improves with the greater degree of anaplasia when the tumours are irradiated, since the more malignant the cell type, the greater its radio-sensitivity. The paradoxical situation thus arises that the more malignant tumours may offer a better prognosis with irradiation, but worse with surgery.

VI. The Anatomy (Topography) rather than the Cytology of the Tumour as the Basis of Histological Grading.

We would suggest that the problem of grading and prognosis based on cytology has been obscured *because histological data have frequently been considered apart from, and not in conjunction with, clinical findings.* The more malignant type of cell, as evidenced by its more abnormal appearance (hyperchromatism, polymorphism, basophilia, size, etc.), proliferates more rapidly and therefore tends to produce an advanced stage of growth earlier than a less malignant type; this is apparently what Hueper means by "potential malignancy." If, however, these highly malignant cells are proliferating within a cystic duct, the stage of the disease is still early and prognosis favourable. On the other hand, if the tumour as judged from the test section shows cells with few mitoses or variations of size and shape, but with lymph nodes or more distant areas already invaded, the stage is manifestly advanced and prognosis obviously unfavourable. At the time when the patient is treated, the important question for prognosis seems to be, not so much what is *the type* of the malignant cell or tissue, but what is *the position* of the malignant cells. In other words, prognosis demands a knowledge rather of the anatomy or topography of the growth than of its cytology. The clinical aspects of the tumour indicate the position of the malignant

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cells in a general way; microscopical examination can show this in a more exact and detailed manner. It can indicate whether the cancer cells are still, in the main, confined to the ducts (Fig. 13); whether they have ruptured the duct walls, with infiltration of the surrounding stroma (Figs. 14 and 15); whether the lymphatic channels are invaded (Figs. 16, 17, 19 and 21), with the probability that the lymph nodes are already involved, or whether the malignant cells have gained access to the blood stream (Fig. 18), with the likelihood of distant metastases forming. *Examined in this way, the histological features of a tumour illustrate its "actual" as well as its "potential" malignancy; they amplify, supplement and correct the clinical findings, whereas, considered solely as cytological appearances, they are often contradictory and therefore of little help in prognosis.*

VII. The Correlation of Clinical and Histological Grading.

Put briefly, the relation of this method of histological grading to the clinical grades already defined is as follows:—

(a) *Grade I.*—The earliest stage of malignant growth is confined within the tubular glandular structures of the mamma, that is, it is a malignant hyperplasia situated within the mammary ducts (Fig. 13) which may be more or less normal in calibre or may show cystic dilatation of varying degree. The favourable prognosis we should expect at this stage is borne out by end-results, which show a higher three- and five-year survival in duct cancer than in any other type of malignant growth, not excepting colloid. It must be remembered here that the histological diagnosis "duct cancer" does not in all cases exclude tissue invasion. With a pure duct cancer, prognosis would be even more favourable. As already mentioned, the cell type is immaterial, if the growth is still confined to the ducts. The next stage of malignant growth shows rupture of the duct walls and infiltration of the periductal tissues (Fig. 14). We have found little to suggest that immediate invasion of the lymphatic channels occurs when duct boundaries are transgressed. In the atrophic breasts of elderly subjects, changes associated with post-menopausal involution obliterate, to a large extent, the smaller lymph and blood vessels necessary for functional activity, and malignant invasion of lymphatic channels may be a considerably delayed phenomenon. Malignant spread in these circumstances may thus form large areas of infiltrated stroma

HISTOLOGICAL GRADING OF MAMMARY MALIGNANCY.



FIG. 13.—Duct cancer (Grade I): (*a*) malignant ductule; (*b*) malignant small duct; (*c*) malignant cystic duct.

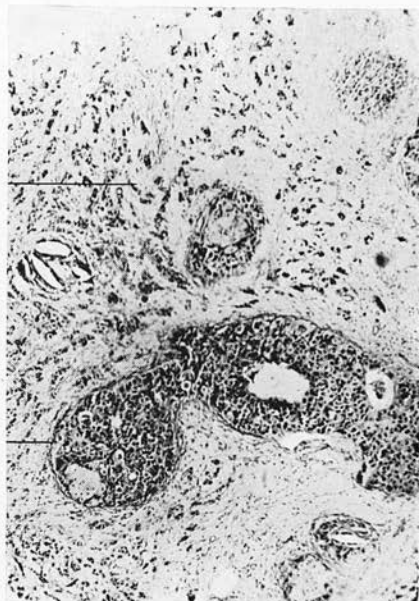


FIG. 14.—Duct cancer with malignant infiltration of connective tissues: (*a*) malignant small duct; (*b*) tissue infiltration. (Grade I.)

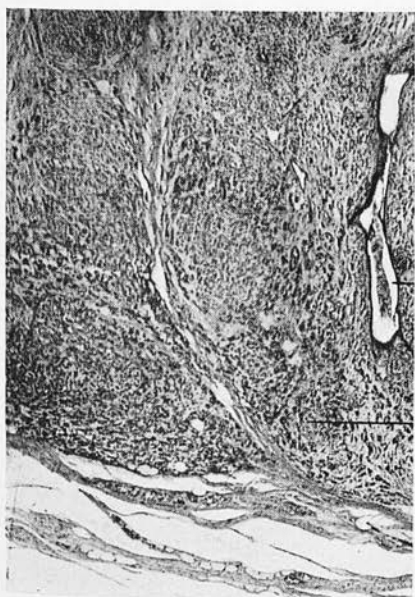


FIG. 15.—Edge of a nodule formed by malignant infiltration of connective tissues (*b*); (*a*) a non-malignant duct. (Grade I.)



FIG. 16.—The advancing edge of a malignant tumour, showing (*a*) tissue infiltration as in Fig. 15; (*b*) lymphatic invasion in infiltrated area; (*c*) lymphatic invasion beyond the nodule. (Grade I.)

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(Fig. 15) before the lymph stream is invaded; Fig. 16 shows the spreading edge of such a growth at a later stage, with both stroma and lymphatic involvement. The clinical course of three such Grade I. tumours (Figs. 29, 30 and 31) is described later in this paper, under the section dealing with the treatment of cancer at this stage (pp. 90-91). The position of the lymph channels in relation to the mammary ducts in a quiescent tissue is well brought out in Fig. 20, which shows tissue from an inactive fibro-adenoma being invaded from an adjacent scirrhus cancer. The lymph channels normally patent near the glandular structures are no longer in evidence in the dense periductal stroma, those permeated with malignant cells lying at a considerable distance from the duct walls.

These two phases of tumour growth, intraductal malignant proliferation and periductal stroma infiltration preceding the invasion of lymphatic channels, correspond to clinical Grade I.

(b) *Grade II.*—Actual invasion of the lymph stream in the breast itself is, in the large series of sections we have examined, almost invariably associated with invasion of the axillary nodes; histological examination of these confirms whether or not the growth has actually reached Grade II. In rare cases, lymphatic involvement in the primary growth has been found without demonstrable node invasion, but this may be an accident of sectioning. The early stages of axillary involvement are apparently due to malignant emboli carried in the lymph stream to the nearest node, a conception which would explain how infrequently such cells can be found outside the nodes in these cases. A more advanced involvement of a lymph node is seen in Fig. 22, at *y*, with malignant cell emboli in an adjacent afferent lymphatic at *x*. Lymphatic permeation in the axilla would appear to be a much later finding, when the lymph flow has been slowed, or even stopped, by extensive malignant proliferation blocking its movement through the nodes.

(c) *Grade III.*—Clinical Grade III. may be inferred from histological findings in breast and axillary tissue, and *vice versa*, rather than actually demonstrated, for it is not often that material beyond these areas is available for examination, except *post-mortem*. Invasion of the perinodal tissues in the axilla is, in our findings, a late stage of extension, subsequent to much malignant growth within the nodes themselves.

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Invasion of nerves (Fig. 23) has been observed only as a late phenomenon; pain is a late symptom in breast cancer, caused in most instances apparently by pressure on nerves due to invasion of perineural lymphatics, and only rarely by actual invasion of the nerve substance. Invasion of blood vessels has been found also as a late occurrence (Fig. 18); bone and visceral metastases suggest, in the majority of cases, a blood-borne dissemination rarely observed apart from an advanced stage of the primary tumour. Invasion of the pectoral muscles, as in Figs. 25 to 28, Plates VII and VIII, and involvement of the skin beyond the mammary area, as in the growth shown in part in Fig. 27, are other findings usually, though not necessarily, associated with clinical Grade III.

This method of histological grading, which considers as the essential finding the position of the malignant cells, and therefore corrects and amplifies the clinical observations regarding the stage of tumour growth, would appear to hold considerable possibilities of help in estimating prognosis in mammary cancer. It needs much further study, for analysis of the malignant picture is often difficult, and in some advanced cases almost impossible, if tissue from older parts of the growth alone are sent for examination. Here the growing edge will provide valuable information, and it is better that the areas to be examined be left to the selection of the pathologist. We have been fortunate in the opportunity of working at mammary problems with material largely cut in whole-breast sections, but even without this advantage, a grading based on the anatomy of tumour tissue would throw light on the relationships of structure, type of growth, and stage of spread, and thus help in prognosis as well as tend to simplify classification in mammary tumours. It has been brought home to us that, when the many so-called types of mammary cancer are analysed in this way, especially when the whole tumour area is available for microscopical examination, these may be more reasonably regarded as *stages of growth* rather than as inherently different *forms of growth*, if the initial variation in the non-malignant mammary background is allowed for. From this point of view, classification would also help in prognosis, if based on a combination of clinical and histological findings which would take structure, type, duration and stage of tumour extension into account.

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VIII. Prognosis in Relation to Treatment.

We must now turn to the other and equally important aspect of the question of prognosis in mammary cancer, that of treatment. We have emphasised the fact that, from the clinical and histological aspects, the stage of malignant growth when the patient is treated is the controlling factor in the possibility of cure or the prolongation of life. But it is obvious that, however early the stage of growth, eradication of the disease is dependent on suitable and effective therapy. The likelihood of spontaneous cure in mammary carcinoma is so remote that it may be dismissed in any consideration of the problem, though in very rare instances in patients of advanced age, the malignant process appears to be at a standstill, for reasons already discussed. These, however, must be considered exceptional cases; practically speaking, if untreated, the patient is certain to die of the disease. The length of time required to accomplish this may vary from a few months to over twenty years, but the average duration of life after the discovery of cancer of the breast is thirty-eight months, a calculation based on figures supplied to the Departmental Committee of the Ministry of Health,³³ which it is necessary to keep in mind when assessing the value of treatment. The choice of suitable and adequate treatment thus takes the first place in estimating prognosis. The question of the best form for treatment to take is a problem which has not been solved, but the actual choice lies between operation, irradiation, and a combination of the two.

A. Surgical Methods — (a) *Radical Operation.* — In early cases, as already mentioned, surgery remains the method of choice, but in spite of the fact that the radical operation has been more or less standardised for the last thirty years, there are still certain differences in technique, and now and then new procedures are suggested in an attempt to make the operation even more radical. Lane-Clayton³ states that reports from a number of centres in this country show that the accepted radical operation consists in the removal of the breast, the two pectorals (excluding the clavicular portion of the large pectoral), the axillary contents and adequate portions of skin and deep fascia. Occasionally, the small pectoral is left in position. Most clinics now prefer the plastic operation, which, although it aims at removing an adequate area of skin, attempts to close the

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wound by extensive undermining of the skin edges and ingenious dove-tailing which uses any redundant tissue to make good deficiencies, and thus avoids the necessity for skin grafting. Sampson Handley³⁵ favours this type of operation, as he believes that it is the wide dissection and removal of the fascia with its lymphatics which is the most important point, but Dean Lewis and Rienhoff,³⁶ writing from Johns Hopkins Hospital where Halsted first perfected his skin-grafting operation, quote figures which show a slight balance in favour of this as opposed to the plastic operation, which they regard as proof of the need for the sacrifice of a larger skin area. Bartlett³⁷ has recently published details of a very extensive operation which leaves a large raw area to be covered by grafting, and Danis,³⁸ of Brussels, also claims that his results are improved by removing a very large area of skin. Another point of some importance in technique is that the Report of the American College of Surgeons,³⁹ published in 1929, shows that only 26 per cent. of patients whose small pectoral was not removed survived five years, against 33 per cent. of cases where both pectorals were sacrificed, a point also brought out in some of the German figures.

Examination of the plates (Figs. 1 to 4 and 29 to 31), which show large sections of breasts containing malignant tumours, illustrates certain difficulties met with in surgical treatment. Those showing carcinoma of the first grade (Figs. 29 to 31, Plate VIII) make it clear that any of the accepted types of radical operation will eradicate the disease, but owing to the error associated with clinical grading, we must accept the proviso that the small pectoral be included, so that small foci of malignant cells which may be present between it and the large pectoral are eliminated. The importance of the removal of a large area of skin becomes evident when we look at Fig. 24, Plate VI, for malignant cells are seen passing up the ligaments of Cooper to reach the surface at a point far from the centre of the tumour. Davis says,⁴⁰ "if the growth is deeply seated, only a comparatively small amount of skin need be sacrificed," and Handley³⁵ speaks of removing a pyramid of tissue with the apex at the skin, but in cases such as that illustrated, this would almost certainly leave cells capable of producing a local recurrence. The anatomical arrangement of the breast tissues makes wide local dissemination round the tumour probable even at a comparatively early stage, except in cystic growths, and the fact that the appearance of nodules in or near the scar is

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still quite a common occurrence—Weyvill's figures⁴¹ show 207 in 401 cases and Perry's,³¹ 52 per cent. of all recurrences—suggests that this must be remembered when an incision for the removal of the cancer-bearing mamma is being planned.

(b) *Endothermy*.—Operative technique is modified to some extent by the use of endothermy, which facilitates operation when used for the radical amputation and gives another method of attack, the "*coagulation sur place*" of the French school, which may be of service when fixation makes the local condition inoperable. The advantage claimed for the endothermy knife is that it seals off the lymphatics and small blood vessels as it passes through them, but the question is sometimes asked whether we gain anything by this when emboli of cancer cells have almost certainly already passed through the lymphatics and in many cases have reached the lymph nodes. It cannot be expected that endothermy, any more than any other form of treatment suggested up to the present, can reach cancer cells which have passed beyond the accessible area but the numerous sections we have examined show that there are countless malignant cells surrounding the palpable tumour, and as these can only be detected by the microscope, it is almost certain that the instrument used for the dissection will pass through small collections of these cells and scatter them through the wound. The sharpest scalpel must cause trauma, some lymphatic channels will be torn and gaping, others will be compressed, and as the inevitable manipulation of bringing the skin flaps together proceeds, there is likely to be suction which may draw cancer cells lying on the wound into the vessels and pass them along to glands or the blood stream, at a time when the patient's resistance is lowered by shock. This suggestion is not capable of proof, but is put forward as a possible explanation of the idea, frequently expressed, that diathermy prevents dissemination of the disease. In the personal experience of one of us, the operation is actually easier if performed with diathermy, which saves much catgut for tying off small vessels and prevents loss of heat in the operation area. We therefore definitely advise its routine employment. *Coagulation sur place* has been little used in Great Britain, but is an accepted method in France and in Sweden. The technique is not difficult, and the resulting scars surprisingly good, but the convalescence is trying for the patient and one hesitates to recommend it if there is an alternative method available.

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B. Treatment by Irradiation—(a) *Radium*.—Having now accepted the fact that if we are to depend on operation alone it must be as complete as possible, let us go to the other extreme and consider the possibility of treatment by irradiation only.

There are few clinics where irradiation plays the major part in the treatment of operable cancer of the breast, and probably none where it is never supplemented by surgery, but figures are now available showing five-year survivals which we can compare with our operative results. As a rule, it is considered necessary to combine interstitial radium with external irradiation either by radium or Roentgen rays, and there are two methods which we must consider, that of Keynes of St Bartholomew's Hospital, who uses radium only, and that practised by Lee and Pack⁴² of the Memorial Hospital, New York. Keynes' method⁴³ is now well known and consists in placing a large number of needles of different lengths, with a linear intensity of 0.5 mgrms. of radium element (R.E.) to the cm. into the breast and surrounding tissues, including the axilla, the supraclavicular nodes and the intercostal spaces. The dosage is to a certain extent empirical, approximately 1 mgrm. of R.E. being allowed for each 2.5 sq. cm. of mammary tissue and the radium left in position for seven days. Since 1930, Keynes has considerably modified his method of arranging the radium needles in the axilla and aims at securing a cross-fire effect. At the Memorial Hospital, attention has been directed to obtaining a dose of irradiation lethal to the cancer cells throughout the area treated. The work of the physicists, Failla and Quimby,⁴⁴ in co-operation with the clinicians, Lee, Pack and Adair, under the direction of Ewing, has produced results which must arouse interest. Their present technique has only been in use for about three years, so that figures are not yet available, but it is evolved from the gradual improvements in methods of irradiation since 1920, and is therefore the result of careful trial and observation over a long period. The unit of dosage is the skin erythema dose (S.E.D.) and is that amount of irradiation which, after a single application, will produce in 80 per cent. of all cases a faint reddening or bronzing of the skin after three weeks, and in the other 20 per cent. will produce no visible effect. Quimby and Lee⁴⁵ have shown that to destroy the malignant cells in a mammary carcinoma it is necessary to deliver about twelve times the S.E.D.

HISTOLOGICAL GRADING OF MAMMARY MALIGNANCY.

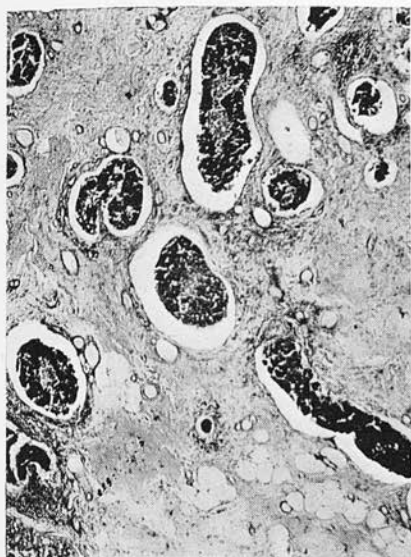


FIG. 17.—Invasion of lymphatic channels in the primary growth. (Grade II.)

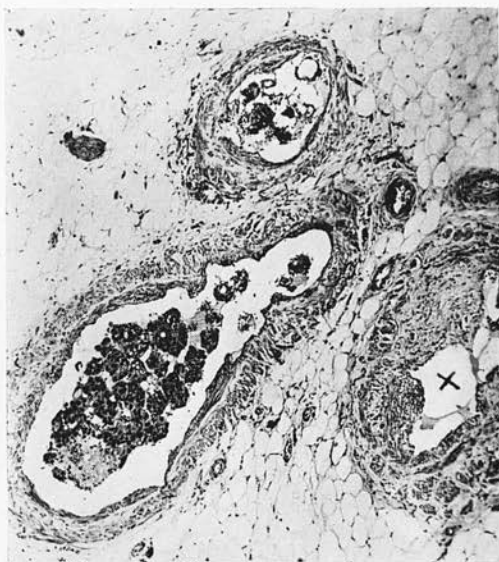


FIG. 18.—Invasion of blood vessels in fatty tissue of axilla; (X) vessel showing no invasion, but marked endophlebitis. (Grade III.)

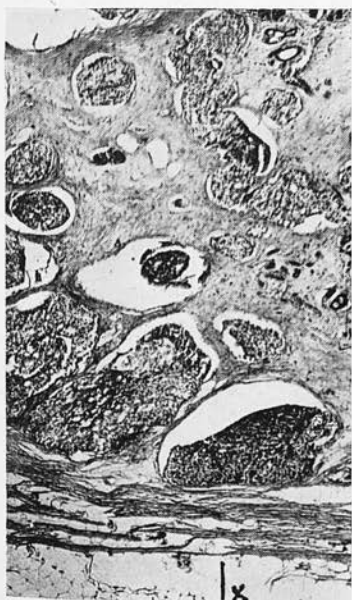


FIG. 19.—Invasion of large lymphatic channels on posterior aspect of breast tissue, adjacent to pectoral fascia (X). (Grade II.)

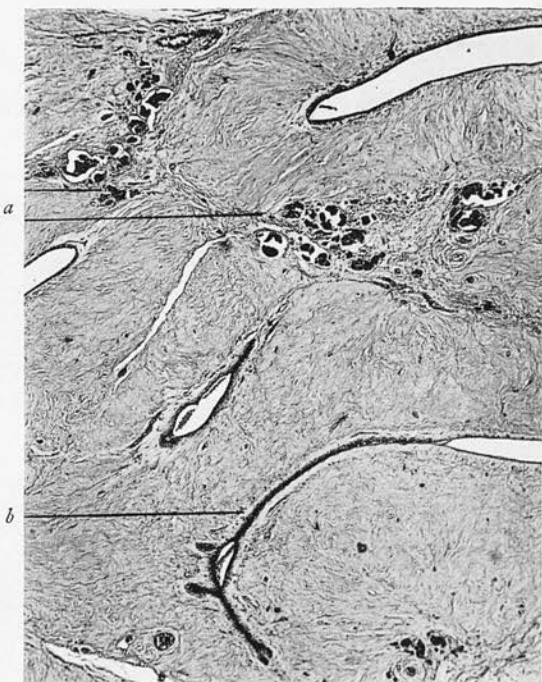


FIG. 20.—Area from a quiescent fibro-adenoma, showing lymphatic invasion from an adjacent scirrhous tumour. Note the distance of the malignant cells (a) from the duct walls, and the absence of lymphatic and blood vessels in the immediate vicinity of the glandular tissue (b). (Grade II.)



FIG. 21.—Emboli of malignant cells in lymphatics moving up towards nipple; the whole breast area is shown in Fig. 34. (Grade II.)

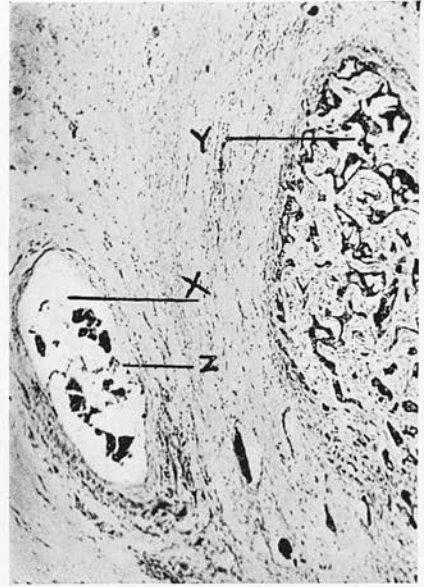


FIG. 22.—Axillary tissue, showing malignant cell emboli in an afferent lymphatic (X), with valve (Z), and adjacent invaded lymph node (Y). (Grade II.)

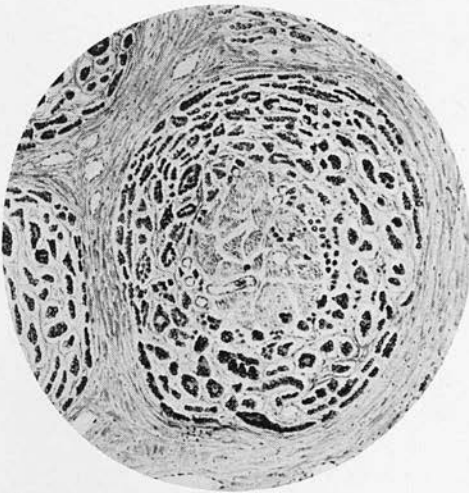


FIG. 23.—Extensive invasion of nerve trunks of brachial plexus (post-mortem material), showing malignant cells in the nerve substance and in the perineural lymphatics. (Grade III.)

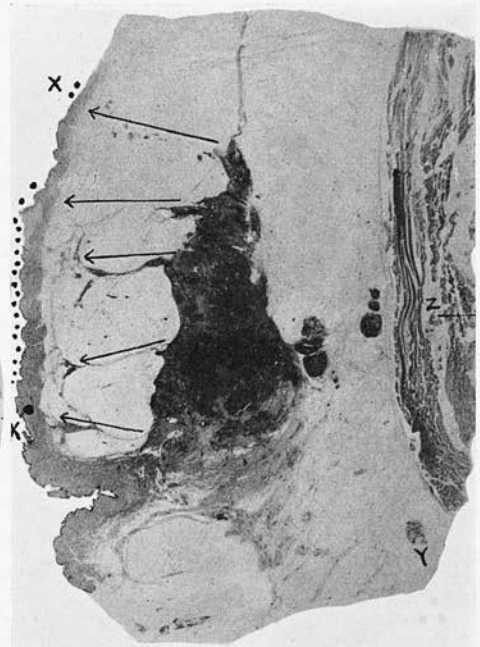


FIG. 24.—Showing extensive microscopic invasion of the dermis (X—X), a lymphatic involvement due to spread of malignant cells up Cooper's ligaments, and indicating the necessity for removal of a wide area of skin; (Z) muscle invasion. (Grade III.)

GRADE III. TUMOURS, SHOWING VARIED TYPES OF PECTORAL MUSCLE INVASION.

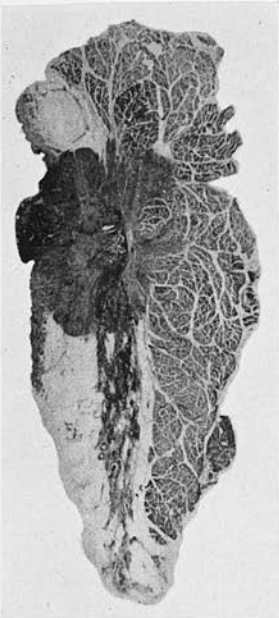


FIG. 25.—Direct extension of malignant growth from breast to deep muscle, with fixation and destruction of pectoral fibres.

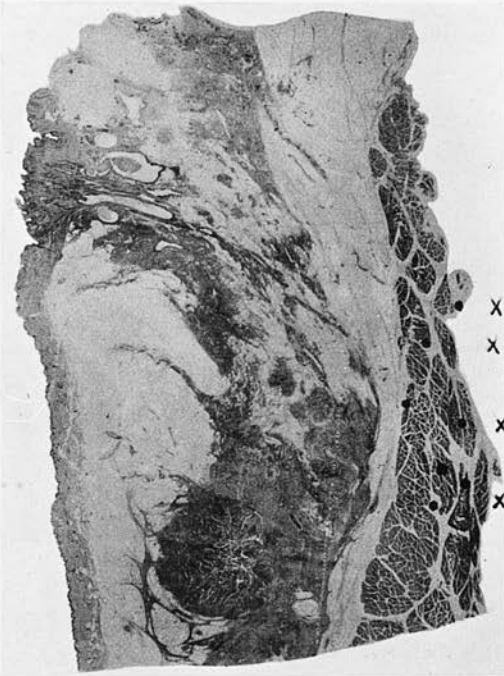


FIG. 26.—Microscopic malignant foci in deep muscle due to lymphatic spread, without clinical fixation; some of the malignant cell collections are marked (x).



FIG. 27.—Larger foci in pectoral fascia and muscle, which suggest arrest and proliferation of malignant cells round lymphatics, *i.e.* a later stage of the condition seen in Fig. 26.

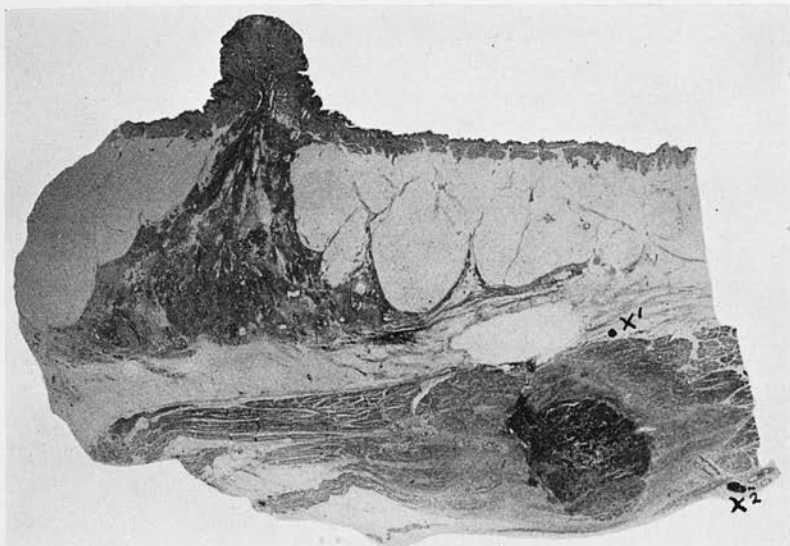


FIG. 28.—A large malignant nodule in deep muscle, with slight fixation; X¹ shows a microscopic focus in the fascia, and X² minute lymph nodes deep to muscle, not invaded.

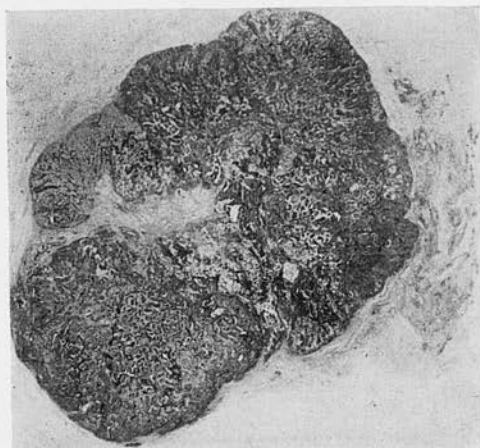


FIG. 30.—A Grade I. tumour, clinically suggested a benign growth and was shelled out, but recurred in the operation scar a year later. Radical operation then found no lymph node invasion.

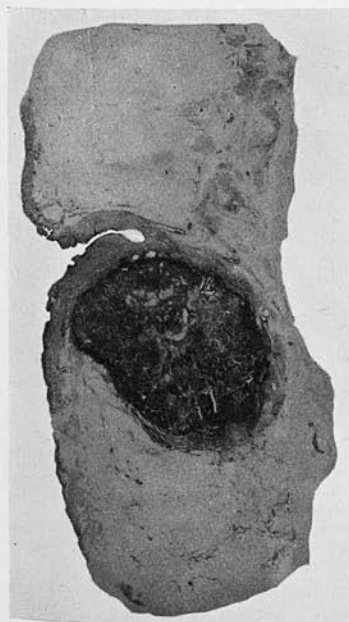


FIG. 29.—A Grade I. tumour "cured" by radical operation, when patient was 72; alive and well, with no sign of recurrence nine years later.

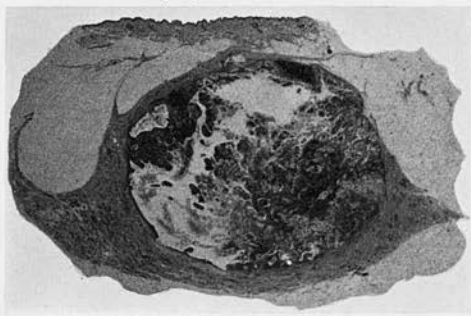


FIG. 31.—A Grade I. tumour—papillary adenocarcinoma—in a young patient; removal of segment of breast, followed by radical operation when reported malignant; lymph nodes not invaded. No later history available.

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throughout the tumour, and they have determined the percentage of the radiation falling on the skin which arrives at any given depth in the underlying tissue. This shows that, with the methods of external irradiation at present in use, it is difficult to deliver more than one and a half times the S.E.D. to the deepest part of the tumour, so that they consider it necessary to use both interstitial and external irradiation for all cases treated by irradiation alone. In suitable cases, Lee and Pack⁴⁶ now recommend the use of gold capillary tubes charged with radon, which are introduced through a trocar needle, and removed when the measured dose has been delivered. This gives a dose diffused as equally as possible over the area to be treated, and makes a high dosage possible without serious ill effects. The transfixation tubes are inserted not only into the breast, but all round it, into the axilla, and below the clavicle. Seeds are also inserted into lymph nodes which are definitely large and hard. This method of treatment is followed by marked fibrosis which may impair the movements of the arm, and must never be followed by surgery, as the wounds will heal with great difficulty.

Although the chances of success with such carefully planned treatment are certainly increased, examination of large sections, e.g. those shown in Figs. 26, 27, 28, and 34 indicates the great difficulty of ensuring that every malignant cell receives a lethal dose of irradiation. It is generally accepted that it is not the tumour only, but the whole *corpus mammae* which must be effectively irradiated, and Figs. 26 and 27 show multiple malignant foci in the muscle, which would also have to be included in the area receiving a lethal dose. It is never possible to be certain from clinical examination whether muscle is invaded, as small foci, apparently carried as emboli in lymphatics, may be present although there is no fixation to suggest that the muscle be irradiated (Figs. 26 and 28). When muscle is invaded by direct extension of the malignant growth, as shown in Fig. 25, the clinical picture is different, as fixation is inevitable. The problem of the axilla is no less difficult, as danger lies not only in the palpable lymph nodes, but in the tiny nodes, possibly no larger than a grain of rice, which may show almost complete replacement by malignant cells (see Fig. 32). The size of the lymph nodes in this section may be compared with that of the large non-malignant ones in Fig. 33, from a Grade I. tumour.

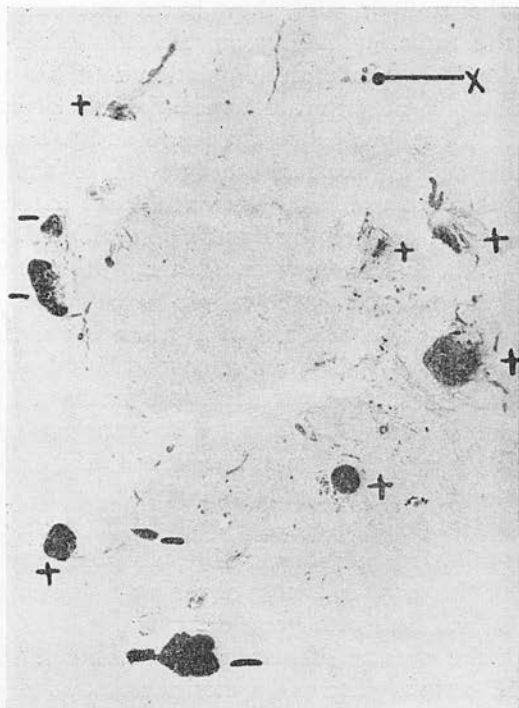


FIG. 32.—Axillary contents, with malignant (+) and non-malignant (-) lymph nodes; x shows invasion of blood vessels as well as of lymphatics. (Actual size.)



FIG. 33.—Enlarged, but non-malignant lymph nodes in axilla, in a Grade I. tumour; the node sinuses show marked endothelial proliferation. (Actual size.)

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(b) *Combination of Radium and Surgery.*—In a series of cases treated at the Memorial Hospital, pre-operative irradiation with interstitial and surface radium was followed by radical operation performed not less than six weeks after the completion of irradiation, which delivered smaller doses than those just described. This work is too recent to quote figures for comparison, but Lee and Pack⁴² believe that in well-defined



FIG. 34.—A clinically defined tumour, showing extent of malignant spread; *x*, malignant emboli in lymphatics near nipple (see Fig. 21); *y*, lymphatic invasion at opposite periphery of breast tissue.

tumours, the devitalisation of the cancer cells before operation not only in the breast, but also in the axilla, will prevent the appearance of metastases, and is therefore worth the expenditure of time and trouble and the expense.

In other clinics, when operation follows irradiation, it is usually a local mastectomy to remove a residual tumour, but radium is sometimes used at operation, as described by Handley,³⁵ Trout and Petersen,⁴⁷ and others; Freund⁴⁸ of Vienna advocates the method of large doses of radium or Roentgen rays to the unsutured wound at the time of operation.

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(c) *Roentgen Rays*.—Roentgen rays are usually thought of as a palliative treatment in inoperable cancer, but several clinics, notably those of Pfahler⁴⁹ in Philadelphia, Hummel⁵⁰ in Frankfort, and Hintze⁵¹ in Berlin, have treated a series of primary operable cancers of the breast with X-rays alone. The technique for the irradiation of primary cases does not, however, differ in essentials from that of pre- or post-operative irradiation and it is only necessary to refer briefly to the principles underlying modern therapy. The penetrating rays of short wavelength generated at 180 to 200 KV are now in general use, and the divided dose technique elaborated by Coutard,⁵² on the experimental findings of Regaud at the Fondation Curie, has found many adherents. Pfahler has developed his saturation technique on similar lines; the doses are also divided, but begin with a large dose, after which repeated doses are said to maintain a saturation of the tissues which destroys the cancer cell. Regaud considers that Pfahler's radio-physiological explanation of the phenomena is unsound, but that as the method arrived at is practically the same as that of Coutard, the results are good. Holfelder has added to the radiologists' method the tangential irradiation of the breast and surrounding tissues, which aims at delivering the full lethal dose to the chest wall through different ports, in such a way that the underlying lung is little affected, and the reservoirs of blood in the thoracic organs are not subjected to heavy irradiation.

IX. The Choice of Treatment.

Having now glanced briefly at the methods of treatment available, we are in a position to discuss which of them is most likely to modify the hopeless prognosis of the untreated case and prolong life to the normal span. In the first place, the greatest emphasis must be laid on the necessity for early treatment, and this raises the question of so educating the medical profession and the public that advice is sought as soon as any deviation from the normal is observed. Of late years there has been much propaganda, but opinion is still divided on the question of public instruction and the possibility of periodic examinations. Reimann and Safford⁵³ of Philadelphia, speaking at the International Conference on Cancer in 1928, on the influence of the educational campaign on the interval between discovery of the tumour and consultation, said that, although

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during the years from 1900 to 1927 there had been a steady decrease in the time interval before operation, there was no inflection in the curve indicating that the educational campaign begun in 1914 had had any effect. In spite of this, the decrease must be due to greater knowledge and judicious education should continue. It is most important that the public have confidence in the organisation of cancer research.

To obtain this confidence, it is necessary that each individual case should have the best treatment possible, and we must now consider the choice which we have to make when a woman with a tumour in her breast asks for advice. The responsibility is great, and in a sense is equally so, whether the patient be a woman in the prime of life who has a small tumour without palpable lymph nodes, or an unfortunate, suffering without hope the long agony of invasion of the brachial plexus. Kaplan,⁵⁴ speaking from his vast experience of the terminal stages of cancer of the breast after various forms of treatment, says, "we feel that a good many of them might better have died without the interference they had," and there is no doubt that there are cases where injudicious treatment, such as excessive irradiation, makes the end more intolerable and leaves a legacy of fear which keeps others from the early consultation which has an excellent chance of saving them from a like fate. In the important cancer clinics of Europe and America, it is usual to divide the responsibility for treatment, the patient being seen and therapy discussed by surgeon, radiologist, and pathologist. Regaud⁵⁵ points out that even if we accept surgery as the treatment of choice, the radiologist may be called upon later to treat recurrence, and if he has not had an opportunity of examining the primary lesion, he will be at a considerable disadvantage when he tries to treat the later stages. The site and degree of fixation determines the type of local recurrence, and with early metastases it is very helpful to know what was the condition before operation.

(a) *Doubtful and Early Cases.*—The desirability of biopsy in early cases has already been touched on, and this brings us to the question of the best procedure in those cases where it is impossible to make a definite clinical diagnosis of malignancy. Men with such wide experience of irradiation in the treatment of cancer as Regaud and Schintz⁵⁶ declare for immediate radical operation in Grade I. mammary cancers, but we are at once met by the necessity of deciding whether a tumour confined

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to the breast and freely movable is malignant or benign. In America the problem is more serious because of the insistence on mastectomy as a mutilating operation, but the average age of these patients is over fifty, the breast is not an essential organ, and we find it hard to believe that the psychological effect is as great as some authors maintain. We therefore believe that amputation of the breast should be done in every doubtful case. The varied clinical picture presented by Grade I. cancers is well brought out in the three tumours illustrated in Figs. 29, 30, and 31.

The condition shown in Fig. 29 suggested an advanced stage of malignant growth with indrawn nipple, in a patient aged 72 years; the nipple condition had, however, developed just after the menopause 20 years previously. The growth was fixed to the skin, but movable over the deeper tissues. A radical excision was done; large breast sections showed no involvement of the dermis or epidermis by the growth, which suggested origin as a papillary tumour in a cystic duct, with beginning infiltration of the surrounding connective tissues. There was no evidence of lymphatic invasion in the mammary area and the axillary nodes examined were not involved. This patient was seen nine years later; the local condition was satisfactory, with no sign of recurrence, and the patient's general health was good for her age, then 81.

The tumour illustrated in Fig. 30 was removed from a patient of 70, who came to hospital because of severe abdominal symptoms associated with a gastric ulcer. During examination a nodule was found in the breast, which she said had been present for two years but was not increasing in size. The nodule was smooth in outline and freely movable under the skin and on the deeper structures; it was diagnosed as an adenoma and shelled out easily through an overlying incision. Microscopically, it proved to be an encephaloid type of malignant growth, suggesting origin in papillary formations in one or more cysts. There were several areas of mucoid degeneration or "colloid cancer." This patient was re-admitted to hospital twelve months later, with a lump in the breast of a month's duration, involving the scar of the previous operation, but still without evidence of spread to the axilla. Radical excision was then performed, and no involvement of lymph nodes was found at operation or by histological examination. No further notes of this case are available, but it is significant that in this Grade I. tumour, though there was recurrence in the scar due to inadequate treatment of the primary growth, the nodes were still free a year later.

The third Grade I. tumour, illustrated in Fig. 31, was in a patient

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of 37 years. The lump was noticed three months previous to operation, when her youngest child, whom she had not nursed, was 15 months old. The growth was freely movable, without evidence of axillary involvement; malignancy was not suspected and the involved segment of the breast alone was removed. Histological examination revealed a papillary adeno-carcinoma, of a very malignant cell type, with giant cells and numerous mitoses. As in the two cases described above, there was early evidence of malignant infiltration beyond the cyst walls, but no further spread into tissues or lymphatic channels. The radical operation was done shortly after and the axilla found free from malignant growth.

It happens that these three Grade I. tumours all suggest origin in a papillary type of growth in one or more cysts, a condition favouring much proliferation and increase in size of the tumour before actual spread into the surrounding tissues or invasion of lymphatics occurs. Large, cellular tumours of medullary type may thus be removed at the stage we have defined as histological Grade I., a fact which can explain why statistics show that prognosis in these growths is more favourable than in the scirrhus form, where invasion is earlier and extensive.

(b) *More Advanced Cases.*—The majority of cases of cancer of the breast, as already noted, have reached, when first seen, a stage at which it is no longer possible to be reasonably certain that all the tissues invaded by malignant cells can be removed by operation, and we must consider whether better results may not be obtained by one of the other methods of treatment which have been described. It is quite impossible to lay down any rules, and a great deal of work remains to be done before the questions which we have raised can be answered. Tables have been prepared which include figures from most of the important clinics for purposes of comparison. None of the figures are absolute; so few clinics give the number of patients actually applying for treatment that this is not possible, but they are reasonably comparable, being percentages of the number treated alive five years later. Only primary cancers are included and in most cases only those confirmed by histological examination. This does not apply to cases treated by irradiation only. It is not suggested that a five-year survival can be regarded as a cure; recurrences many years later make it difficult to regard any case of cancer of the breast as cured, but three years is too short a period, and ten years, although operative figures are available, gives no chance of comparing the results of

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modern radiological technique, so that five-year figures give the best basis for comparison.

Results of Radical Operation for Cancer of the Breast. 5-Year Survivals.

Reported by	Clinic.	Group I Alive.	Group II Alive.	Group III Alive.	Total Alive out of all Cases Traced.
Lane-Clayton . .	English Hospitals	241/363	155/530	87/425	562/1504 37%
Leeds Cancer Com- mittee	Leeds Hospitals	63/74	18/97	21/115	102/286 35.7%
White, W. C. . .	Roosevelt Hospital, N.Y.	39/55	19/97		58/152 38%
Harrington . . .	Mayo Clinic	417/656	292/1203		709/1859 38%
American College of Surgeons . .	9 Hospitals, Eastern States	59/103	43/305		102/408 25%
Klingelstein . .	Mount Sinai, N.Y.	11/16	6/41		15/57 28%
Lewis and Rienhoff	Johns Hopkins	19%*	81%*		156/502 31%
Greenough and Simmonds	Massachusetts General Hosp.	15%*	85%*		83/320 26.5%
Meier	Aarau	6/8	20/125		26/171 14.6%
Hoffmann	Heidelberg	24/40	51/209		75/249 30%
Anschütz	Kiel	100%†	33%†	12.5%†	39/107 36.4%
					1927/5615 34.3%

* = Percentage of cases treated (not survivals).

† = Percentage of survival rate for the group.

Results of Radical Operation with Post-operative Radiation in Cancer of the Breast. 5-Year Survivals.

Reported by	Clinic.	Group I.	Group II.	Group III.	Total Alive out of all Cases Traced.
Webster	Middlesex Hospital	45 cases	...	127 cases	77/182 42%
Pfahler 1902-1927 .	Philadelphia	54 "	...	264 "	171/318 52%
Schreiner	Buffalo	30/46	10/43	0/0	40/89 44%
Portman	Cleveland	7 cases	64 cases	32 cases	52/103 50%
Schmitz	Chicago	18/20	14/51	0/0	32/71 45%
Adair, 1916-1926 .	Memorial Hospital, N.Y.	49/137		0/0	49/137 38%
Billich	Rostock	31/40	32/71	9/91	72/202 35%
Wassink	Holland	28/30	...	23/102	51/132 38%
Westermarck . . .	Radium-hemmet	14/20	33/100	5/42	52/162 32%
Hummel (Holfelder)	Frankfurt	8/8	54/82	0/0	62/90 69%
Hintze	Berlin Biersche Klinik	11 cases	...	172 cases	97/183 53%
Wintz	Munich	35/66	...	6/50	41/116 36%
					793/1785 44%

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The number of clinics where a series of patients has been treated by irradiation only is comparatively small, so that there are not enough figures available to draw up a table for comparison, but such figures as have been published are of great interest. Pfahler⁴⁹ treated 50 primary operable cases by irradiation only and of these 41, or 82 per cent., were alive five years later, while of 158 inoperable cases, 48, or 30 per cent., lived five years, a very striking result. From the Memorial Hospital, New York, Adair⁵⁷ reports 8 out of 37 advanced cases alive for five years, but the new technique of Lee and Pack has only been in use since 1930, and the only information they have been able to give so far is that of the 15 cases, 8 operable and 7 inoperable, treated during that year, all were alive and free from symptoms in November 1931. The same author reports a series of 137 cases treated by operation with radon implants to the axilla, supra- and infra- clavicular nodes at the same time; of these, 49, or 40.6 per cent., lived five years. Schreiner⁵⁸ treated 14 operable and 159 inoperable cases by irradiation alone. Of the first group, 6, and of the second, 12 lived for over five years, and he is emphatic regarding the beneficial effect of the treatment both on length of life and the severity of symptoms.

The report of the Medical Research Council for 1932,⁶ which includes the figures from Keynes' Clinic at St Bartholomew's Hospital, gives 26 primary cases treated over five years, of which 9 are alive. During more recent years, the numbers have increased and 170 cases were treated during 1927 and 1928, of which 91 are alive. Of these, Keynes treated 46, of which 23 are alive.

In general, these figures are similar to the better operative results, and although it may be argued that in some cases the diagnosis of malignancy may have been incorrect, it seems probable that they also include a number of cases in which no operation could have been attempted.

(c) *Late Cases.*—With these results before us, we are in a position to consider whether it is possible to increase the percentage of survivals in the more advanced cases. If, as we have already stated, operation is to be recommended when the disease appears to be limited to the breast, we are bound to include a number of cases where histological examination reveals invasion of the axillary tissues and a good prognosis can no longer be given, but we are still left with the cases

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where clinical examination finds definite signs of disease in the axilla. If we operate on these cases, we are almost certain at one point or another to cut through a line of malignant spread, as some of the whole-breast sections show very clearly, and various suggestions have been made how this can be avoided. In many clinics, treatment of such cases begins with irradiation, either with surface radium, used at a distance of 4 or 5 cm., or deep X-ray therapy, and according to the response obtained, this is followed either by operation or by interstitial irradiation, with further surface therapy later. It is interesting to note here that the skin appears to be more tolerant to a mixed therapy by radium and X-rays than it would be to the same doses, measured in energy received, of either of these used alone. The question of relying on irradiation only for these cases is at present so controversial that many surgeons hesitate to recommend it, except in cases where no other treatment is possible, but the method is a new one and has been much abused, and it would be unfortunate were we to allow initial failures to close a path along which progress may still be made. The biological effects of rays of short-wave length when absorbed in the living cell are still far from certain. M'Lennan⁵⁹ states there had been a tendency to take the view that there was practically little advantage in the use of radium, and that radiations at a voltage of 370 KV were amply sufficient to treat all cases of cancer, but he concurred with the opinion of many workers in this country and in America that further biological experiment with X-radiations produced at high voltages is necessary before any opinion regarding the relative clinical value of radium can be helpful. The important fact for us is that we are dealing with a science which is still in its infancy, every case treated by irradiation is an experiment, and it is only by collective research in large centres that we can hope to obtain data which may serve as guide for those who look to the medical schools for progress in the treatment of disease. The possibilities of radium at a distance must be investigated, and more accurate methods of calculating dosage are now available to allow us to combine this with interstitial irradiation or with surgery, provided that it is remembered that irradiated tissues heal with greater difficulty than do normal tissues. On the other hand, the great improvement obtained in certain clinics when post-operative prophylactic Roentgen radiation is a routine treatment, gives another definite

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line of research which does not negative the radical surgery often felt to be essential. It would not be wise to be dogmatic about the figures we show, as the selection of cases may always be the reason for improved results, but they are certainly suggestive, and in other situations, such as the larynx (Coutard ⁵²) and the tonsil (Berven ⁶⁰) five-year survivals have been obtained in cases admittedly hopeless before irradiation was introduced. With these facts before him, the surgeon cannot afford to disregard irradiation in the treatment of those patients whose disease he knows to have passed the limits of the breast.

(d) *Local Recurrence*.—It is also important that radium may help in the treatment of local recurrence and nodules in the chest wall; even those involving bone in these areas often do well. Pfahler has 81/408 cases of recurrence alive for five years after treatment of the recurrence, *i.e.* 19 per cent. Haas ⁶¹ has 10/179, and Radiumhemmet ⁶⁰ 14/83. These small figures could be increased by taking similar numbers from other clinics, as many recurrences have to be treated, but these are enough to show that prognosis in recurrence, though much worse, is not yet hopeless.

(e) *Distant Metastases*.—Distant metastases are another and more serious problem. Pfahler, Adair and Berven (*loc. cit.*) all believe that it is worth while to treat bone lesions by X-rays, and describe the formation of new bone after irradiation and complete relief of pain. From this it would seem that palliation ought to be attempted when a lesion in bone is detected in a patient whose general condition is still good. Metastases in the thorax respond, to some extent, to X-ray treatment, but the value of this still appears to be doubtful. For metastases in the liver and peritoneal cavity and for infiltration causing oedema of the arm or brachial neuritis there is little to be done. Brachial neuritis may be so severe that Adair advises cordotomy. It must, however, be remembered that radium to the apex of the axilla and deep in the supraclavicular region may also cause neuritis; it is not so agonising when fibrosis following radium is the cause, but it is always a serious complication.

X. Summary.

1. The importance for prognosis in mammary cancer of the absence or presence of axillary lymph node invasion is brought out by a consideration of percentage survivals in the literature.

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This finding draws a dividing line between favourable and unfavourable cases, and apparently outweighs all other data, such as duration and type of growth, age at operation, etc.

2. The clinical grading of mammary cancers on this basis of extension of growth, checked where possible by histological examination, would seem necessary in all attempts to estimate prognosis and evaluate treatment.

3. Various methods of histological grading described in the literature are discussed, with special reference to such appearances as differentiation and anaplasia, fibrosis and lymphocytic cell infiltration.

4. A combination of anatomical (topographical) and cytological features is suggested as the basis of histological grading, with emphasis on the *position* rather than the *type* of the malignant cells. This method combines clinical and histological findings as interdependent factors influencing prognosis.

5. In all cases where there is a tumour in the breast and doubt exists regarding malignancy, simple mastectomy is advisable. Various procedures to lessen the error in clinical diagnosis are discussed.

6. Grade I. tumours, that is, early growths without axillary involvement, show a high percentage of survival, and possibly permanent cure, with radical operation, which would therefore appear the treatment of choice at this stage of the disease.

7. Cases at all later stages of growth show very low survival rates when treated by surgery only. Some supplementary therapy should therefore be considered in these grades.

8. Published figures suggest that post-operative irradiation with Roentgen rays definitely improves the chance of survival; the methods of applying radium after operation are so varied that no estimate of their value is yet possible, but recent figures are encouraging.

9. Available statistics show that treatment by gamma radiations alone gives results similar to those by surgery, but the numbers so far are very small.

10. The treatment of local recurrence and metastases is discussed.

Prognosis in Mammary Carcinoma

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THE DIAGNOSIS AND TREATMENT OF
DOUBTFUL MAMMARY TUMOURS

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THE DIAGNOSIS AND TREATMENT OF DOUBTFUL MAMMARY TUMOURS

ARISING from our work on the pathological examination of tumours removed from the breast, we have paid special attention to the analysis of a number of operations performed on patients with breast tumours whose nature could not be determined in advance of operation. Where the condition is definitely malignant, treatment is urgent and is more or less determined by the character and extent of the tumour, the experience of the surgeon, and the facilities available. At the other end of the scale are those cases—probably a large number, though unrecorded—with temporary and possibly painful mammary enlargement usually associated with menstruation or the menopause. These rarely call for surgical interference and, in most cases, are not referred to a surgeon. Between these two groups—the definitely malignant growths and the temporary hyperplasias—lie, from the diagnostic point of view, the benign tumours and the group generally referred to as doubtful, borderline, or suspicious tumours, in which there is insufficient evidence from the history or the clinical findings to justify immediate treatment for carcinoma. Procedure in these clinically doubtful cases ranges from local excision of the suspicious lump under local anaesthesia in the surgical out-patient department to radical operation; in the latter case, the patient is occasionally even denied the benefit of the doubt, as operation begins with axillary dissection. The French school, and to a less extent the American, seem over-anxious to avoid what they call “unnecessary mutilation” and frequently advocate local resection of a suspected area, on the basis that simple amputation is too much for a benign growth, and too little for a malignant one. It is difficult to gather what is the procedure in this country, or to what extent biopsy or frozen section is used as an aid to diagnosis. The clinical diagnostic error recorded in the literature in doubtful tumours is considerable and it is likely that many doubtful groups cannot be recognised before operation. The surgeon who has to make the decision as to the type of operation in doubtful cases is faced with a grave responsibility. If he decide to do a radical operation for a condition which turns out

to be benign or a local excision of one which proves biologically to be definitely malignant, he makes a grave mistake in treatment. The divergence of view in the literature is illustrated by such recent papers as Wainwright's¹ and Bloch and Wechsler's²; Bloodgood, speaking of cystic disease, an important group of the doubtful lesions, thinks that, with rare exceptions, simple mastectomy is illogical.³ One of the few papers we have noted which advocates simple amputation (for duct papilloma) is that by Lepper, Baker, and Hartog in this journal.⁴ As an extreme example of the lengths to which exploratory interference can be carried, one may quote from Prof. Herzler's recently published monograph on the surgical pathology of the breast. This author, in the diagnosis of what he terms preclinical carcinoma, advocates "making slices a quarter of an inch thick through any suspicious area . . . not forgetting the part that extends towards the axilla. When extensive exploration fails to disclose a malignant area, the tissue so mutilated must be resected. If the nipple is preserved, a fat flap is transplanted . . . and the breast sufficiently restored so that no notable deformity results. When in the exploration nothing can be found in the breast, the axilla should be explored." In a number of the two-stage operation cases we are studying, the first operation was a local tumour excision, though the tissue radically removed soon after showed invasion of the axillary lymph nodes.

In view of these differences in precept as well as in practice, we have tried from our pathological material to find a guide to procedure that might not be too drastic if the lesion turn out to be benign and not too dangerous if it prove malignant. In order to make our conclusions clear, it is necessary to refer to diagnosis as well as to treatment.

Diagnosis

These benign and doubtful mammary lesions, which give rise to considerable difficulty in diagnosis, may conveniently be divided into the following groups: (1) benign tumours; (2) chronic infections; (3) cystic changes; (4) early carcinoma; (5) acute carcinoma, simulating infection; (6) pregnancy and lactation tumours; and (7) fat necrosis.

BENIGN TUMOURS

The important forms are the fibro-epithelial tumours, which include two types, (a) the fibro-adenomata, and (b) the papillomata, though inter-

mediate forms, such as those which Ewing describes as papillary intracystic fibroadenomata may occur when cystic changes are also present.

Fibroadenomata.—In young subjects the circumscribed fibroadenoma presents little difficulty; the diffuse form, fibroadenomatosis, may be bilateral and is usually a temporary overgrowth which responds to conservative treatment. In older patients the fibroadenomata give greater difficulty in diagnosis, for although the single tumour in an otherwise unaffected breast is clinically and histologically similar to that occurring at the earlier ages, these tumours may be multiple, they may be associated with cyst formation, and they may coexist with undetected malignancy in the surrounding tissue.

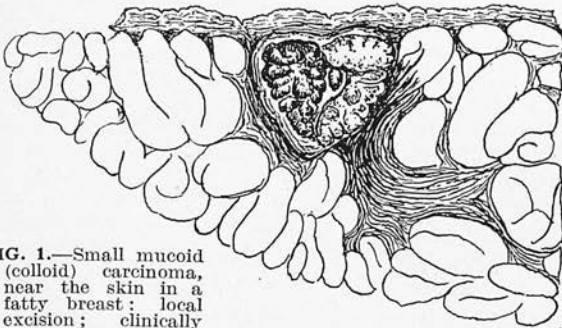


FIG. 1.—Small mucoid (colloid) carcinoma, near the skin in a fatty breast: local excision; clinically fibroadenoma.

The accepted signs of a fibroadenoma, mobility and encapsulation, do not necessarily supply a definite diagnosis in these older patients, for Luff⁵ found that 51.2 per cent. of a series of 1400 malignant growths showed no fixation, and our material provides a number of instances in which a movable, apparently or actually encapsulated carcinoma has been excised on the assumption of its benign character (Fig. 1), or in which the radical operation has been done for a large fibroadenoma (Fig. 2). Without entering on a consideration of the meaning of the term "precancerous," we may state that we are unable to agree with the view that fibroadenomata exhibit any greater tendency to become cancerous than any other portion of the glandular tissue of the breast. These tumours apparently always originate in *adenosis*—that is, in an increase of glandular tissue of normal or exaggerated physiological type, with a coincident fibroblastic activity, and

although all varieties of tumour structure occur, ranging from adenoma to almost pure fibroma, according to the predominance of one or other tissue element, we have encountered no instance of malignant development in the *epithelial* content of such growths. Many of Bloodgood's borderline tumours are adenomatous growths,⁶ and though the abundance and complexity of the glandular tissue in these cases led, in many instances, to the diagnosis of a precancerous lesion or even adenocarcinoma, his experience that none of these cases, followed for many years, had later trouble, even after incomplete operation, supports our contention that they are essentially benign. On the very rare occasions when a fibroadenoma becomes malignant, it forms a sarcoma, but the few cases in our series suggest that when this happens, the growth soon gives definite clinical evidence of malignant development. The term precancerous would need justification if applied to mammary lesions. It has often been pointed out that we can say of no non-malignant mammary condition that it will certainly become carcinoma; in view of the high incidence of malignant development in the breast, it is, however, equally difficult to be certain that it will not become carcinoma. The examination of 400 benign and over 1000 malignant breast tumours, many at an early stage of development and cut in whole breast sections, has nevertheless provided no evidence that carcinoma originates in an increase of glandular structures which we call adenosis, and which we do not regard as "precancerous." This question has been discussed in an earlier study by one of us,¹ where the position was maintained that carcinoma in the breast is the end-stage of a process which develops not as an adenosis (Fig. 3) but as an epitheliosis (Fig. 4), or epithelial cell proliferation within glandular structures, which results in the production of intraductal malignant cells, with later invasion and dissemination. This appears to us a fundamental point in the histological diagnosis of doubtful mammary tumours. When proliferation results in adenosis, or as is more usual, in fibroadenosis or fibroadenoma, there is no likelihood of carcinoma, but where epitheliosis, of papillary or "solid" type, is much in evidence, the eventual outcome cannot be predicted, if the tissue is not removed. In older subjects the two types of epithelial cell activity coexist in the same tissue without giving diagnostic signs.

Papillomata.—The cell proliferation in these tumours is more definitely an epitheliosis and the

outcome is uncertain, as it is in other situations. The formation of atrophic cysts of Bloodgood's "blue-dome" type, with the wall entirely denuded or lined only by scanty degenerating eosinophil cells, the remains of an epithelial overgrowth which is frequently papillary in structure, indicates that proliferation of this character has taken place and has retrogressed, but apart from this type, papillomata in general should be regarded with suspicion, and in many cases are probably precancerous in the ordinary acceptance of that term. They may occur singly, usually in the larger ducts, but, as Cheatle and Cutler have demonstrated,⁸ they are often multiple, and may be so small as to be macroscopically undetectable. The larger forms usually

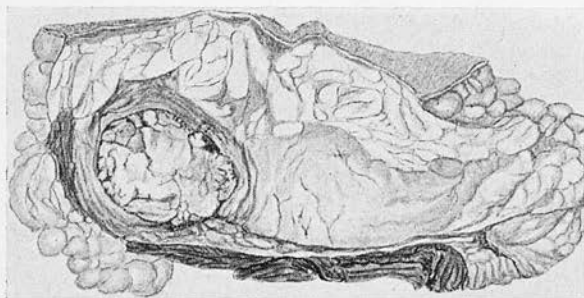


FIG. 2.—Fibroadenoma—no suggestion of malignancy.

produce discharge from the nipple, but this is not in itself a diagnostic sign, nor, if present, does it necessarily help to localise them. Examination of many cellular ("encephaloid") carcinomata in large and small sections, especially at an early stage before dissemination, suggests that a large proportion of these mammary tumours began as papillary formations.

CHRONIC INFECTIONS.—CYSTIC CHANGES

When the chronic condition is the late stage of an earlier acute lactation or pregnancy mastitis which resolved without incision, the history is helpful, but a hard, more or less circumscribed tumour with fixation in breast tissue and possibly nipple retraction may give a clinical picture closely resembling carcinoma (Fig. 5), and may also be found in nulliparous patients. The axillary lymph nodes are usually palpable, though softer than if invaded by

malignant growth. Chronic infection of the breast may also be of tuberculous or syphilitic origin, but both conditions are very rare.

Breasts with *cystic changes* cause much uncertainty in diagnosis. These cases come under observation most frequently at an age-period when the possibility of malignant development must be borne in mind, and should they coexist, a causal connexion is often and unjustifiably assumed between the cysts and the carcinoma. The atrophic cyst of the blue-dome type may be single and of considerable size, and not be noticed for a long time, but its presence does not prevent independent carcinoma appearing in another part of the breast. It is this possibility which lies behind the uneasiness with which cystic disease is regarded. In some cases the single simple cyst can be diagnosed by palpation, especially in thin elderly subjects, but the irregularly thickened, "lumpy" breast, with smaller multiple atrophic cysts, may also contain an undetected early cancerous growth.

EARLY CARCINOMA

There are no diagnostic signs indicating an early malignant change, which may equally well supervene on a previously benign tumour of longer or shorter duration as in an apparently normal breast. The wide variation in the physiological structure of mammary tissue at "the cancer age" has also to be taken into account. As MacCarty has stated,⁹ early carcinomata are discovered, not because the surgeon actually detected them, but because he had in mind the probability of their presence and removed the mamma on suspicion. The signs associated with malignant growth—nipple retraction, fixation, lack of definition of the tumour area—are, in general, evidence of extensive malignant spread, but, on the other hand, are not necessarily evidence of malignancy at all. There are various types of early carcinoma: (a) early cancerous development in a benign papilloma; (b) early duct cancer, called by Ewing diffuse duct cancer; (c) a very small carcinoma in a breast otherwise apparently normal on palpation (Fig. 1); (d) early carcinoma associated with localised or diffuse cystic changes; and (e) malignant tumours of the skin overlying the breast with secondary invasion of the mammary tissue. We give two examples illustrative of difficulties which arise.

Mrs. A. B., aged 49; enlargement of both breasts, more evident on one side, with intermittent pain and tender-

ness. Simple mastectomy on the more suspicious breast. Microscopically multiple atrophic cyst formation with some adenosis; in one area a small carcinoma originating in epitheliosis in a group of small ducts with early invasion of the surrounding stroma. The patient is well nine years after treatment.

Mrs. C. D., aged 48; lump in the breast present for over a year with steady growth, recent ulceration. Clinically an indurated area in the breast, underlying and firmly attached to the ulcer. Radical operation; several enlarged nodes in axilla. Microscopically a basal-cell carcinoma, without node invasion. Patient alive and

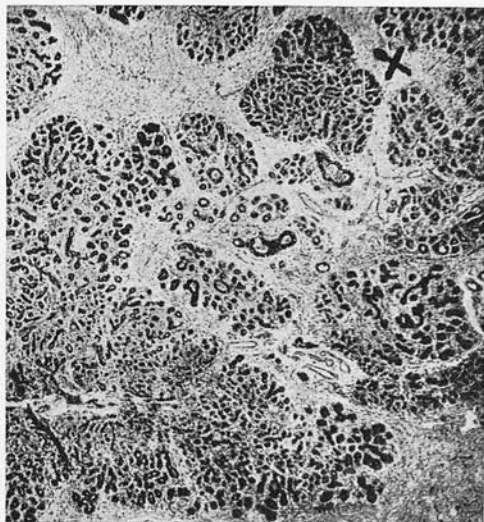


FIG. 3.—Adenosis. ($\times 40$.)

well four years later. This was a skin tumour with secondary involvement of the breast.

ACUTE CARCINOMA SIMULATING INFECTION

This is a rare form of malignant growth. It is usually diffuse—a carcinomatosis—and from the few cases in our experience is exceptionally difficult to diagnose before treatment. A carefully considered history will, in some cases, reduce the likelihood of error, if the possibility of malignancy is borne in mind. An infective lesion of the breast is rare apart from pregnancy and lactation, and the local heat of the tumour is apparently due to the marked

congestion of the malignant tissue and not associated with a rise of body temperature. The following is an instructive case.

Miss E. F., aged 39; diffuse enlargement of right breast for five months; treated for three months as inflammatory condition, then incised by family doctor, no pus; surgeon called in consultation. Biopsy showed malignancy. On admission breast enlarged, hard, very prominent, hot and absolutely fixed; a few palpable axillary nodes. Treated by surface irradiation, which made radical operation possible. Whole breast sections showed malignant development in the whole of the mammary area from skin to deep muscle, both of which were invaded (Fig. 6); one axillary node involved.

PREGNANCY AND LACTATION TUMOURS.—FAT NECROSIS

Pregnancy and lactation tumours are also rare. They are usually missed in their early stages and, according to most authorities, are invariably fatal with surgical treatment. Some of the cases we have examined in large sections suggest that a small lesion, possibly a benign tumour, was present prior to pregnancy, as the malignant area showed no functional hyperplasia; but, in all cases, mammary enlargement associated with physiological hyperplasia and function is likely to conceal the early stages of cancerous development. We cite one of a number of cases in our collection.

Mrs. G. H., aged 37; stationary tumour in breast for six years. Immediately after birth of child, very rapid growth; seen by surgeon six weeks after confinement, radical operation, death within six months. Whole breast sections showed a very malignant growth, invading and destroying the lactating tissue, with lymphatic and blood-vessel invasion and axillary involvement. At the periphery was a small malignant papilloma, derived apparently from the stationary tumour, and possibly the source of the invasive growth.

Fat necrosis is another rare mammary lesion of which we have little experience. Clinical diagnosis of this lesion demands histological examination to rule out the more serious condition.

Treatment

Before deciding on the extent of treatment necessary in these benign and doubtful mammary tumours, the surgeon will consider various points in the history—age, duration of the growth, previous pregnancy and lactation, presence or absence of pain, discharge from the nipple, infection—and in the examination—mobility or fixation, fluctuation, size, consistency,

and definition of the lump, nipple retraction, and the condition of the axillary lymph nodes. None of these signs or symptoms is in itself diagnostic, but a careful evaluation of each may provide a signpost which points to a benign or malignant growth. Age is an important factor, for while we agree with

Cheatle (loc. cit.) that, with the exception of women under 25 years, the age of the patient should carry little weight in the differential diagnosis of mammary carcinoma, we consider that no tumour of the breast in a woman over 35 years can be regarded as certainly

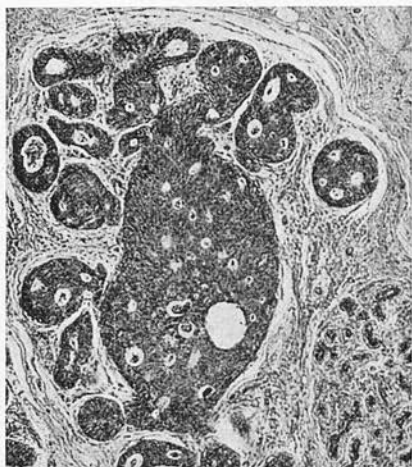


FIG. 4.—Epitheliosis. ($\times 40$.)

benign. In some clinics such aids to diagnosis as biopsy, cellular smears, or frozen sections are used, and others lay stress on transillumination or X ray examination. Our material provides no data on these methods, except local removal of tumours, and one or two instances of deliberate biopsy.

The surgeon who decides to operate on a doubtful tumour has several roads open to him—namely, local excision of the tumour, simple mastectomy, and radical operation.

LOCAL EXCISION

This is adequate treatment for fibroadenoma in a young patient and possibly in certain chronic infections. Partial resection is also advocated by some surgeons for duct papilloma in the main ducts, but there is too great likelihood that these are multiple, and they are not easily located. The danger of inadequate tissue removal in older patients is well brought out in a considerable number of doubtful cases in our series, and we prefer not to resect the tumour in order to preserve mammary tissue which

in most of these patients is atrophic and incapable of further function. Mastectomy should be done in these older patients. If the resected tissue prove to be malignant on histological examination, further treatment is urgent. The following cases are instructive.

Miss I. J., aged 33; swelling in breast for two years, increasing in size; some pain and occasional yellow discharge from nipple last few months. Clinically, hard, irregular swelling medial to nipple, no fixation, nothing in axilla. Local excision of nodule showed complex papillary growth in ducts near nipple. Sections showed proliferation in layers of an atypical cell, very suggestive of malignancy with invasion. Radical operation eight days after local excision. Malignant nature of growth proved by recurrence in supraclavicular nodes same side 13 months later; area treated by beam (bomb) therapy, and nodes became softer and smaller, but were still palpable four months later.

In this case it is possible that dissemination to the supraclavicular nodes had occurred before local excision, but if not, it is likely that spread was hastened by incision and manipulation at removal of the nodule and, in that case, might have been avoided by primary simple mastectomy.

Mrs. K. L., aged 50. Lump, clinically fibroadenoma, removed from breast; no microscopical examination. Two months later two nodules in scar; two months later nodules showed signs of ulcerating and nodes palpable in axilla. Radical operation attempted, but numerous hard nodes in axilla and along internal mammary artery out of reach. Death six months after this—i.e., ten months after excision of primary tumour.

SIMPLE MASTECTOMY

This procedure is advisable in all cases where doubt exists in the mind of the surgeon that malignancy is present, with the two exceptions already mentioned, acute carcinoma and pregnancy and lactation tumours, where surgical interference should be limited to biopsy for diagnosis by electric cautery. With these exceptions, removal of the mamma and examination of the gross pathology of the tissue will solve the problem of diagnosis in a large proportion of these doubtful cases. Should the condition prove malignant, the radical operation can at once be proceeded with; if benign, nothing further is necessary. If the question cannot be decided by the appearance of the tissue, a choice must be made between the completion of the radical operation, a two-stage operation if microscopical examination confirm the

suspicion of malignancy, or irradiation of the mammary area without further surgery. It has been advocated that should carcinoma be present, the radical operation forms a better block dissection if the axilla be cleared first, but this procedure rules out diagnosis by examination of the cut surface of the amputated mamma. Even in cases of obvious malignancy, when the method is permissible, it seems to have no special advantage. Contrary to most opinion in the literature, the cases of two-stage operation in our series indicate no danger in this method if radical removal be not delayed. We have been able to follow cases treated by two-stage operation for three and more years. Lane-Clayton's

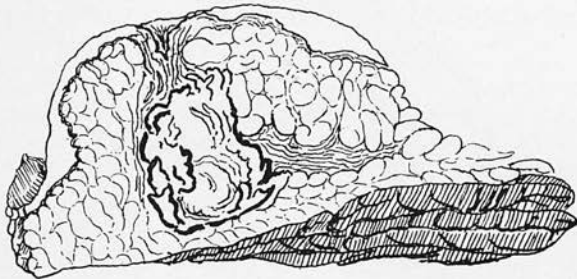


FIG. 5.—Chronic abscess, clinically malignant; radical operation.

figures show a five year survival-rate of 81·8 per cent. in cases treated by two-stage operation compared with 74·3 per cent. for radical operation.¹⁰ This result is to be expected, since cases so treated are clinically so early that if time be not given for dissemination they remain at grade I. The two-stage procedure has, however, obvious practical difficulties, and our experience suggests that the necessity for it will be restricted to a very small number of cases if the morbid anatomy of the mastectomy material be carefully examined. The value of mastectomy is shown in the following cases.

Miss M. N., aged 33; lump in breast three months' duration; examination showed both breasts unusually large and full with prominent nipples; tumour in one breast upper outer quadrant and axillary tail, irregular and diffuse. Age of patient and bilateral enlargement suggested benign condition. Mastectomy of breast with tumour, which on section obviously malignant; radical operation completed at once. Microscopically duct cancer with early tissue invasion; axillary nodes not

involved. Alive with no signs of disease two years and three months later.

Mrs. O. P., aged 47, para-2, both nursed three months ; no previous trouble. Lump in breast five or six months, hard nodule size of marble, upper inner quadrant, slight attachment to nipple, which very slightly indrawn ; no palpable axillary nodes. Mastectomy showed large cyst under tension ; microscopically atrophic in character with thick fibrous wall ; some adenosis in surrounding tissue. No sign of further trouble one year and ten months later.

Mastectomy with axillary dissection is possible, but not relevant to our argument.



FIG. 6.—Acute carcinoma simulating infection (see history in text, Miss E. F., aged 39).

RADICAL OPERATION

Present statistics indicate that the highest survival-rates in mammary carcinoma are obtained in cases where the radical operation is performed for early tumours. If, therefore, examination of the gross pathology after mastectomy for a doubtful tumour show that the condition is malignant, the radical operation should at once be proceeded with. This is the accepted treatment for early carcinoma at most clinics, and we need not cite examples. The following cases illustrate the radical removal of the breast for a non-malignant growth, a not-infrequent procedure in our series.

Mrs. Q. R., aged 55 ; lump in right breast for three weeks with slight discharge from nipple ; clinically two hard areas in this breast, no fixation ; one hard small irregular ill-defined lump in left breast with slight fixation to skin but not to deep tissues ; a palpable node in left axilla. Bilateral radical operation with two months interval. Neither breast microscopically malignant ;

patient shows no sign of disease $2\frac{1}{2}$ years later, but there is very marked limitation of movement at both shoulders.

Miss S. T., aged 49; painful thickenings in breast for three weeks; two lumps palpated, one suspicious, hard, and attached to skin. Radical operation; several enlarged nodes in axilla. Large and small sections showed no malignancy in breast or axillary tissue, but cystic disease and some fibroadenosis. Patient alive with no sign of disease three years later.

SURGERY AND IRRADIATION

We have discussed in this paper the surgical treatment of doubtful tumours of the breast because the cases we are investigating do not provide sufficient data to compare the results of surgery and irradiation. Adequate irradiation for carcinoma involves heavy dosage and must not be undertaken lightly. It is, therefore, like radical operation, a treatment for proved malignancy, and we believe that the diagnosis ought to be made by simple mastectomy with immediate examination of the gross pathology of the tissue. In this connexion it is appropriate to refer to the scruples which some surgeons have felt in doing a mutilating operation such as the removal of a breast when local incision would have sufficed. That the psychological effect of such removal might be injurious can hardly be denied, but in our view this possibility has been allowed to weigh too heavily, and it is noteworthy that the women surgeons with whom we have discussed the matter lay little stress on this factor. Where it is impossible to predict in advance whether the lesion is malignant or benign, we do not think that this consideration should prevent mastectomy.

Once malignancy is established, either at operation or by the histological examination of sections, it must be decided whether radical operation or planned irradiation offers the best chance of survival. We believe that with increasing facility for treatment by irradiation more cases will be treated by this method; statistical comparison will become possible, and a knowledge of results will guide our choice.

Summary and Conclusion

1. Benign and doubtful mammary lesions, grouped as (a) fibro-epithelial tumours, (b) chronic infections, (c) cystic changes, (d) early carcinoma, (e) acute carcinoma simulating infection, (f) pregnancy and lactation tumours, and (g) fat necrosis are discussed in relation to some diagnostic difficulties.

2. The choice of treatment of the doubtful tumours is described under (a) local excision of the tumour area, (b) simple mastectomy, and (c) radical operation.

3. Analysis of a large series of doubtful tumours, with known later history, suggests that the two-stage operation is not dangerous but is undesirable. In women over 35 years simple mastectomy with immediate examination of the gross pathology of the breast and submission of the tissue for histological opinion is the method of choice for diagnosis. Should the tumour appear malignant to the naked eye, the radical operation should be completed at once.

The facts presented seem to us to justify the conclusion that in women of cancer age with a doubtful tumour of the breast, diagnostic mastectomy should be performed as the best initial stage of treatment, except in cases of acute ("inflammatory") carcinoma and pregnancy and lactation tumours.

This work has been done in the laboratory of the Royal College of Physicians and in the follow-up department (tumour service) of the Royal Infirmary, Edinburgh. The material on which it is based has been supplied by cases treated in the Royal Infirmary and the Hospital for Women and Children, Edinburgh, and in various other hospitals and private clinics. We wish to acknowledge our indebtedness to the laboratory committee of the Royal College of Physicians, to the surgical staff and the pathology department of the Royal Infirmary, and to the Carnegie Trust for the Universities.

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A Histological Study of the Normal Mamma in Relation to Tumour Growth

I.—Early Development to Maturity

BY

E. K. DAWSON,
Carnegie Research Fellow.

(From the Research Laboratory of the Royal College of Physicians, Edinburgh)



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

I.—EARLY DEVELOPMENT TO MATURITY.

By E. K. DAWSON,
Carnegie Research Fellow.

*(From the Research Laboratory of the Royal College of Physicians,
Edinburgh.)*

Foreword.

MUCH of the tissue on which this study of normal and pathological growth in the breast is based was collected by Dr James W. Dawson as material for his intended investigation of mammary tumours. The study of this tissue, which includes a very large series of whole breast sections, was undertaken by me in collaboration with Professor Lorrain Smith, in an attempt to correlate the various phases of growth, function and atrophy of the breast with the incidence of malignant development in the organ. This was to be followed by a detailed study of the actual malignant process. The death of Professor Lorrain Smith in 1931 and my own occupation with other aspects of mammary pathology has delayed the completion of this physiological work.

The value of Professor Lorrain Smith's approach to any pathological problem was appreciated by all who realised and were stimulated by the breadth and freshness of his biological outlook, and in paying tribute to his memory, I am conscious of the inadequacy of this attempt to incorporate some of our discussions together into a consecutive treatment of the subject.

I am greatly indebted to the Laboratory Committee of the Royal College of Physicians for the courtesy and many

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facilities afforded my work. I wish also to record my appreciation of the assistance given me by the British Empire Cancer Campaign, by a grant during the investigation and by meeting the cost of illustration.

A detailed histological investigation of mammary tissue requires perhaps some justification, for most writers on the pathology of the breast assume a knowledge of its normal microscopic anatomy and of its physiology. An initial difficulty encountered, however, in this study was the wide variation of structure observed in apparently normal tissue. The interpretation of these variations and their significance are by no means settled matters, and yet some estimate of their importance is essential in a consideration of the pathology of the mamma. Creighton¹ was of the opinion that "the whole problem of breast tumours, malignant and innocent, is unique, for the reason that there is no uniform standard of normal structure and function from which to deduce the pathology, but an amount of variation from time to time and from individual to individual which is without parallel in any other organ of the mammalian body." M'Farland² also found many puzzling variations in his study of mammary tissue and received no help from the literature as to what was normal in development or involution, since text-books assumed that, apart from lactation, all breasts looked alike. He examined 200 apparently normal breasts and, from his histological study, suggested that different structural types might be established.

This diversity of structure in the normal mamma may explain some of the difficulty experienced in deciding as to the presence and extent of pathological change, a difficulty met with at all stages of mammary growth or quiescence, but especially evident in involuting and senile tissue. Examination of normal material in this study has emphasised this difficulty. It has suggested that "normal mammary tissue" might be defined, not so much in relation to the amount of epithelial and stroma elements accepted as the norm for a particular age or phase of mammary structure, but rather in relation to the type of growth considered physiological for that age or phase of the breast. I have therefore attempted to describe what I interpret as physiological types of growth in the breast at different periods, and to ascertain at what stages in normal growth, maturity and involution, pathological developments may

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emerge. It is possible that problems in mammary pathology may be more hopefully attacked in this way, which regards tumour growth as a progressive deviation from physiological development, function and senescence, rather than as an abnormality unrelated to these phases. An example will illustrate this method of approach. So-called lobular or glandular mastitis is observed at almost any age in the functioning period of the breast; in its early stages, it may show a histological picture of increase in the number and size of lobules, that is, an "adenosis," which is often microscopically indistinguishable from that found in the early glandular increase of pregnancy. Epithelial activity in the breast in both early pregnancy and in this type of "mastitis" is essentially physiological in type, but in the latter case the growth is regarded as pathological, because the normal appropriate stimuli of pregnancy are absent and because the increase frequently affects only a part of the mamma. A clearer understanding of the genesis of this type of pathological growth might be reached if it were related more definitely to normal growth activity in the tissue and termed a pathological adenosis rather than classified as a "mastitis." Such considerations prompted a more detailed examination of normal mammary tissue at various ages and phases than is usual as a preliminary to the study of its pathology. How far different structural types of normal mammary tissue might be established, as M'Farland suggested, is uncertain from my present findings, but the marked variation in the gross and microscopical picture of normal menopausal and post-menopausal tissue is strikingly demonstrated in my material. This appears to demand more exact correlation of histological findings with functional data (menstrual, lactational, etc.) to throw light on the genesis of abnormal developments at the later periods, which are predominantly associated with the emergence of malignant growth.

This investigation is a histological study of mammary tissue, with special reference to the development and activity of its epithelial content. I have purposely omitted discussion of the stimuli responsible for growth and function in the human breast, as the action of these has been dealt with in detail by numerous writers, such as Loeb,³ Cheatele and Cutler,⁴ and others, who discuss the experimental work and give an extensive bibliography. The tissue changes to be described here follow the main phases

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in the life-history of the mamma—I. Early development to maturity; II. Functional activity in pregnancy and lactation, and III. Involution and quiescence with the onset of the menopause. The possible emergence of benign and malignant tumour formation at these various stages is discussed.

I. Early Development to Maturity.

A. *In the Embryo.*

B. *From Birth to Puberty.*

Tumour formation.

C. *From Puberty to Maturity.*

The type of mammary growth.

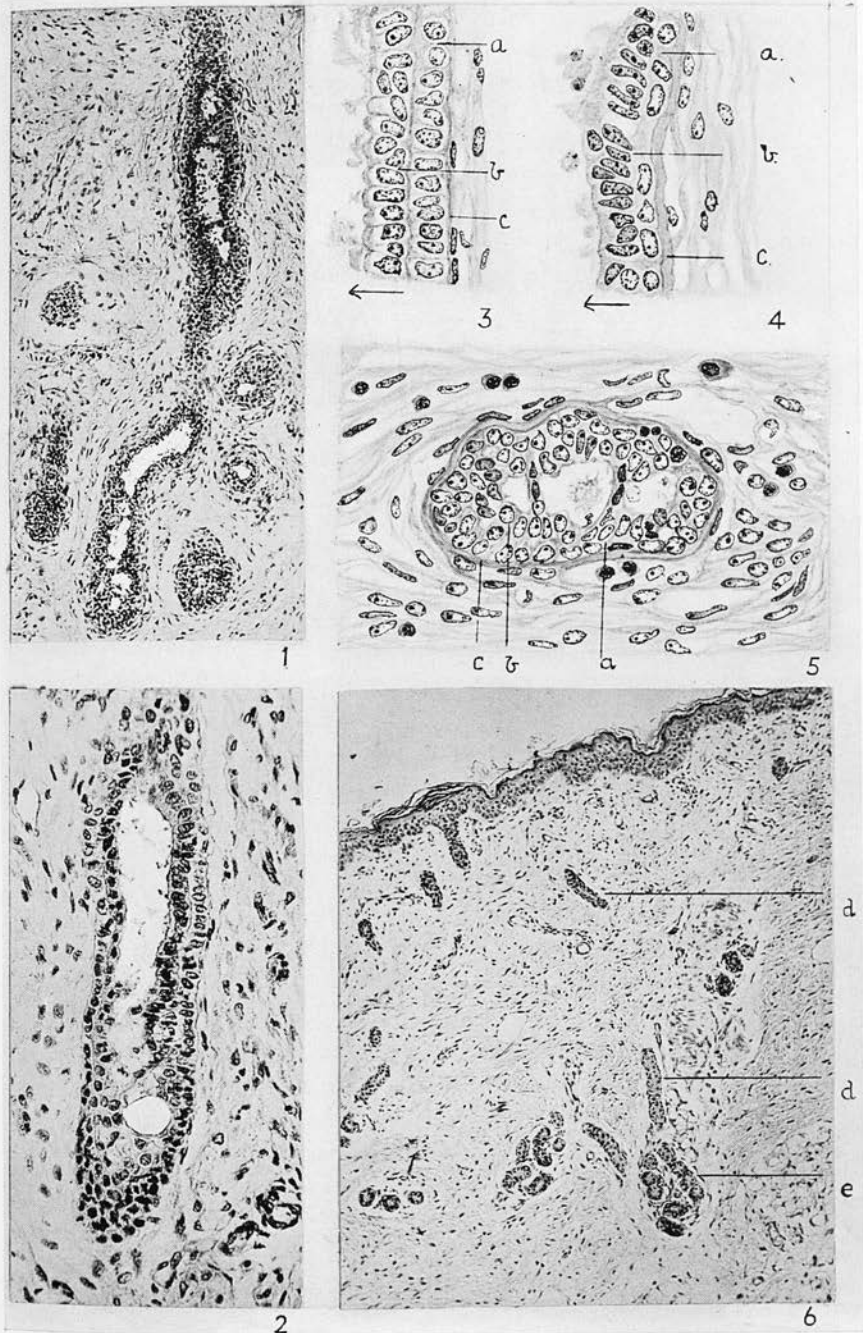
Tumour formation.

(a) Benign tumour.

(b) Malignant tumour.

A. In the Embryo.—The foundations of the glandular structure of the breast are laid down during foetal life. The first indication of the formation of the mamma is the appearance, before the sixth week, of the milk streaks, two comparatively broad zones of skin on the antero-lateral aspects of the thorax and abdomen, which are, according to Bresslau,⁵ represented in birds by the brooding patches. These zones of skin are characterised by taller epithelial cells and an increased vascularity of the subepidermal tissue,⁶ but at this stage show no downgrowth from the epithelium or development of glandular structure. In the sixth week, the central part of each milk streak is elevated to form the milk line or mammary ridge, an epidermal thickening with the specially differentiated dermis below. In the human subject, by the third month of foetal life, the nipple anlagen have formed in the thoracic area and the rest of the ridge has disappeared. The nipple at first is a lens-shaped thickening; later it assumes the characteristic knob-shaped form common to the placentals,⁵ but is not raised above the surrounding skin until after birth.

In the fifth month of foetal life, growth of the mammary epithelium begins to extend downwards in the form of solid buds which form cords of epithelial cells passing into the subjacent connective tissue. These epithelial cords become canalised and converted into ducts. Examination of foetal



FETAL TISSUE.

Fig. 1, Mammary ducts at 8 months, $\times 50$. Fig. 2, Mammary duct at 8 months, $\times 300$.
 Fig. 3, Mammary duct wall, showing two cell layers, at 8 months (arrow points to lumen),
 $\times 600$. Fig. 4, The same, at 9 months, $\times 600$. Fig. 5, Mammary duct at 9 months,
 $\times 500$. Fig. 6, Sweat gland tissue in mammary area, at 8 months, $\times 40$.

a, basal cell layer; *b*, inner cell layer; *c*, basement membrane; *d*, sweat duct; *e*, sweat glands.

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material from eleven cases suggests that this transformation of solid cord into duct begins by a desquamation and lysis of the central epithelial cells (Figs. 1 to 5); the fully-canalised duct has a wall of two layers of epithelial cells, a basal layer and an inner layer next the duct lumen (Figs. 2 to 4). Of the two, the basal cell tends to be flattened, spheroidal or cuboidal in form, while the cell of the inner layer is more columnar (Fig. 4), but variations of this are not uncommon. Some observers describe the ducts as lined by a single layer of columnar epithelium, with the nuclei arranged at different levels, giving the impression only of two layers of cells, but the material I have examined at this stage of development and at later stages does not appear to support this view. It shows the definitely double-layered duct wall illustrated in Figs. 2, 3 and 4, which seems to be the normal structure of the non-secreting glandular tissue, that is, apart from pregnancy and lactation, or non-involution after these functional phases. Surmont and his colleagues of the French school⁷ recognise two types of epithelial cells in the mamma, which they consider can be distinguished very readily at the foetal stage, an outer "myo-epithelial" layer, and an inner layer of "secreting cells proper" which line the lumen. They think, however, that the myo-epithelial layer is of little importance in human mammary tumours, though it shows marked proliferation in certain pathological formations in animals. I have been unable to identify any muscle cells in immediate proximity to the epithelium, and the proliferation of the outer or basal layer of the duct wall, with the subsequent formation of purely carcinomatous tumours, seems to exclude any suggestion of myoblastic origin. Outlining the duct wall is the membrana propria or basement membrane, apparently composed of connective tissue fibres compressed by the expansive downgrowth of the epithelial structure. Ewing⁸ is of the opinion that foetal breast tissue is characterised by the absence of a membrana propria; my material shows this already defined before birth, though at later stages it is sometimes difficult to identify. The structure of the glandular tissue will be considered in detail when the mature mammary tissue is described and illustrated. A passing reference may be made here to the rarity of epithelial mitotic figures observed in foetal tissue and to the presence of paccinian corpuscles in the *corpus mammae*.

When foetal life ends, the formation of the breast in both

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sexes is equal; an elementary system of ducts has been laid down, but without lobular structures or true secreting tissue. Its general appearance is indicated in Fig. 7, which shows the whole mammary area in a full-time foetus. The nipple is not yet elevated beyond the level of the surrounding skin; sebaceous glands are connected with the mammary duct openings in the skin, but sweat glands and hair follicles are found only beyond

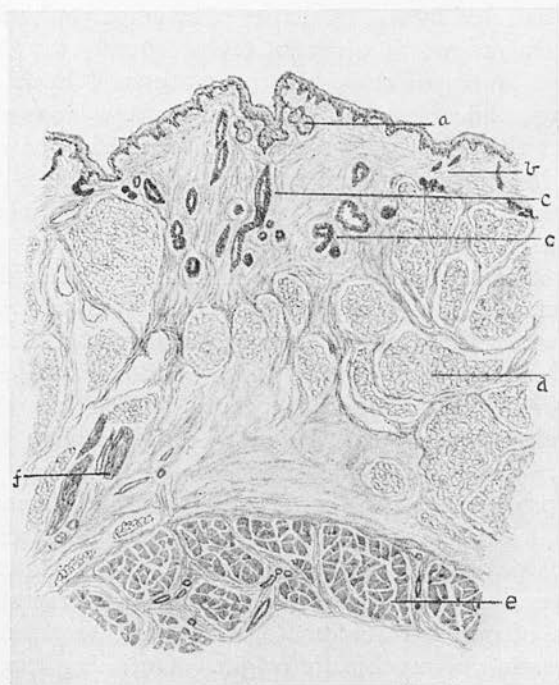


FIG. 7.—Whole mammary area in a full-time foetus.

a, sebaceous glands; b, sweat glands; c, mammary ducts; d, fatty tissue;
e, pectoral muscle; f, nerves.

the nipple zone. Some observers have described the presence before birth of small lobules, formed by branching of the deep ends of the large ducts, but I am unable to confirm this finding in normal foetal material. It seems probable that lobules are not usually formed until the breast is approaching the functional development associated with the onset of puberty.

An anatomical point may be mentioned here, though it has been discussed in detail in a previous study.⁹ The presence of apparent sweat gland tissue in the mature *corpus mammae*

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is described by several writers and interpreted as a developmental anomaly or a metaplastic change or a normal finding. Ewing upholds the last view, and considers that a variable number of sweat glands are normally distributed throughout the breast tissue and empty their secretion into the lobular mammary ducts. A recent study by Lee, Pack and Scharnagel¹⁰ of the material from which Ewing made his original observations supports this position, as they find small sweat glands at the base of the nipple in the loose connective tissue which is traversed by the true lacteal ducts. This "sweat gland epithelium" is regarded by them as a possible source of later malignant development in the breast, and accounts, in Ewing's and Lee's opinion, for approximately 25 per cent. of all mammary cancers. Creighton¹¹ went so far as to say that all malignant epithelial growth in the breast originated not from "proper mammary structure" but from "tubular glands like large sweat glands," at a time when the true mammary tissue was involuting. Later writers avoid this extreme position, but many observations indicate the uncertainty with which this apparent sweat gland tissue in the *corpus mammae* is regarded. Though it is now accepted that the breast is genetically a modified sweat gland, Lustig,⁶ in a detailed investigation by serial sections of fifty foetal breasts from the earliest stages to birth, found only sebaceous glands associated with mammary development from the nipple anlage; sweat glands and hair follicles were present only beyond this area. It is difficult to distinguish histologically the various epidermal downgrowths of early foetal life, but before birth definite structural differences between mammary and sweat gland tissue are evident (*cf.* Figs. 1 and 6), and my examination of mammary material of all ages, which includes a large series of whole breast sections with the nipple and a wide area of skin, supports Lustig's findings and gives no evidence of the inclusion of glandular tissue of sweat gland character in the nipple or normal *corpus mammae*. The presence of a similar cytoplasmic staining reaction in sweat gland structures and mammary cysts, papillary growths and carcinoma is not necessarily proof of a sequence in malignant development, which would demand a demonstration of the stages in this transition. In my material, the derivation of what Lee and his colleagues describe as "apparent sweat gland tissue," with eosinophilic epithelium, has been traced to normal adult mammary parenchyma, and its characteristic

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cells ascribed to degenerative changes associated with cyst formation and epithelial cell atrophy. These are described later in these studies.

The mammary duct when canalised is lined by two epithelial cell layers, a basal layer and an inner cell layer formed from this. Growth in length necessitates the formation of additional basal cells at the terminal growing point; some of these basal cells produce inner lining cells, others remain as basal cells at the growing tip, so that further growth in length of the duct may continue. An analogous process is seen in the skin. These accumulations of basal cells are found in all actively-growing mammary duct tissue, being especially evident during foetal and puberal growth, in the small duct proliferation characteristic of early pregnancy and in other conditions where new glandular structure is being rapidly formed. Krompecher¹² considered that such cells, seen for example in fibro-adenomata of rapid growth, form foci of basal cell proliferation with dangerous possibilities, but these cell accumulations are also evident in physiological activity. They are to be observed in all normal growing mammary duct tissue, and they may be regarded as *the normal provision for further growth*. This conception is supported by Coen's work¹³ on experimental aseptic wounds of the breast; he found that by the 9th day, mitoses were evident in the small ducts, and from these areas, buds were observed growing out as "solid heaps of cells, like an acinus without lumen" into the newly-formed fibrous tissue of the wound. This new well-vascularised stroma was laid down prior to the epithelial outgrowth. The small collections of lymphocytes near the growing ducts are apparently the normal response to the presence of degenerating epithelial cell products, associated with canalisation.

The basal cells, which are usually rounded, cuboidal or flattened, often present a marked contrast to the more columnar-shaped cells of the inner layer (Fig. 4); the tendency to desquamation and degeneration of the inner cells apparently indicates an instability associated with some degree of differentiation, in comparison with the more stable, less differentiated basal cells. This point will be discussed in connection with proliferation and degeneration of the epithelial tissue at later phases of mammary activity.

When dichotomy occurs in the duct, the growing tip forms two centres of growth, and from each a new segment of duct

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develops. Growth then proceeds, with the formation of the same type of structure, but the new segments are shorter in length and apparently narrower in calibre. This diminution in size and length of segment seems progressive with each new division, though there are probably many variations in the form of structure laid down. When the level of the smaller ducts is reached, dichotomy is, in general, replaced by more complex branching, but this is a later phase. During foetal growth, no smaller glandular elements, that is, no ductules arranged in lobules, have been observed.

When the foetus is born and takes up independent life, the subsequent development of the mamma does little more than keep pace with the general growth of the body, until the approach of puberty.

I have had no opportunity of examining histologically material from cases of so-called infancy mastitis (mastitis neonatorum), where enlargement of the breast and "secretion" were noted as clinical appearances. There are apparently authentic cases in which true milk secretion in the infant has occurred and persisted for some time after birth, but the histological picture necessary to establish the presence of true secreting tissue, similar to that formed in pregnancy and lactation, is not available. Histological evidence of coagulum and desquamated cells in the foetal ducts is, however, a usual finding. In a case of maternal eclampsia with death of the foetus at term, the foetal mammary ducts examined were greatly distended by proliferating and desquamating cells, the desquamation extending even to the basal layer. This was associated with marked congestion and interstitial hæmorrhage, which, to the naked eye, defined the outline of the mammary tissue in a striking manner (Fig. 8.) But the cellular débris in the ducts here suggested, not a secretory activity, but excessive epithelial proliferation with subsequent desquamation and lysis, caused apparently by toxic factors associated with eclampsia. Examination of normal tissue at birth shows a similar but much less exaggerated picture of epithelial activity, and seems to point to normal growth processes rather than to secretory function. Where the epithelial cell increase in the ducts is excessive, with desquamation and lysis, there may be discharge from the nipple, but this is found at any age and is not, strictly speaking, secretion. Secretion in the mamma, in my conception of the term, implies the formation of differentiated tissue and the activity of specific

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secreting cells, the secretion being produced and discharged without necessary destruction of these cells. It seems doubtful if such secretory tissue is normally found in the human breast except in the mature organ, and then its formation is apparently limited to the period of pregnancy and lactation. Confusion in the interpretation of various histological appearances in breast tissue might be avoided, were this narrower definition of secretion adhered to. Though most observers agree that no "true glandular tissue" is found in the breast at birth, and that therefore no "true secretion" is possible, the contents of the ducts at this early stage of development are frequently described as secretion. Keynes¹⁴ considers the breast a gland which throughout life is exhibiting some secretory activity, and explains "infancy mastitis" as an abortive attempt

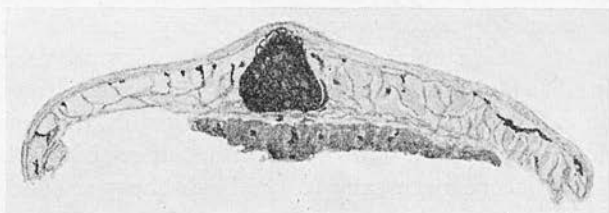


FIG. 8.—Full-time foetal material (maternal eclampsia)—actual size.

of the gland at birth to fulfil its ultimate function of lactation. Berka¹⁵ speaks of "the colostrum secretion of the new-born," though such appearances, he admits, are not associated with the formation of secreting alveoli; he finds that real secreting tissue is not observed except in pregnancy and lactation or after incomplete post-lactation involution. Lewis and Bremer¹⁶ describe the discharge at birth of a milky secretion similar to the colostrum which precedes lactation, but such "secretion" consists, in their opinion, mainly of leucocytes with or without ingested fat; Maximow¹⁷ found it contained little but degenerating epithelial cells. Abraham's investigations¹⁸ showed that when this "secretion" has ceased in the breasts of new-born infants of either sex, it can be reinitiated and maintained for a considerable time by the injection of an ovarian hormone, but in adults, such injections have no influence on the amount of *milk* secretion, a finding which suggests that maternal ovarian substances, supplied through the blood before birth or during lactation, act on infant mammary tissue as a

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growth stimulant rather than as an agent inducing true secretory activity. The "secretion" found in the breast at this stage would appear, except in rare cases, to be evidence of normal or excessive epithelial growth, with desquamation and lysis of the proliferating cells subsequent to the canalisation of the solid duct structures, rather than evidence of secretory function in any true sense of the term. This interpretation brings it into line with discharge from the nipple found at other ages, even at advanced ages when true secretory tissue is obviously no longer present.

B. From Birth to Puberty.—The development of the mammary structure makes little progress between birth and

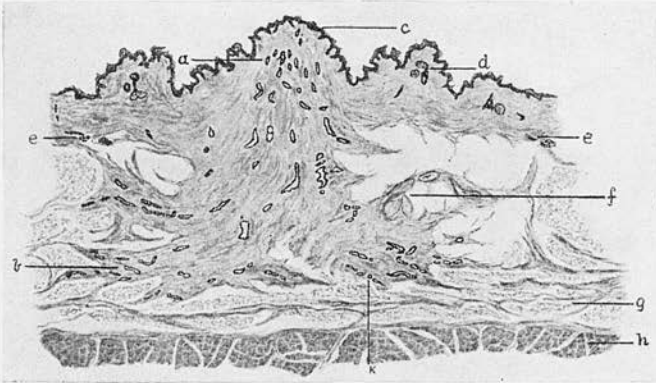


FIG. 9.—Normal breast tissue, child of 8 years.

a, large mammary ducts; *b*, small mammary ducts; *c*, nipple; *d*, sebaceous gland and hair-follicle; *e*, sweat glands; *f*, nerve with pacinian bodies; *g*, pectoral fascia; *h*, pectoral muscle; *k*, small ducts shown microscopically in Figs. 12 and 13, Plate II.

puberty. It remains, as it were, a rudimentary framework on which later growth will build. There is a limited growth, largely an elongation of ducts, according to Loeb,³ and some branching, but apparently only sufficient to keep pace with the general growth of the body. In rats, Myers¹⁹ found growth discontinuous during this period.

The whole mammary area from the normal breast of a child of 8 years is illustrated in Fig. 9. It shows considerable expansion of the *corpus mammæ* in comparison with the development pictured in Fig. 7, but no complex branching of small ducts to form lobules, even in the peripheral areas. The two-layered structure of the duct is observed throughout the glandular tissue (Figs. 12 and 13, Plate II., from longitudinal and transverse sections of the small duct *k* in Fig. 9); the

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duct wall at other ages is shown on the same plate (Figs. 10 to 19).

Tumour Formation between Birth and Puberty.—Pathological growth in the breast in the pre-puberal period is very rare, and I have so far found no case of epithelial or stroma malignancy recorded in detail in the literature. The youngest malignant case quoted by Ewing is 17 years; Creighton mentions 13 cases of breast cancer under 13 years of age among 882 patients with malignant mammary growths treated in Berlin between 1882 and 1899, but no histological findings are given. Among 1412 breast cases reported on by Dr J. W. Dawson in the routine material of the Laboratory of the Royal College of Physicians, Edinburgh, during the seven years between 1919

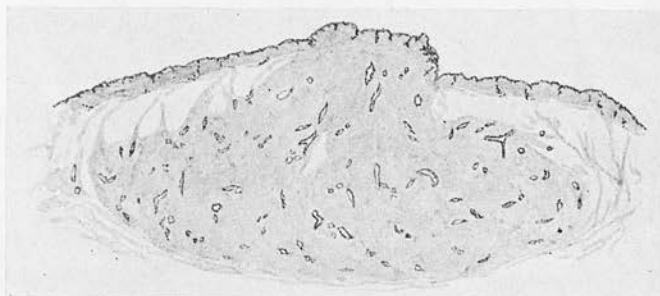
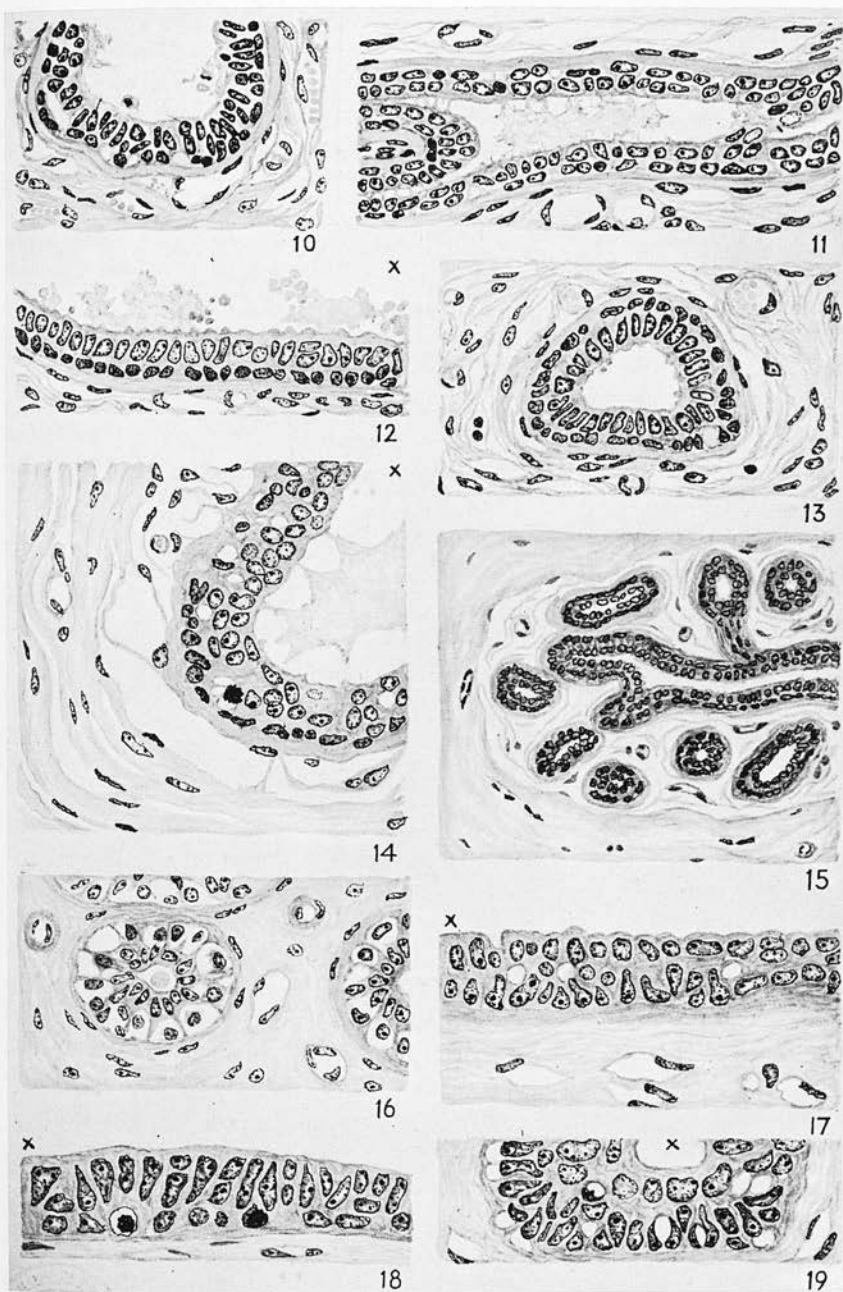


FIG. 20.—Mammary gland, boy of 9 years, with unilateral diffuse enlargement—actual size.

and 1926, only two were under 10 years and neither was malignant. One of these was an infant of 2 months, with small suppurative foci in the breast associated with a cellulitis, not necessarily mammary in origin; the other was a boy of 9 years, who showed diffuse unilateral mammary enlargement of slow growth during the year previous to operation. Sections of the whole breast of this case (Fig. 20) showed glandular and connective tissue activity producing a generalised peri-canalicular fibro-adenomatous condition, without any attempt at localisation by capsule formation. It may be questioned whether such a growth should be called a "tumour," except in the wide sense of a "swelling" of the breast. Ewing describes both localised and diffuse fibro-adenomata, but most other writers restrict the term to circumscribed formations and regard the diffuse form as one of the types of mammary hypertrophy, which may begin before or at puberty, or early in pregnancy or at other times,



NORMAL MAMMARY DUCTS AT VARIOUS AGES.

Fig. 10, at 9 months. Fig. 11, at 5 years. Fig. 12, at 8 years (*cf.* Fig. 9, *k*). Fig. 13, at 8 years (*cf.* Fig. 9, *k*). Fig. 14, case of *pubertas præcox*, 3 years 11 months (*cf.* Fig. 21). Fig. 15, at 30 years. Fig. 16, at 28 years. Fig. 17, at 19 years. Fig. 18, at 18 years. Fig. 19, at 19 years. (x indicates lumen of duct.)

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as the result of abnormal or excessive growth stimuli. In this case of the boy of 9 years, the glandular overgrowth, though unilateral and occurring in a male, was still more or less physiological in type, but was becoming pathological by reason of its irregularity and excess, as evidenced by the marked proliferation and partial desquamation of the lining cell layers and the consequent dilatation of the ducts. All the benign enlargements of the male breast in my material, occurring at various ages up to 60 years, are of this type of diffuse glandular and stroma overgrowth usually called gynecomastia, and give no suggestion of malignant epithelial development. Semb²⁰ records the same finding in his cases. He restricts the term fibro-adenoma to a well-demarcated formation with a capsule, and calls this diffuse type of growth "fibro-adenomatosis" or diffuse hypertrophy. In his opinion, it is similar to gynecomastia and the puberty hypertrophies which are relatively common in boys. The term *fibroadenosis*, which describes the glandular and stroma increase, without implying the presence of actual tumour formation of fibro-epithelial origin, would seem preferable in many cases, with the restriction of the term fibro-adenoma to the localised, clinically encapsulated growths. Fibro-adenosis, -adenomatosis and -adenoma may be regarded as successive phases in this type of benign tumour formation.

Such hypertrophies in the male breast indicate that stimuli to mammary growth are not necessarily confined to the ovarian hormones, though in the female these are apparently the more immediate agents which affect mammary activity. In this connection, I am indebted to Mr Dott and Miss Herzfeld for the opportunity to examine mammary material from an obscure case of precocious puberty in a girl of 3 years 11 months. The sexual development of the child corresponded to that usually seen at 10 or 12 years, but the pelvic organs, in their naked-eye and microscopic findings, gave little evidence of being the primary cause of the precocity. There was a cerebral lesion, associated with fits and facial weakness. Microscopically, the mammary tissue showed a development comparable with the general sexual precocity (Fig. 21); there was considerable formation of smaller ducts and the beginning of terminal grouping as lobules, an appearance characteristic of early puberty growth. Much of the glandular tissue showed proliferation of the inner lining cells and a vacuolated cytoplasm (Fig. 14, Plate II.); a few mitotic figures were observed in the basal

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layer. It should be mentioned that menstruation had occurred during and since the first year of life and a section of the ovary showed several corpora lutea.

Judging from the number of reported cases, benign hypertrophy of the breast is very rare before the period of accelerated growth initiated by the onset of puberty. Malignant

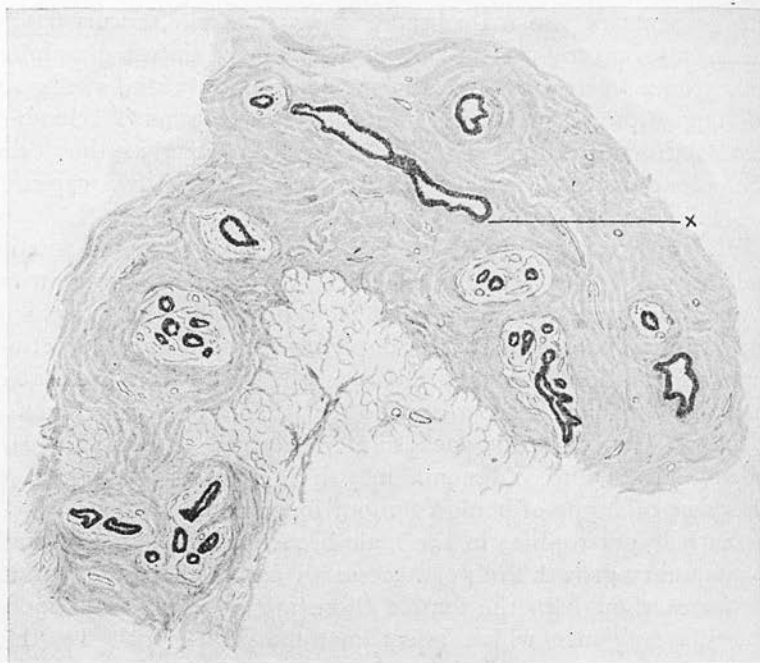


FIG. 21.—Mammary tissue, showing early lobule formation, girl of 3 years 11 months. (Case of *pubertas præcox*.)

x, the duct wall shown in Plate II., Fig. 14.

development, of carcinomatous or sarcomatous type, is practically unknown.

C. Puberty to Adult Life.—With the approach of puberty, the rudimentary mamma begins to show growth activity both in the glandular tissue and in the surrounding stroma. Glandular increase is seen initially in the formation of solid epithelial buds from a considerable length of the terminal part of the ducts already laid down (Fig. 22, *a* and *b*); these sprouts, in turn, form other short tube-like segments (Fig. 22, *d*), thus repeating on a smaller scale the type of growth

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observed at an earlier stage of development. Gruber's description²¹ of mammary growth in a girl of 13 years, "numerous milk ducts with beginning sprouts" coincides with my findings. Structural groups of small ducts or *ductules* are thus gradually formed and surrounded by a loose connective tissue which is

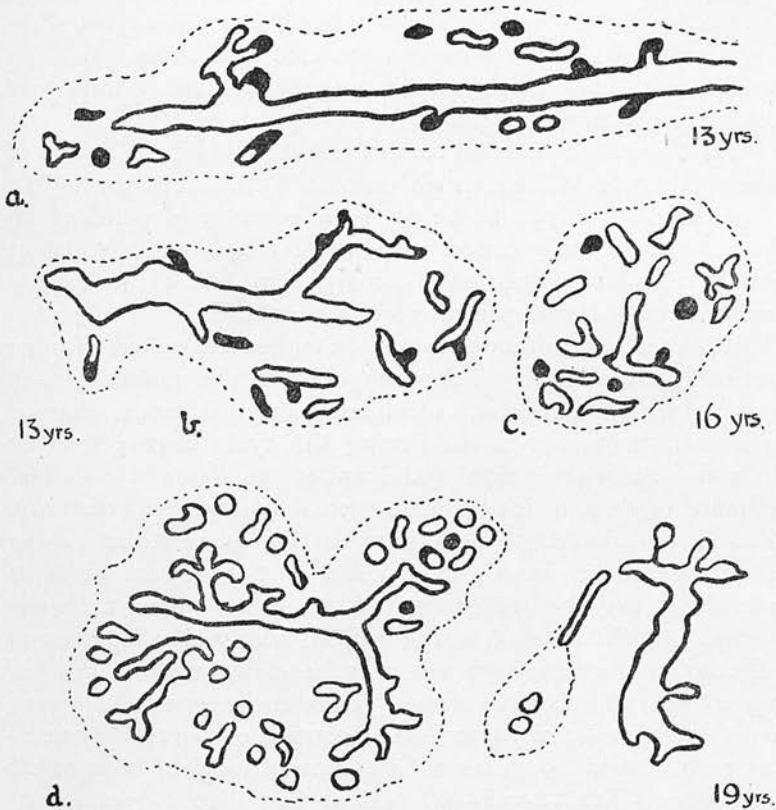


FIG. 22.—The developing lobule—the dotted line indicates the limit of loose lobular connective tissue.

a, 13 years; b, 13 years; c, 16 years; d, 19 years.

more cellular than the general supporting stroma of the breast (Figs. 22, c and d and 23). These groupings of ductules, described by Lewis and Bremer (*loc. cit.*) as "small scattered groups of duct-like tubes," are called *lobules*, and their formation is confined to the female, there being normally no puberty growth of any magnitude in the male breast. The structure of the terminal duct and ductules which together form the

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lobule is illustrated in Fig. 15, Plate II., and shows the two-layered epithelium, the basement membrane and the surrounding loose intra-lobular connective tissue already referred to. The actual microscopic appearance of a lobule varies with the plane of the section; if this is coincident with or parallel to the length of the duct, the tube-like structure of the lobular elements is emphasised, but if at right angles, these appear as isolated, more or less rounded structures. In most cases, as we should expect, these appearances are combined in the lobular section (Fig. 22, *d*).

This growth in size and complexity of the lobule begins at puberty and, in Dieckmann's opinion,²² continues until "the adult lobule" is produced; it is apparently dependent on sexual maturity associated with general bodily development and results in a mammary enlargement which is usually permanent until menopausal retrogression sets in.

With the onset of menstruation, changes associated with the recurring sexual cycle are superimposed on the general growth initiated with the approach of puberty, but the actual changes in human mammary tissue during the cycle have yet to be defined. Such definition would appear to demand a careful estimate of data which indicate sexual and general maturity, as well as knowledge of the menstrual phase, and in the absence of these details, comparison of tissue from different individuals may be misleading. Even when menstruation is normal in initial onset and duration, bodily development as reflected in mammary growth may be slow, and this in itself may explain what is often termed "an infantile type of mammary tissue." Berka (*loc. cit.*) described breast tissue from two "normal" cases of 18 and 19 years, which showed marked histological differences. The 18-year-old patient had died of pulmonary tuberculosis, and though there was no mention of amenorrhœa, she was described as "generally under-developed." The other, who died of burns, was "well-developed" and the breast tissue showed in comparison more abundant glandular structures and, in particular, larger lobular groupings. Berka notes that all the glandular tissue, in both cases, showed two-layered epithelium. Similar variations are indicated in my material, and illustrated in Figs. 23 and 24. Fig. 23, of tissue from a well-developed 16-year-old patient who died of sinus thrombosis after a very short illness, shows small but well-formed lobules surrounded by loose connective tissue, while Fig. 24, of tissue from a "normal"



FIG. 23.—Normal mammary tissue from a well-developed girl of 16 years.

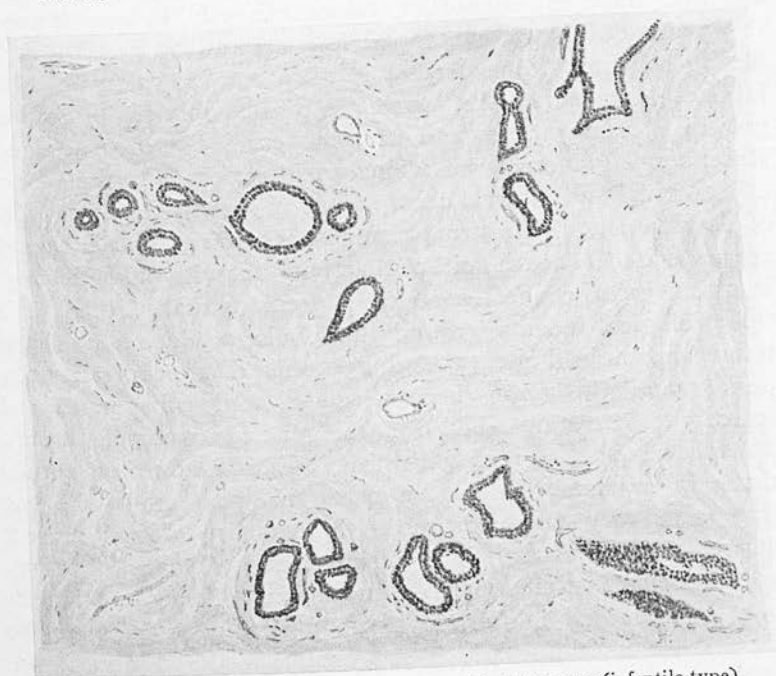


FIG. 24.—Normal mammary tissue from a girl of 19 years (infantile type).

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case of 19 years, cut in several sections at different levels, gives little evidence of definite lobule formation. It has been contended, however, that such variations are due, not to general bodily development influencing mammary growth or to the stage of lobular enlargement, which Dieckmann considers progressive from puberty to adult life, but to the phase of the menstrual cycle at which the tissue is removed for examination. A detailed discussion of this point is not relevant here, but the opinions of various observers and my own findings may be briefly indicated. The extreme positions in regard to the degree of epithelial activity during the cycle are represented by Rosenberg²³ on the one hand, and by Dieckmann (*loc. cit.*) on the other, and there are numerous supporting and intermediate observations. Rosenberg's examination of post-mortem material indicated that in the menstrual interval, lobules are not found, only milk ducts in a dense stroma; he considered that lobules are re-formed in the premenstruum and, after the period again involute and disappear. Luchsinger and Centano²⁴ Ingleby²⁵ and others agree with Rosenberg. Dieckmann, on the other hand, considers that, when the lobule has been formed, it remains during the menstrual interval and he found it even during continued amenorrhœa of six or seven months. The full development of the lobule is, in his opinion, a gradual growth of many years and in some cases is never attained. Rosenberg's glandular variations are therefore interpreted not as menstrual and interval changes, but as growth stages or types of development. Menstrual changes, according to Dieckmann, are associated not with epithelial activity but with fluid exchange in the lobular connective tissue; premenstrually, there is a "physiological œdema" round the lobule, producing the loose tissue shown in Figs. 15 and 23; this disappears after the period, and the fibres become dense and collagenous and scarcely to be distinguished from the general supporting stroma. Maximow's view agrees with this. Examination of normal tissue in my material also supports this position in showing that, with very rare exceptions, lobules are always present during the menstrual interval in tissue which is not yet approaching post-menopausal involution. Moreover, lobules may be observed in normal tissue for many years after the menopause, a finding which suggests that the disappearance of the smaller glandular structures involves a gradual involution and thus negatives the conception of their rapid formation and

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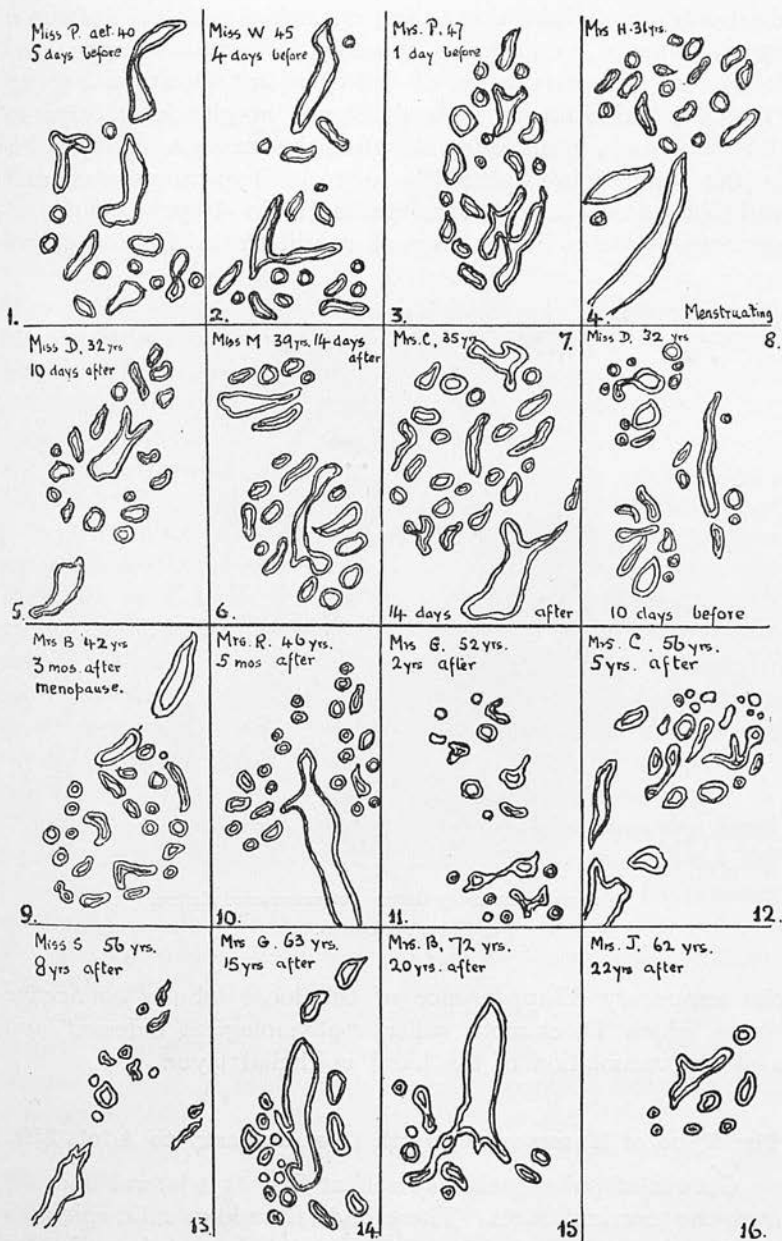


FIG. 25.—Normal mammary tissue, showing menstrual phases (1 to 8) and post-menopausal phases (9 to 16).

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disappearance with each recurring menstrual cycle, as postulated by Rosenberg. Outline diagrams of normal average-sized lobules at different phases of the cycle are shown in Fig. 25 (1 to 8), and indicate little difference in glandular content; the lobule at various intervals after the menopause is shown in the same figure (phases 9 to 16). Typical premenstrual and intermenstrual pictures are seen in Figs. 15 and 16 respectively; the intermenstrual condition in Fig. 26 shows

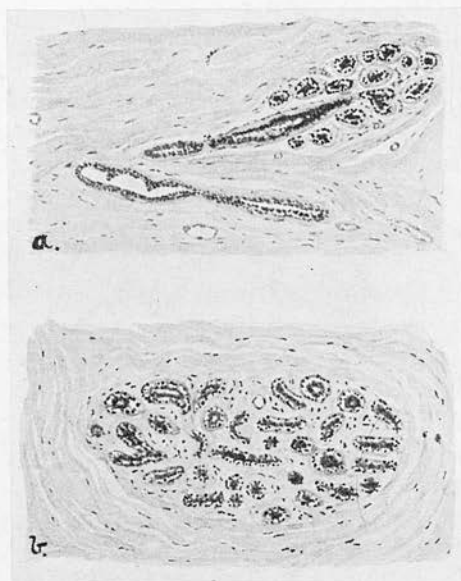


FIG. 26.—Mammary tissue—intermenstrual picture.

a, aged 39; *b*, aged 20.

the temporary disappearance of the loose lobular connective tissue which Dieckmann called "physiological œdema," and also the vacuolation of the basal epithelial layer.

The Type of Mammary Growth from Puberty to Adult Life.

Growth at puberty shows itself at first as a lateral budding from the terminal ducts. These buds, formed as solid epithelial outgrowths, hollow out, gradually lengthen and form further subdivisions. By this lateral sprouting and growth, lobules of varying size are gradually built up as groups of ductules, and the mature condition of the breast thus produced, with a

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coincident increase of lobular and supporting stroma and fatty tissue. Dieckmann calls this lobule formation, observed after puberty, a "functional growth," in contrast to the "structural growth" seen in the simpler, mainly dichotomous glandular tissue increase typical of earlier mammary phases. Since this "functional growth" is the framework on which, during pregnancy, is produced the abundant secreting tissue needed in lactation, this description is, to some extent, justified, though it would be more accurate to reserve the term *functional structure* for the actual secreting tissue, rather than including the lobular framework on which this is formed. Such a restriction would emphasise the morphological and physiological differences between "structural" and "functional" glandular tissue, for, with pregnancy, it appears that a new type of mammary structure is produced. In the non-pregnant subject, though the form of glandular tissue laid down progressively after puberty is more complex, the type of growth is essentially the same as that already described in growth phases from embryonic life onwards, that is, the proliferation of basal epithelial cells to form solid buds, which hollow out and elongate to form new duct tissue with a two-cell layered wall. Normally, all glandular formations produced at and after puberty, including the smallest new structures, the ductules, are, in my opinion, structural and not functional or secreting tissue. Growth goes no further than this in the non-pregnant subject. In some tissue, it may be difficult to demonstrate the two epithelial layers, as the basal layer is not necessarily continuous, but the structural lobule, the "lobulus non-lactans" or "lobulus tubulosus" of Dieckmann appears essentially different from the "lobulus lactans" or "lobulus alveolaris" produced during pregnancy and lactation, which is a one-layered glandular formation.

Terminal dilatation of the ductules in a lobule varies in degree; it is obvious in some tissue, but normal fully-developed lobules frequently show little or no terminal dilatation in comparison with the calibre of the rest of the structure.

The growth of the lobule, by increase in the length and complexity of the group of ductules which compose it, is apparently a gradual process, initiated at puberty and continuing until the mature breast has been formed. There seems, however, no standard size which can be accepted as "a normal lobule" for any particular age. By 25 years, Dieckmann found many "end-ramifications" building large complex lobules (*cf.*

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Fig. 22, *d*); on the other hand, the 19-year-old tissue of Fig. 24 shows only the beginning of ductule grouping in contrast to that from the 16-year-old case, with definite, fairly complex lobular formations (Fig. 23). It seems possible that in the breast, as in the uterus, normal maturity of tissue may never be attained, and glandular development thus remain permanently "infantile" in type. Such a possibility raises interesting questions—how far would such tissue meet the demands of lactation and might the inability of some women to nurse their children be associated with such mammary aplasia? The size of the mamma is, however, not necessarily an indication of the degree of glandular development, for many observers consider that post-puberty enlargement is produced mainly by an increase of the stroma and fatty tissue. An apparently hypertrophic breast may therefore be associated with general bodily adiposity rather than with normal or excessive glandular tissue increase.

The Possibility of Tumour Growth between Puberty and Adult Life.

(a) *Benign Tumours.*—The stimulus to growth at puberty and during the subsequent years until the mature mammary gland has been formed may be so great that tumour results in the developing tissue. The fibro-epithelial growths which become evident at this period—13 to 20 years or so—are, in the great majority of cases, localised or "encapsulated" fibro-adenomata, though diffuse hypertrophies are occasionally observed. Ewing considers it probable that the localised tumours arise from "superfluous or misplaced portions of breast tissue containing both adenomatous and connective tissue elements." Cheatle, on the other hand, thinks they are to be regarded as abnormal exaggerations of the physiological growth characteristic of this stage of mammary activity. Ingleby and others who accept Rosenberg's observations regarding epithelial increase and regression during the menstrual cycle, connect such tumour formation with some local upset which has marred the regular development of the cyclic changes. The histological structure of the developed tumours often gives little clue to their mode of origin; their usually rapid growth and, to the patient, their unexpected appearance, may account for the fact that they are rarely available for study at an early stage of development. But whatever view of their origin is accepted, it does not affect

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the importance of the evidence these tumours give of the greatly accelerated growth of the mamma initiated by the onset of menstruation.

The term fibro-adenoma logically includes all benign tumours in which both glandular and connective tissue elements participate; in ordinary usage, however, papillary formations are not included in this group, and I use the term here in the more restricted sense. I have observed no papillary adenomata at this stage of mammary growth, all the benign tumours in my material being fibro-adenomata. The following case of a girl of 13 years is illustrative of the rapid growth at puberty. Two months after the onset of menstruation, a slight undefined swelling was noticed in the left breast; this was treated with surface applications, but grew so rapidly during the two weeks before admission to hospital that sarcoma was suspected. Clinically, the tumour was large, soft, rounded and movable, about the size of an orange. The breast only was removed, and several years later the patient was well and the operation area satisfactory. The material removed was prepared as very large sections which included all the mammary tissue as well as the entire tumour area. The mammary tissue gave no evidence of pathological upset; it showed the early stages of the glandular and stroma activity already described and illustrated as typical of puberty. The rapid expansion of the tumour was due to a simultaneous proliferation of epithelial and fibrous elements, which produced a marked exaggeration of the type of growth seen in the normal mammary area, with larger and longer ducts and a more cellular and vascular connective tissue. This type of tumour is not uncommon at this period and even when it gives the clinical picture of a circumscribed growth, histologically it suggests rather a hyperplasia or a hypertrophy of normal mammary tissue.* Gruber (*loc. cit.*) points out this divergence between the clinical and microscopical aspects in such tumours and describes one removed from a girl of 12 years. Several weeks before this patient was seen, a painful swelling appeared in one breast; this was removed through an incision which left the breast more or less intact. The growth was the size and shape of a small apple, but when examined microscopically,

* Since this study was completed, a detailed discussion by R. L. Oliver and R. C. Major of the condition they term cyclomastopathy has appeared in the May 1934 issue of the *American Journal of Cancer*, which takes this view.

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there was no evidence of any tumour formation. Gruber considered that the "tumour" was only an unusually active manifestation of growth following the early changes associated with the onset of puberty in a girl described as very hysterical. The hardness felt generally over the rest of the breast before operation quickly disappeared after. Berka described similar tumours, clinically diagnosed as adenomata, but microscopically showing only glandular tissue normal for the stage of development. He observed that "one receives for examination tumours clinically described as adenomata or fibro-adenomata, which histologically cannot be considered as such, since microscopic characteristics of tumour-like proliferation are absent . . . on the contrary, their structure is identical with physiological mammary tissue; only the tumour-like appearance clinically and macroscopically suggests anything but normal breast." Kuru, Cornil and Coen reported similar cases in girls, where the tumours showed no histological difference from normal mammary tissue.

An examination of the structure of such tumours in my material at different ages shows, in most cases, that the new tissue produced is comparable with the normal developing mamma for that age. At the earlier ages, the connective tissue, surrounding and distorting the larger ducts, predominates in the tumour, while later, as we should expect, the smaller glandular tissue is more evident, though there is considerable variation in the amount and arrangement of the two structural elements. Frequently no histological evidence of a capsule is present, even when, to the naked eye, the defined tumour area suggests an easy "shelling out." The formation of a capsule, when microscopically apparent, may be ascribed to the stretching and condensation of existing tissue round a rapidly-enlarging growth, rather than to the formation of any new structure identifiable as such.

The diffuse form of mammary hypertrophy, which Ewing calls massive fibro-adenoma, is apparently much rarer than the circumscribed tumour at this stage, and comparatively few cases are on record. In a case of diffuse hypertrophy in a girl of 13 years, reported by Greig,²⁶ there was amenorrhœa after the first and only menstrual period, a finding which suggests loss of control by the ovary over normal post-puberty mammary development.

(b) *Malignant Tumours.*—Mammary growth at and after

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puberty, whether resulting in diffuse hypertrophy or in circumscribed fibro-epithelial tumour formation, is primarily a glandular activity—adenosis—with a secondary connective tissue proliferation. It is difficult to understand why such glandular tissue increase should not occasionally pass from adenosis through adenoma to malignant growth, but apparently this does not happen. Although reference is made in the literature to "carcinoma arising in fibro-adenoma," I have not yet found described and illustrated any case of malignant epithelial growth which convinces me regarding its origin as an adenoma or a fibro-adenoma, nor does any of the large number of these benign tumours examined by me suggest the likelihood of such epithelial malignant transformation. A fibro-adenoma may be invaded by malignant tissue arising elsewhere in the breast or it may share in a malignant activity evident outside its boundary, but these benign tumours, as such, show no greater likelihood to become cancerous than the rest of the glandular tissue of the mamma. This position is supported on the clinical side by the extreme rarity of mammary carcinoma before the age of 25, a period when adenomatous tumours are not uncommon. Examination of two of the rare malignant growths which emerge in these years has shown no genetic association with preceding adenomatous tumour formation. Wevill²⁷ found only 6 cases under 30 years of age in a series of 1082 mammary carcinomata treated at the Royal Infirmary, Edinburgh, between 1905 and 1931, and none under 25. In an unselected series of over a thousand breast cancers investigated, I have observed only 2 cases under 25 years; both were 23 at the time of operation, one giving a history of 18 months' duration, and both were duct carcinoma. If malignant growth arise in a fibro-adenoma, it is of sarcomatous type, but in my material such tumours occurred in older patients and I have so far encountered no sarcoma of the breast in a young subject; the possibility of such development is regarded by most observers as practically negligible. It seems therefore justifiable to assume that *adenosis is an essentially physiological response to growth stimuli which affect mammary activity*, and though the new tissue produced may be excessive in amount, exaggerated in type and unequal in distribution, for the dividing lines between adenosis, adenomatosis and adenoma are not easily drawn, as Adami pointed out,²⁸ at no stage has any association with malignant epithelial development been traced. Carcinoma

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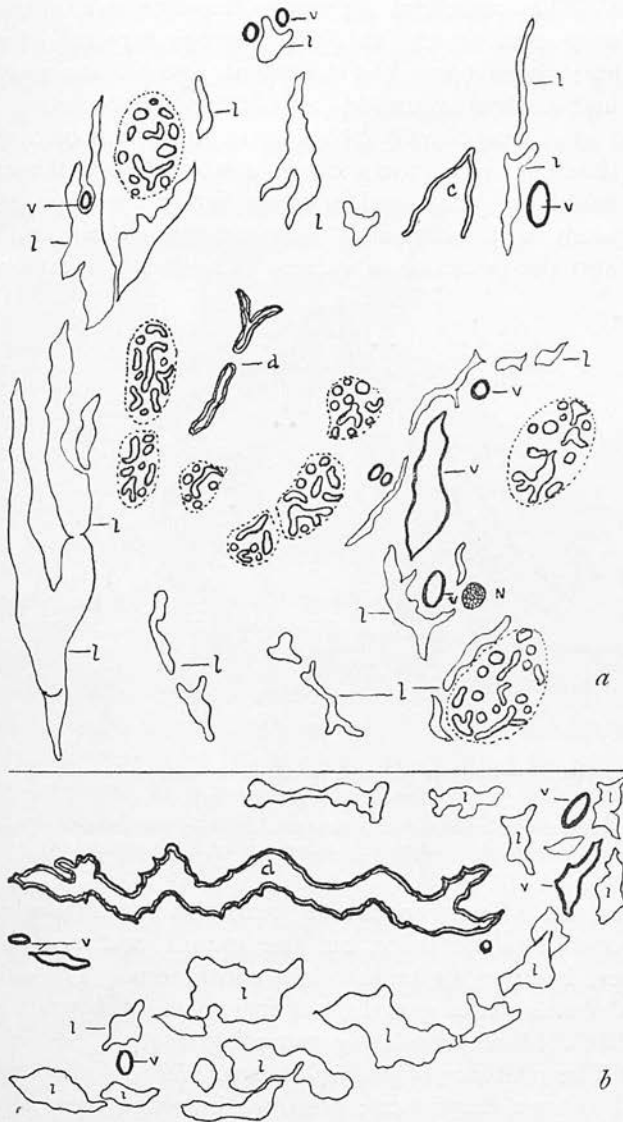
in the breast would appear to be, at any age, the end-stage of a pathological process which shows itself as epithelial proliferation within glandular structures—*epitheliosis*—and not as *adenosis*. This distinction between epitheliosis and adenosis has been discussed in an earlier paper²⁹; it will be studied again later in this investigation, in connection with carcinoma arising in association with pregnancy and lactation and in the later involutional mammary phases.

The malignant growths removed from the two patients of 23 years showed no special characters to distinguish them from carcinoma in mature mammary tissue, observed at later periods; they therefore call for no comment at this point. Wainwright³⁰ found that the youngest proved case of mammary cancer in a male subject was 23 years old; I have examined no malignant male case under 30 years.

One or two points in the anatomy of the mamma may be dealt with briefly at this stage.

(a) *The Lymph Vessels*.—The lymph drainage of the breast in relation to the regional lymph nodes has been studied in detail by numerous workers (Stiles, Piersol, Mornard, etc.) and is described in the larger anatomy and surgery text-books. The origin and course of the vessels in the mamma seem, however, to need further definition. Cheatle and Cutler describe the lymph system beginning in a plexus of small vessels round the acini, that is, an intralobular origin; White³¹ points to an extralobular origin, in sac-like enlargements lying in the supporting connective tissue. The recognition of lymph vessels and their position in relation to the glandular tissue is of obvious importance in the histological examination of malignant mammary tumours, and both points are best studied in such material. The lymph vessels are shown in normal tissue in Fig. 27, *a*, in relation to lobules; *b*, in relation to a large mammary duct. The direction of lymph flow in the breast is shown in Fig. 28, a diagram adapted from Keith's text-book on *Embryology*. Some of the vessels follow the course of the main ducts to the subareolar plexus (Fig. 28, *a*) passing thence, by the superficial mammary vessels (28, *c*) to the periphery of the breast, on their way to the lymph nodes. Other periductal vessels pass deep, to form the retro-mammary path (28, *f*), anastomosing with the more superficial channels at the periphery of the mammary area. It is important to note that the deep paths are connected with

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l—lymph vessels; v—blood vessels; d—ducts; c—capillaries; N—nerve.

FIG. 27.—Lymph vessels in mammary tissue.

a, in relation to lobules; b, in relation to a large mammary duct.

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lymph vessels which traverse the septa of the underlying pectoral muscles. The superficial mammary vessels communicate with the subcutaneous vessels (28, *b*), by channels traversing Cooper's ligaments; these form an important line of malignant cell dissemination from an underlying tumour to the skin.

The identification of lymph vessels, in normal or malignant breast tissue, is not always a simple matter, though theoretically they should be recognised microscopically by their contents—coagulum with occasional lymphocytes—their endothelial lining and the presence of valves. The larger lymph vessels,

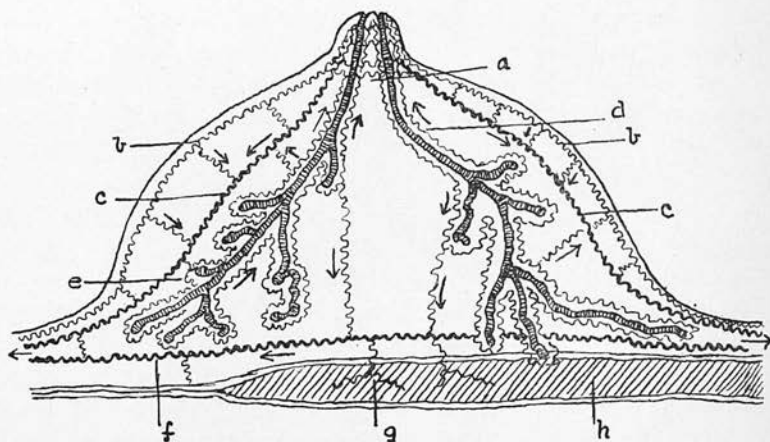


FIG. 28.—Diagram of lymph vessels in the mamma (simplified, from Keith's *Embryology*).

a, subareolar plexus; *b*, subcutaneous; *c*, superficial mammary; *d*, periductal; *e*, perilobular; *f*, deep (retro) mammary; *g*, intramuscular; *h*, pectoral muscle.

such as the afferent channels, near the lymph nodes, have three coats like the veins, but the muscle coat seems less in evidence, because apparently less continuous. The calibre of lymph vessels varies greatly, but in general it appears greater than that of blood vessels of comparable size.

(b) The presence of *paccinian corpuscles* in foetal mammary tissue has been mentioned; positions in which these structures have been observed in the breast at other ages are shown in Fig. 29.

(c) *Montgomery's Tubercles*.—I have been unable to identify these structures, in an examination of a very large number of whole breast sections with the overlying skin. They are described by Lewis and Bremer, for example, as "branched

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tubular glands with a lactiferous sinus and otherwise resembling the constituent mammary gland . . . they surround the nipple as small elevations and become much more prominent in pregnancy, when an oily secretion is produced." Such appearances, are, in my opinion, produced by normal or hypertrophied sebaceous glands, found in abundance in and around the nipple area.

(d) *Elastic Tissue*.—I have made no special study of elastic tissue in the developing mamma up to maturity. Berka

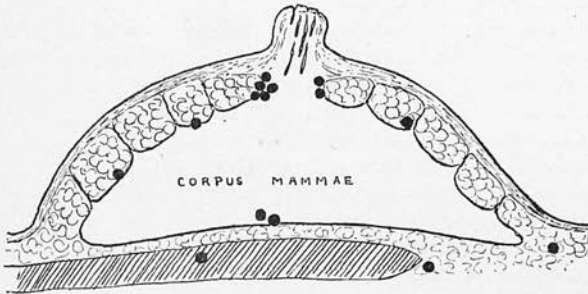


FIG. 29.—Positions where paccinian corpuscles have been observed in the breast.

observed scattered groups of fine elastic fibres in the loose intralobular connective tissue, but Maximow failed to find them in this position. Cheatele finds that the mammary ducts are usually surrounded by elastica, but it may be completely absent. Sections in my material stained to demonstrate the relation to mammary gland tissue show elastic fibres surrounding larger and smaller ducts and also scattered in the interlobular supporting stroma of the breast, but not in the lobule itself, except in older and involuting tissue. Most observers agree that there is a gradual increase of elastic tissue of the breast as age advances, and its distribution is therefore better defined at later stages.

[To be continued.]

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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

Histological Study of Normal Mamma

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 mammae*. There is, however, a wide individual variation in the proportion and amount of the new tissue elements laid down. Glandular

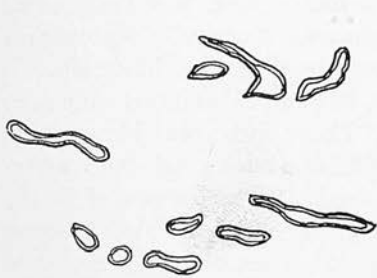


FIG. 1.—Pre-puberty glandular structure (child of 8 years).

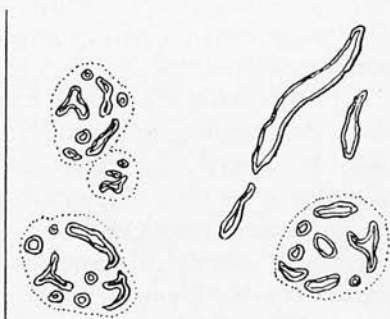


FIG. 2.—Post-puberty structure (girl of 17 years).

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 Geschickter³

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

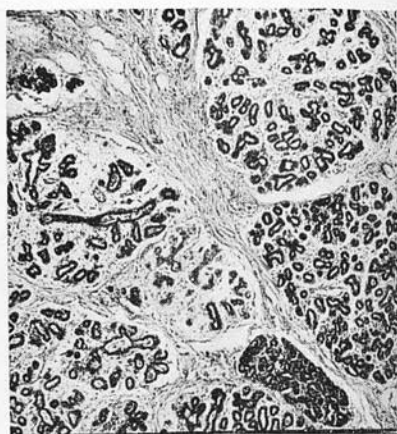
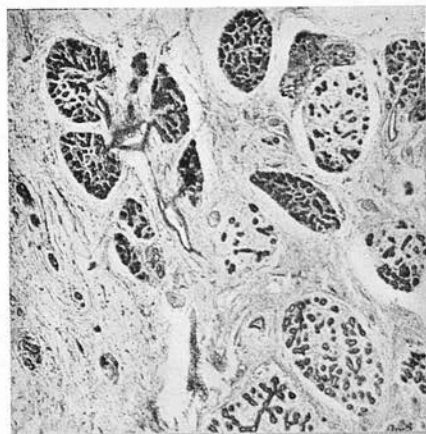


FIG.
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FIG.
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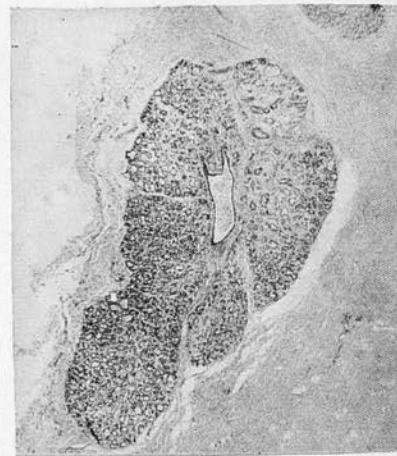
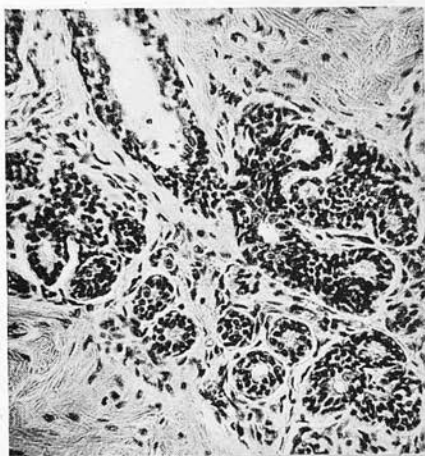


FIG.
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FIG.
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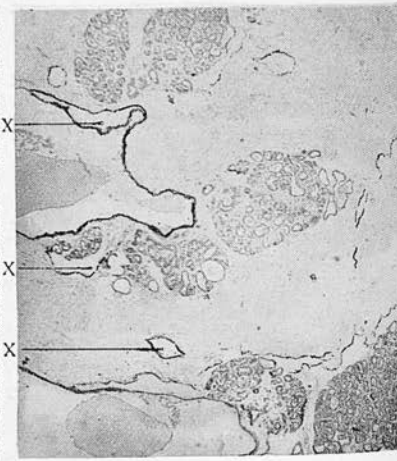
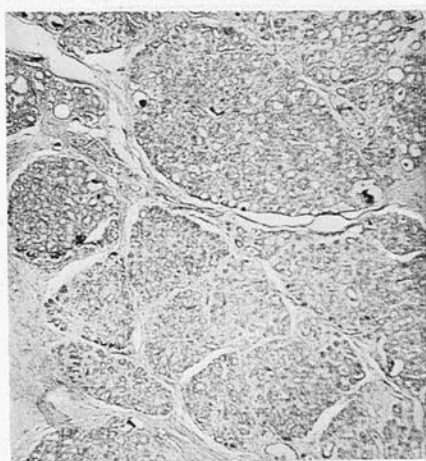


FIG.
11

Histological Study of Normal Mamma

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

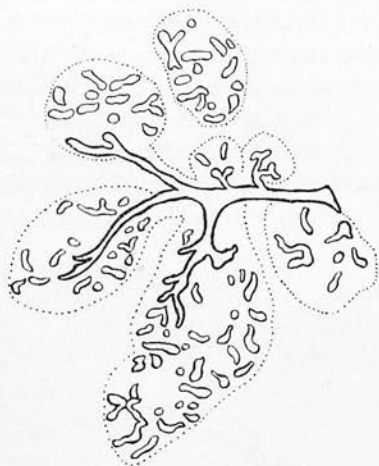


FIG. 3.—New lobule formation in mammary tissue, at 10th week of pregnancy.

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

PLATE I

The Mamma during Pregnancy

- FIG. 4.—Mammary tissue, 10th week of pregnancy, showing early lobular growth (*cf.* text Fig. 3). $\times 20$.
- FIG. 5.—Mammary tissue, 10th week of pregnancy, showing budding of ductules in the lobules. $\times 40$.
- FIG. 6.—Mammary tissue, 3 months' pregnancy, showing 2 cell layers of the ductules. $\times 200$.
- FIG. 9.—Mammary tissue, 5 months' pregnancy, showing a greatly enlarged lobule. $\times 20$.
- FIG. 10.—Mammary tissue, 8½ months' pregnancy, showing lobular enlargement (large fields almost entirely occupied with parenchyma). $\times 20$.
- FIG. 11.—Mammary tissue, 9 months' pregnancy, showing limited lobular growth, with periductal and interlobular lymph vessels (\times). $\times 20$.

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

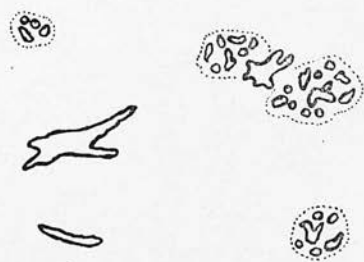


FIG. 7.—Adult glandular structure, nullipara of 21 years.

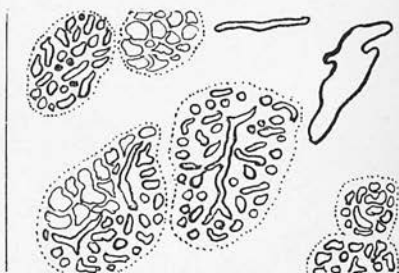


FIG. 8.—Glandular structure in pregnancy.

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

Histological Study of Normal Mamma

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

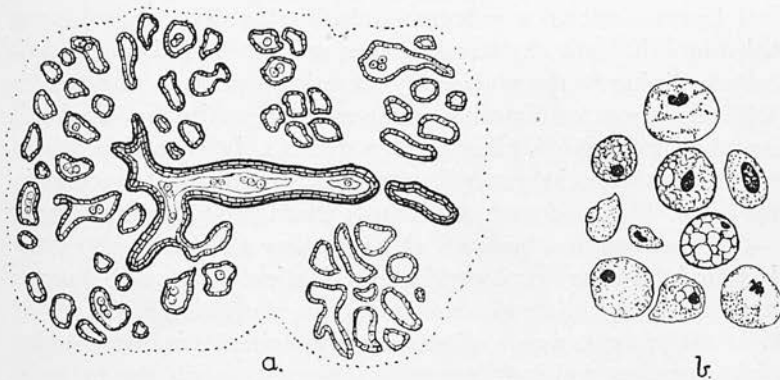


FIG. 12.—(a) Mammary lobule at term, differentiated for lactation.
(b) Colostrum cells, highly magnified.

distinct or separate character" (Broders⁴). 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. 12a). 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

E. K. Dawson

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. Loeb¹⁵ 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.

Histological Study of Normal Mamma

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). Altmann⁷ found that the possibility of lactation was not negated 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.

Histological Study of Normal Mamma

(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 Cutler⁸; Starling⁹ 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. Steinhaus¹⁰ 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. Coen¹¹ and Prym¹² described solid budding and two-layer gland formations at two months, and Gruber¹³ and Berka¹⁴ 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; Steinhaus¹⁰ 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, coincidentally 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. Loeb¹⁵ has observed colostrum formation in terminal tubes (ductules) associated with preceding growth processes, at a time when "alveoli" (acini) are not yet formed, and Gruber¹³ 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. Maximow¹⁷ 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. $\times 65$.
- FIG. 15.—Mammary tissue, 10th week of lactation, showing single-layer structure of acinus. $\times 900$.
- FIG. 16.—Mammary tissue, 10th week of lactation, showing non-secreting ducts (d) and secreting lobules. $\times 25$.
- FIG. 17.—Mammary tissue, 10th week of lactation, showing discharge of secretion (fat). $\times 200$.
- FIG. 18.—Mammary tissue, 10th week of lactation, showing duct (d), secreting lobules at different phases and perilobular lymph vessels (x). $\times 30$.
- FIG. 19.—Mammary tissue, 10th week of lactation, with much undifferentiated lobular tissue (x) and few secreting lobules (y). $\times 20$.

FIG.
14

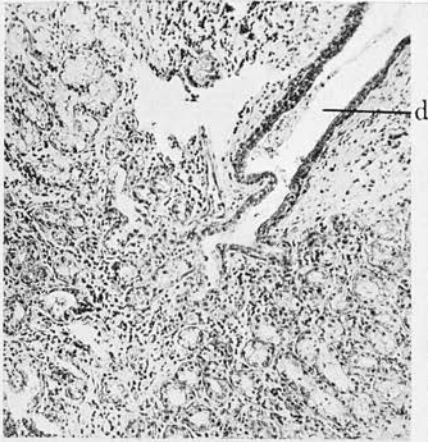


FIG.
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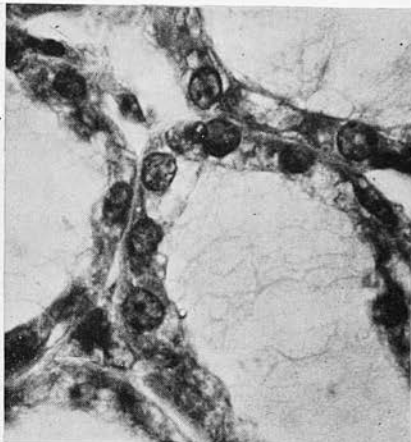


FIG.
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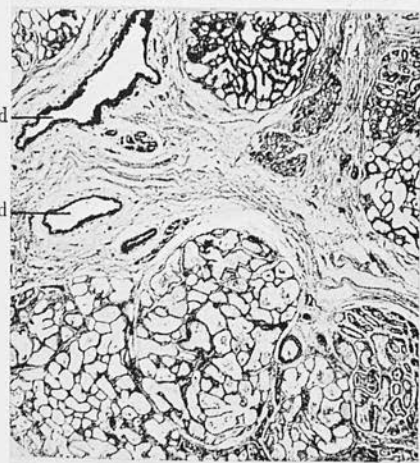


FIG.
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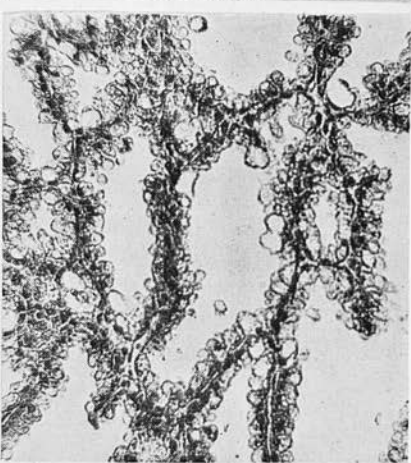


FIG.
18

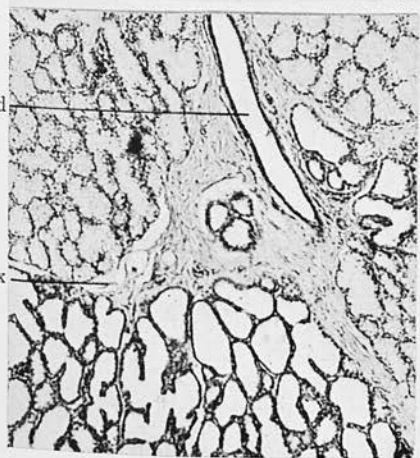
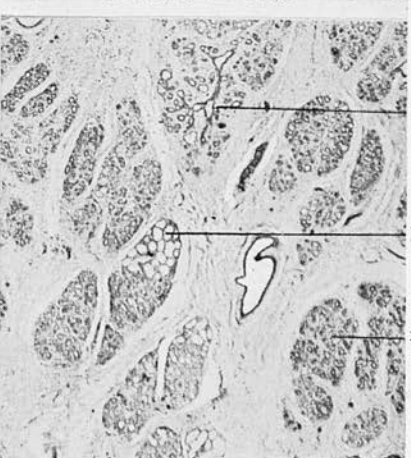


FIG.
19



Histological Study of Normal Mamma

(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).

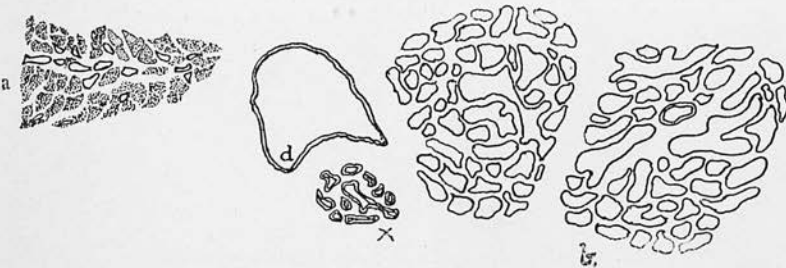


FIG. 20.—Lactating tissue.

a. Diagram from a section. ($\times 1$.)

b. Diagram ($\times 60$), 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 merocrine glands, such as the liver, thyroid, 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 Geschickter³ 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

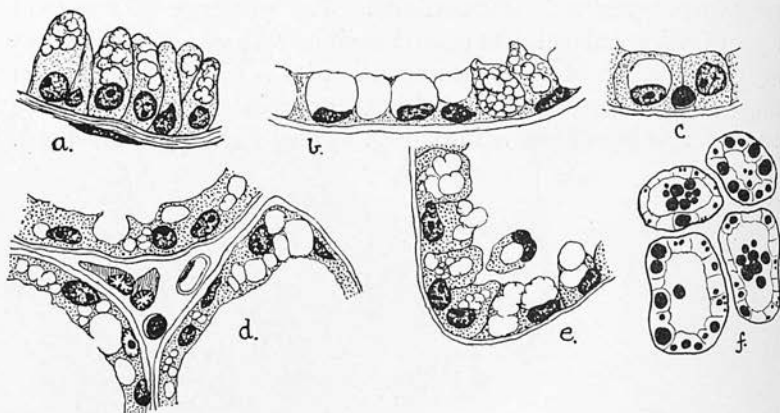


FIG. 27.—Fat secretion in lactating mammary cells.
a-e. Stained by H. and E. *f.* Osmic acid stain.

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. $\times 200$.
 FIG. 22.—The resting stage of the secreting cell, with acini (a) and duct (d) distended with secretion. $\times 65$.
 FIG. 23.—Mammary tissue after 12 months' lactation, showing undifferentiated lobules (x). $\times 20$.

Lymph Vessels in Mammary Tissue

- FIG. 24.—Lymph vessels (x), 5th month of pregnancy. $\times 20$.
 FIG. 25.—Afferent lymph vessels (x) entering axillary lymph node removed during lactation. $\times 20$.
 FIG. 26.—Greatly distended lymph vessel (x) 3 months after lactation. $\times 40$.

FIG. 21



FIG. 22

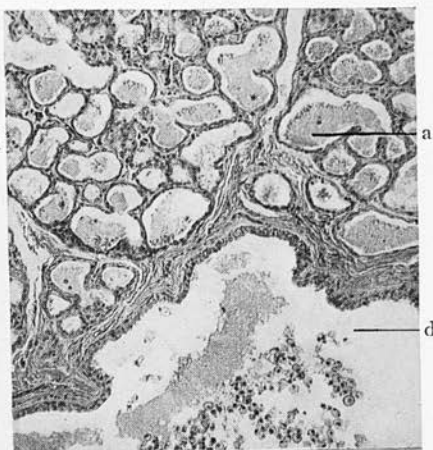


FIG. 23

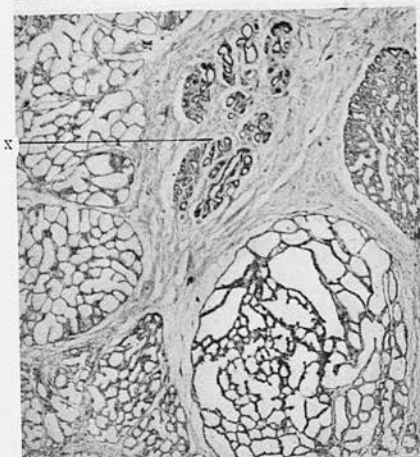


FIG. 24

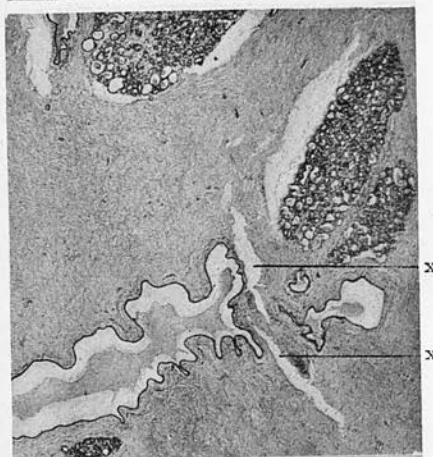


FIG. 25

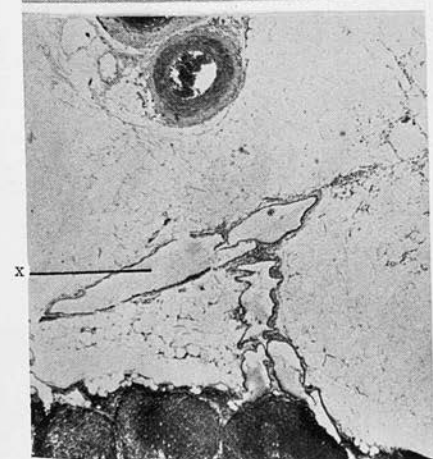


FIG. 26



Lactating Tissue and Lymph Vessels.

Histological Study of Normal Mamma

(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 negated 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 cells¹⁹ 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

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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 Apocrypha²³; Goebel found lactation usual for 3 or 4 years in Egypt,²⁴ and in China, the period may be even longer.²⁵ Lane-Clayton²⁶ 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 Seifert²⁹ observed that the concurrence of pregnancy and lactation was comparatively common. Fordyce³⁰ 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. Loeb¹⁵ 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 Maximow¹⁷ and others, in human tissue, and by Steinhaus,¹⁰ Corner,³¹ Weatherford¹⁹ 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

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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 McFarland³⁴ 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. McFarland³⁵ and Trinca³⁶ 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, Maeder³⁷ and Weatherford¹⁹ 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 body³⁸; 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

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

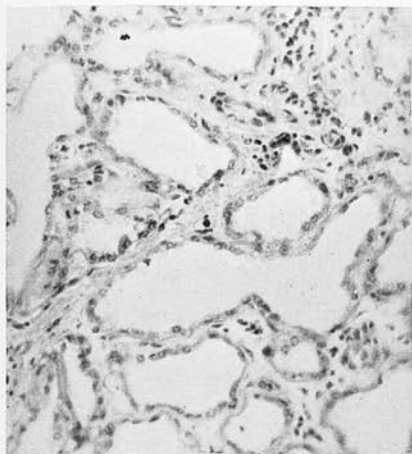


FIG.
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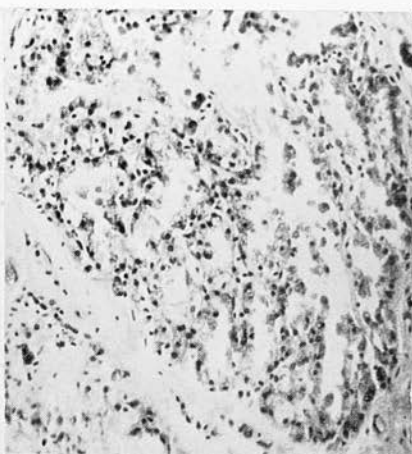


FIG.
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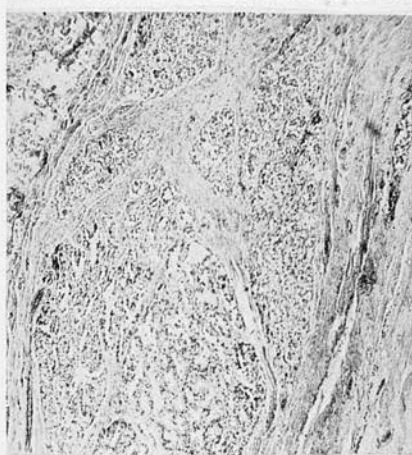


FIG.
31

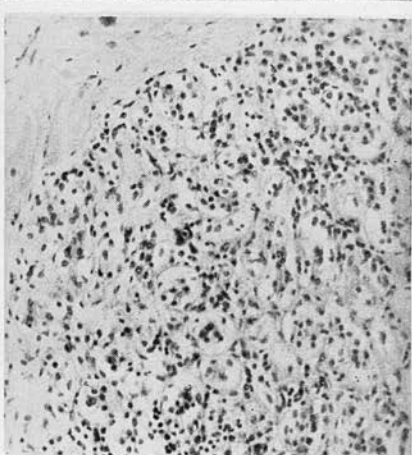


FIG.
32

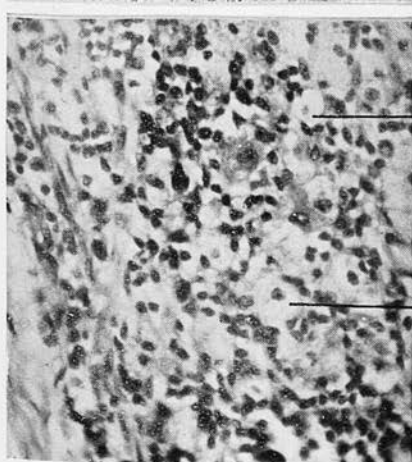
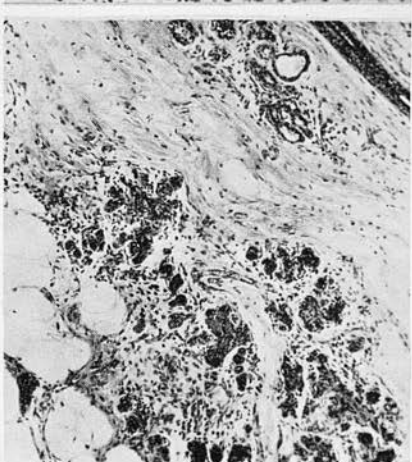


FIG.
33



The Mamma in Post-Lactation Involution.

Histological Study of Normal Mamma

process after lactation is "not a reversed differentiation" (Loeb¹⁵) 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 mammae*, 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-

Histological Study of Normal Mamma

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. Altmann⁷ 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 mamma 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-involutated 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

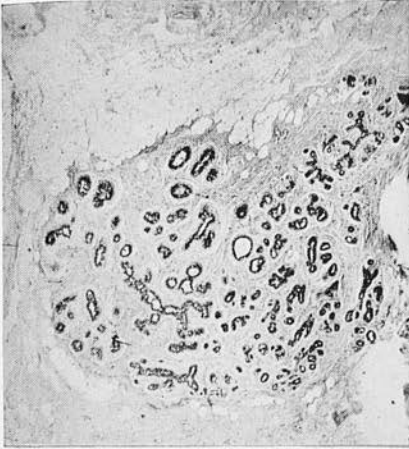


FIG. 35



FIG. 36

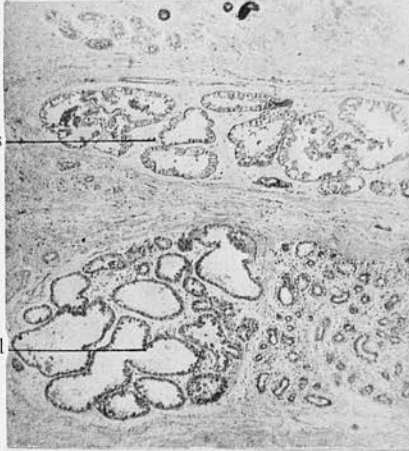


FIG. 37

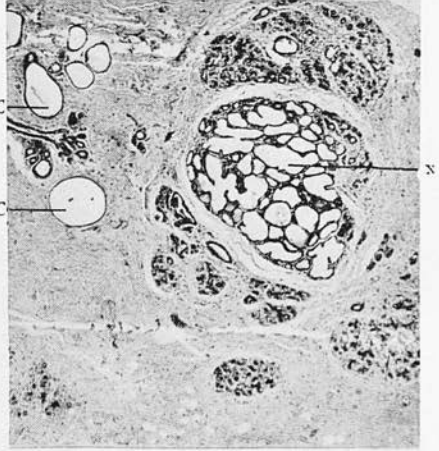


FIG. 38

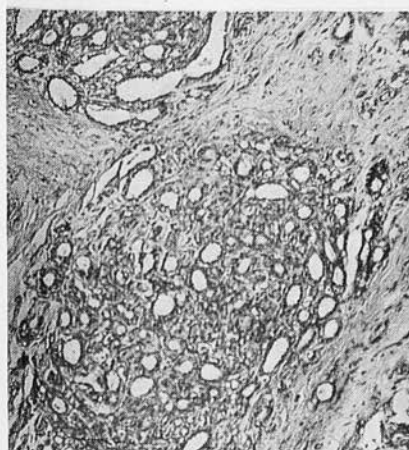
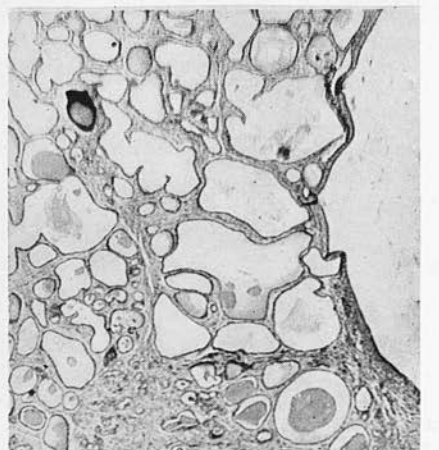


FIG. 39



Abnormal Post-Lactation Involution.

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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 elsewhere³⁹ 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. Keynes⁴¹ 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. Bradley⁴² 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 mammae* 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

Histological Study of Normal Mamma

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.
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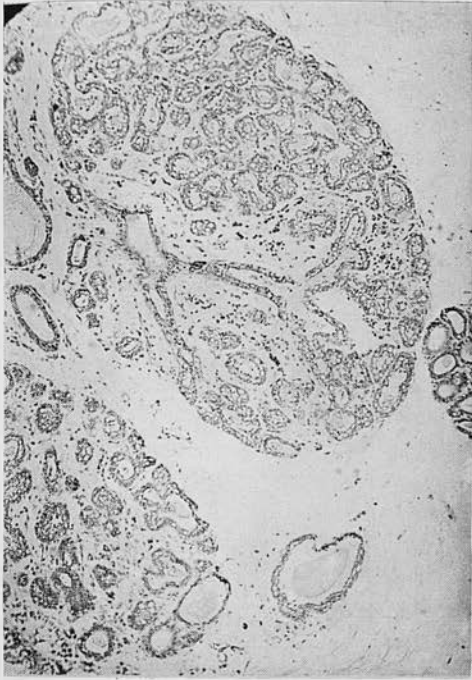
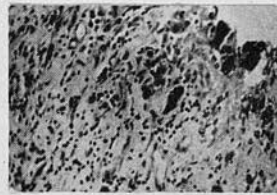


FIG.
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FIG.
42



FIGS.
43
and
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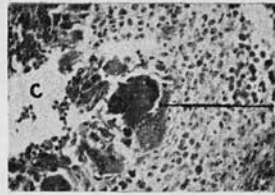
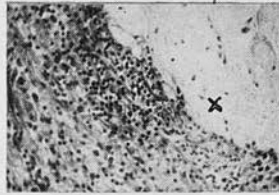
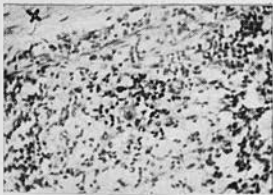


FIG.
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FIG.
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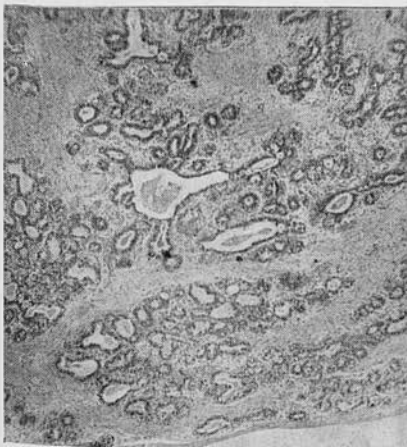


FIG.
47



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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 (galactocoele) 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 mammae*. In older multiparous subjects, the addition of fat in the mammary area may be a menopausal change, that is, part of

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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.

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

II.—THE MATURE GLAND IN PREGNANCY AND LACTATION.

By E. K. DAWSON, Carnegie Research Fellow.

*(From the Laboratory of the Royal College of Physicians,
Edinburgh.)*

[Continued from p. 598.]

6. Infective Conditions in Pregnancy and Lactation.—

Mammary infection with abscess formation shows no special histological characteristics. It may occur at any stage of pregnancy or lactation, but is more usual during nursing, especially in the early months. The openings of the milk ducts on the nipple, normally closed in the resting breast by a plug of keratin débris, are patent during lactation and facilitate infection from the skin surface (Fig. 83 shows two open ducts joining to form a common exit on the nipple). Examination of whole breast sections with single and multiple abscess areas indicates that the infective process extends along the ducts, and later into the surrounding tissues. The subsequent stages, with granulation tissue formation, etc., have already been referred to. The important point about infection in mammary tissue is that the process which leads to abscess formation destroys the glandular structure in the area involved and ends in its replacement by fibrous tissue. Coen¹¹ found, in experimental aseptic wounds of the breast, that the injured area later showed ingrowth of new glandular structures, and this apparently also happens with septic lesions,

as mammary tissue cut in large sections, from patients who gave a definite history of earlier abscess formation with incision and drainage, rarely shows scar tissue. We may assume, therefore, that the activity of a subsequent pregnancy causes glandular proliferation in the affected tissue, as in the rest of the mammary area. There is clinical evidence in support of this, as Bloodgood⁴⁴ and others note that even multiple abscess formation, if rightly treated, is no hindrance to subsequent lactation. The nursing history in a number of cases in my material supports this statement.

Chronic infective conditions in the breast have been referred to and need no further comment. The main difficulty they raise is that of clinical diagnosis. Kilgore⁴⁵ found a greatly increased incidence of tuberculosis of the breast associated with reproduction (9.4 per cent. of all types of lesion) compared with the frequency (1.7 per cent.) in the resting gland, and explains it by a possible "lighting up of latent foci by the increased circulation of functional activity." My material includes no case of pregnancy or lactation mammary tuberculosis.

7. Benign Tumours in Pregnancy and Lactation.—Tumours of any type are rarely found in the breast during pregnancy and lactation.

(a) *Adenoma*.—Though various observers mention the occurrence of these growths, very few cases are recorded in any detail and I have been able to collect only ten from the literature. My own material provides another two cases. The clinical data in the recorded cases are meagre. The ages range from 18 to 35 years; five of the patients were primiparæ, and in seven the tumour was removed during pregnancy. The duration of the growth, as noted by the patient, varied from three weeks to nine years. Most of the histories in this small series suggest a pre-existing, though sometimes undetected tumour, which had been stimulated to rapid growth during pregnancy; some writers, indeed, consider that the "pure adenoma" is a physiologically active fibro-adenoma, occurring only in pregnant and puerperal subjects. Encapsulated tumours, identical in structure with normal mammary tissue have been described apart from pregnancy and lactation,^{14, 36 et al} and these should logically be included in the adenoma group. The term is, however, usually restricted to the type of growth in which the glandular element alone has proliferated, and is

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therefore specially applicable to the benign tumours which become apparent during pregnancy and lactation. If not detected and removed before delivery, the onset of lactation in the breast causes rapid enlargement and secretion in the tumour area. The histological appearance of these adenomata is similar to that of the surrounding mammary tissue and therefore varies with the stage of pregnancy or lactation at which the tumours are removed; they are easily enucleated and, during lactation, show secretion when sectioned. The growth illustrated in Figs. 46 and 47, Plate VI., was excised during lactation and shows, at the higher magnification, secreting tissue like that of the normal breast, but at low magnification a somewhat different architecture, as we should expect, with a branching arrangement of the glandular tissue and irregular lobular structure. The history of my second case is typical of those on record. The first pregnancy, at the age of 25 years, ended in a still-birth at the seventh month. During the subsequent mammary involution, "before the milk dried up," she noticed a lump in the breast. It remained symptomless until the second pregnancy three years later, when it increased in size and "became prominent." After the birth of the second, full-time child and lactation for eight months, a stabbing pain in the lump led to excision four months later. Histologically the tumour was a fibro-adenoma, defined in relation to the surrounding mammary tissue and showing persisting lactation lobules in several areas (*cf.* Figs. 36, 1, and 37). The mammary tissue was apparently involuting slowly, as there were still evident numerous large lobules. The condition suggests abnormal involution after a still-birth, with the formation of a fibro-adenoma which remained inactive until stimulated by the next pregnancy. An area from a small cystic adenoma, which had been painful during pregnancy in a breast not subsequently used for nursing (Fig. 39, Plate V.), showed stasis of secretion with pressure atrophy of the lining epithelium. The dilated structures suggest inactive non-involuted acinar tissue, from this or an earlier gestation.

Some writers have questioned the existence or even the possibility of a lactating adenoma, but as the factors which lead to pregnancy-proliferation and later secretion are systemic blood-borne stimuli, there is no reason to suppose that a localised, possibly pre-existing adenomatous tumour in the breast would be exempt from their influence. Actually,

when such a tumour arises spontaneously, or, in an animal, has been grafted even in areas other than mammary, it shows, during pregnancy and lactation, stages of proliferation, differentiation and active secretion similar to those observed in the surrounding normal mammary tissue.³⁸

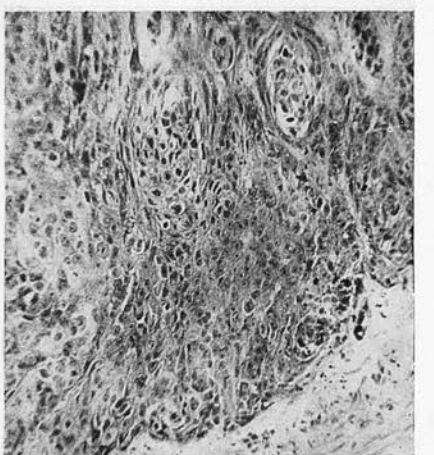
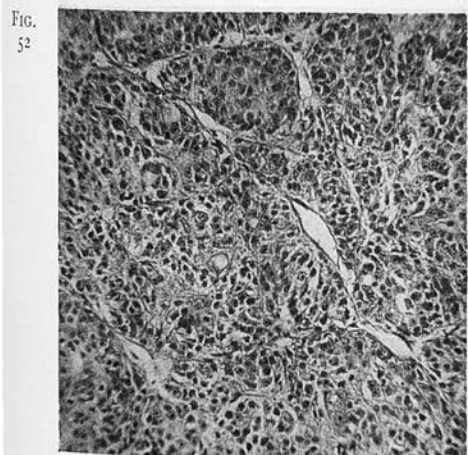
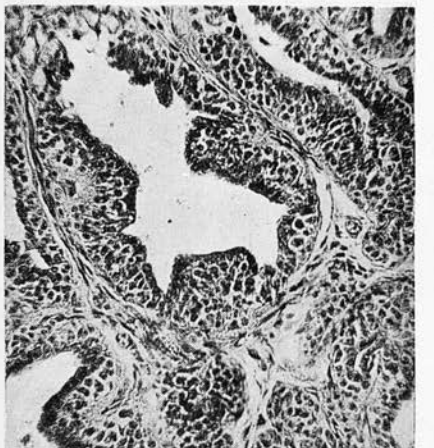
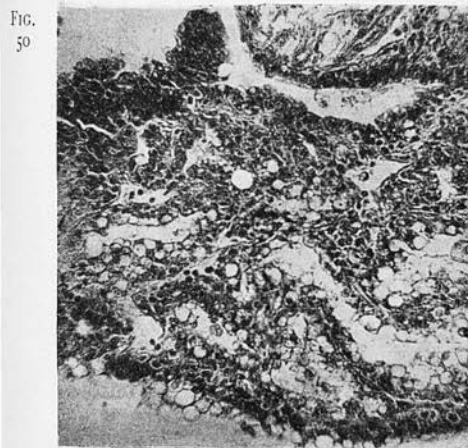
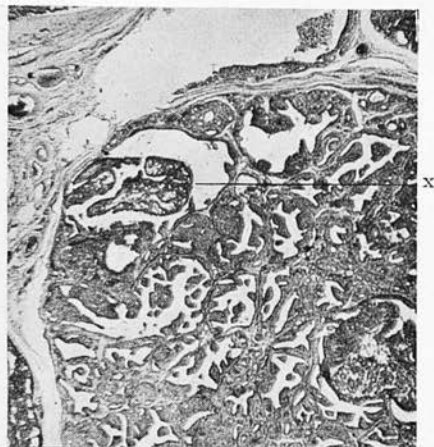
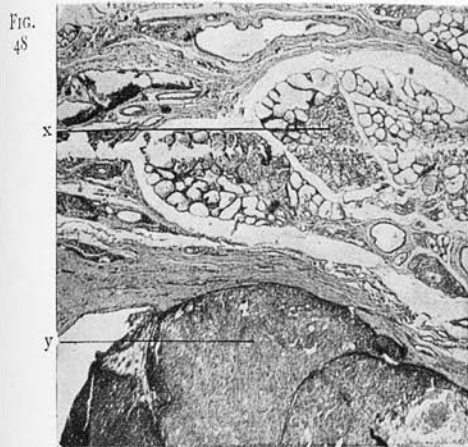
It may be asked why are these tumours so rarely encountered during pregnancy and lactation, when mammary fibroadenomata are, at other periods, of comparatively frequent occurrence. It is probable that, when arising at an early age, they are removed before pregnancy, though, if very small, they might escape detection in the general mammary enlargement associated with that period. Their growth and detection only at a later period of life, especially in multiparous subjects, seems to me a strong argument in favour of the view that these benign tumour formations can arise *de novo* after the reproductive period and are therefore not necessarily of developmental origin.

What happens to an active or lactating adenoma? It apparently behaves like an unused breast and experiments show that it involutes as rapidly or even more rapidly than the surrounding mammary tissue. Most of the cases on record were treated by local excision, but Deaver and McFarland consider that there is no advantage in operating on these tumours during pregnancy or lactation. The diagnosis may be uncertain, but even then, in their opinion, nothing is gained by surgical interference. If benign, the growth will retrogress with mammary involution; if malignant, excision

PLATE VII

Malignant Mammary Tumour in a Lactating Animal (Dog)

- FIG. 48.—Mammary tissue showing normal lactating lobules (x) and a cellular malignant tumour (y), the late stage of a papillary adenocarcinoma, almost filling a cystic duct. $\times 20$.
- FIG. 49.—The benign stage of the papillary growth in a cyst, showing a lactating area (x). $\times 20$.
- FIG. 50.—An area of the lactating papilloma seen in Fig. 49 at x; the entire secreting area is shown in text Fig. 50 A. The secreting tissue is similar to that observed in the normal breast and in the lactating adenoma (Figs. 46 and 47). $\times 200$.
- FIG. 51.—An area of the papilloma seen in Fig. 49, showing basal cell proliferation without secretory activity. $\times 200$.
- FIG. 52.—A later stage of tumour cell proliferation, showing a papillary adenocarcinoma, of basal cell type (*cf.* Fig. 48, y). $\times 200$.
- FIG. 53.—Another area of the same mammary tumour, showing invasion of tissues near the skin by malignant growth of squamoid cell type. $\times 200$.



Malignant Mammary Tumour in a Lactating Animal (Dog).

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is even more definitely contra-indicated, as is discussed later in this paper. The possibility of carcinoma arising in an active adenoma is also considered in the section on malignant tumours in the reproductive period.

(b) *Papilloma*.—I have found no case, recorded in detail or illustrated, of papilloma associated with pregnancy or lactation, though Kilgore⁴⁵ mentions two intracystic papillomata in a list of 96 mammary lesions first noticed during these periods. Bloodgood notes that papillomatous cysts are rare. My

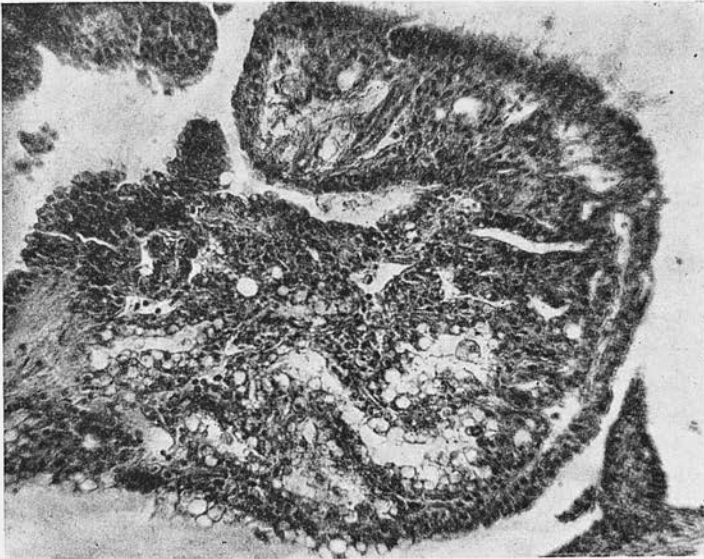


FIG. 50A.—Lactating papilloma (area *x* in Fig. 49, Plate VII.).

material provides one case, a malignant tumour associated with lactation in a dog, in which all stages of cancerous development are visible, from benign papilloma, in part lactating, to a very cellular malignant growth, with invasion of the tissues near the skin. This case seems to me of sufficient interest to describe and illustrate in some detail (Figs. 48-53, Plate VII.), though unfortunately no clinical particulars are available, except that the growth was removed during lactation. The tumour was cut in large sections, which included the whole mammary area and the associated lymph nodes; the latter gave no evidence of malignant involvement. Normal lactating tissue (*x*) is seen in the upper part of the field in Fig. 48; in the lower part is a cyst, almost filled with a very

cellular carcinoma (y); the genesis of this may be traced in the other figures on Plate VII. A papilloma almost filling a cyst is seen in Fig. 49; where it is of simple adenomatous structure, comparable to that of a ductule, the stimulus of pregnancy and lactation has led to differentiation and secretion (Fig. 50, text Fig. 50A), but this is apparent only in a small area (Figs. 49 at x and 50A); the remainder of the papilloma shows desquamation of the superficial columnar cells covering the vascular cores and progressively atypical multiplication of the non-differentiated basal cells (Fig. 51) until a malignant cell type emerges (Fig. 52). Much of the malignant growth is still confined within the cysts (Fig. 48 at y), but invasion has occurred and, in an area near the skin, the cells are assuming a squamoid character (Fig. 53).

These transitions from benign papilloma, in part lactating, to basal cell carcinoma, throw light on the essential nature of the malignant process. It must, in my opinion, be assumed that the papillomatosis was present, and already largely of an atypical character, before the gestation period during which malignancy emerged, since most of the proliferating tissue was unaffected by normal pregnancy and lactation stimuli. Where there was little or no deviation from normal glandular tissue type, the cells, though covering vascular cores instead of lining acini, showed differentiation and actual secretion, processes which, as I have already pointed out, inhibit further growth. But where proliferation of the basal epithelium was evident, the cell was unable to respond to normal physiological stimuli and became progressively atypical and finally malignant. It is difficult to correlate these findings with the opinion of those who consider that the preservation of functional activity in mammary cancer cells results in lowered malignancy. I have not observed "functional activity" in a true sense in any mammary cancer cell. In this case, the power to respond to functional stimuli was lost even before the cell became malignant; its pathological character is attested by its inability to respond, an inability even more obvious in the actually malignant cell.

(c) *Cysts of the Breast*.—I have found no record of cystic conditions detected or treated during pregnancy or lactation, and my material provides no example.

8. Malignant Tumours in Pregnancy and Lactation—

(a) *Incidence of Carcinoma*.—Malignant mammary growths

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associated with pregnancy and lactation are of rare occurrence, so rare indeed that they are only occasionally noted in statistics of cancer. Their incidence, relative to mammary cancer in general, is necessarily small, partly because the majority of malignant tumours in the breast appear after the reproductive period, partly because malignancy is more frequent, at any age, in nulliparous subjects. In a series of 330 mammary cancers treated during 1930-1933, in the Royal Infirmary, Edinburgh, only 5 or 1.5 per cent. were definitely associated with reproduction; the incidence in women under 47 years, the rough limit of the child-bearing period, was 5.7 per cent. This frequency is only about half that reported by Kilgore,⁴⁵ who investigated a series of over 1500 mammary lesions of all types at Johns Hopkins University Hospital. He found that 6.3 per cent. of all mammary lesions were first noticed in connection with pregnancy or lactation, and of these, 49 or 3.3 per cent. were cancer; these comprised 4.5 per cent. of all cancers in the series, and 10 per cent. of those occurring under 47 years.

(b) *The Clinical Picture.*—The clinical features in malignant growth observed during reproduction vary considerably.

i. *Age.*—In my small series of 15 cases, the 5 noted above and 10 from various other sources, the ages at treatment range from 29 to 42 years; only one is under 30 and five are 40 years or over.

ii. *Abstracts of History in the Series examined.*

CASE 1, aged 42, 8½ months pregnant at operation; tumour found 3 months previously, small, increasing in size, painless until a few weeks before treatment. Skin discoloured over the growth and whole breast apparently replaced by hard, firm swelling; skin and deep tissue fixation; large hard axillary lymph nodes. Radical removal. Child still-born. Death 6 months later, with metastases in liver (Figs. 54, 60, 61, 62 and 84).

CASE 2, aged 37, primipara; had stationary tumour in breast for 6 years; immediately after birth of child, tumour grew very rapidly. Breast radically removed 6 weeks after delivery; axillary nodes invaded. Death 6 months later (Figs. 57, 63-65).

CASE 3, aged 36, 2-para, 10 years and 11 months. When nursing second child 7 months old, left breast became painful; considered "a cold"; a month later, felt lump near nipple, but did nothing for another 3 months, when doctor found tumour 3.5 cm.

diameter and enlarged nodes in axilla. No history of injury or inflammation, but not so much milk in affected breast, which was "less filled and gave a shorter feed." Radical removal; nodes found extensively involved. Seven months after, reported as "going downhill rapidly, with multiple malignant deposits in spine, pelvis and ribs" (Figs. 55 and 85).

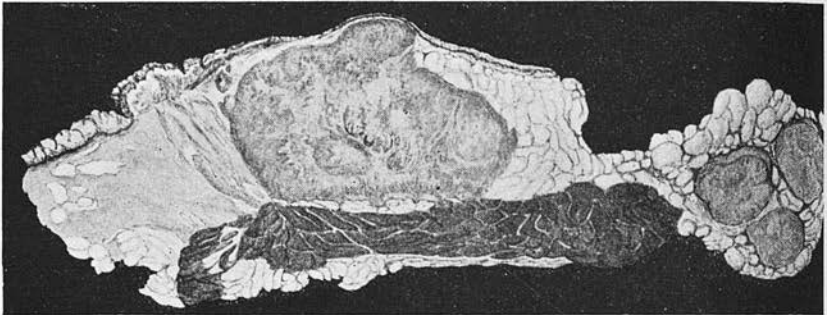


FIG. 54.—Case 1. Large mammary tumour with axillary invasion, in a patient $8\frac{1}{2}$ months pregnant.

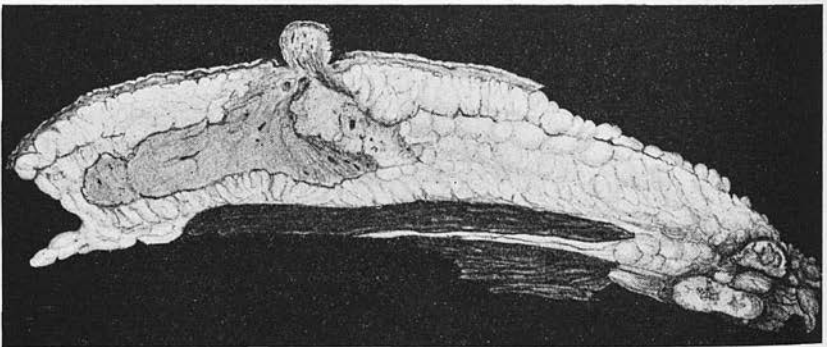


FIG. 55.—Case 3. Mammary tumour found at 7th month of lactation. Extensive axillary invasion at operation 4 months later.

CASE 4, aged 39, 3-para, nursed all children. Swelling in breast found 12 months before examination, during lactation. Lump became more evident as milk decreased, but no obvious increase in size. No nipple retraction, no discharge, slight pain; hard lump with somewhat irregular outline, 4 cm. diameter, in upper inner quadrant; slight fixation, no palpable axillary nodes. Diagnosed clinically benign; simple amputation. Histological examination showed scirrhus carcinoma; radical amputation completed 3 weeks later. No enlarged lymph nodes found. This is a recent case and

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the patient is well without sign of recurrence or metastases 5½ months after treatment (Figs. 56 and 86).

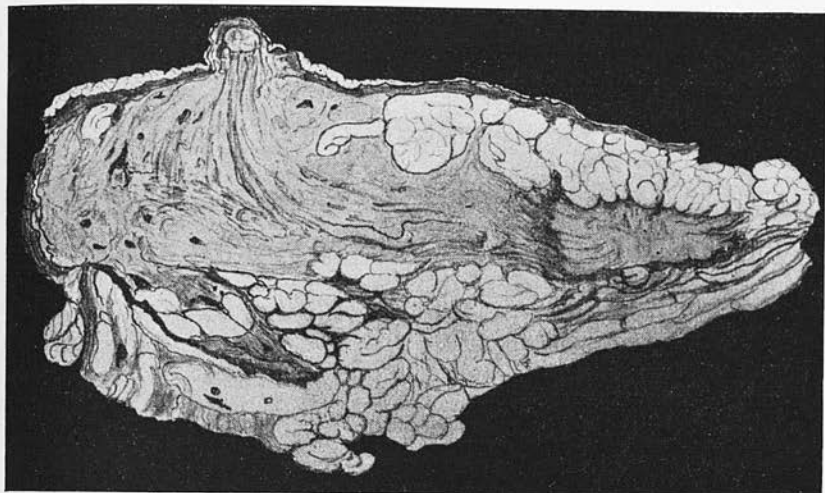


FIG. 56.—Case 4. Scirrhus carcinoma, discovered during lactation.

Malignant Mammary Growth during Pregnancy and Lactation
(drawings of operation tissue sectioned through tumour and nipple).

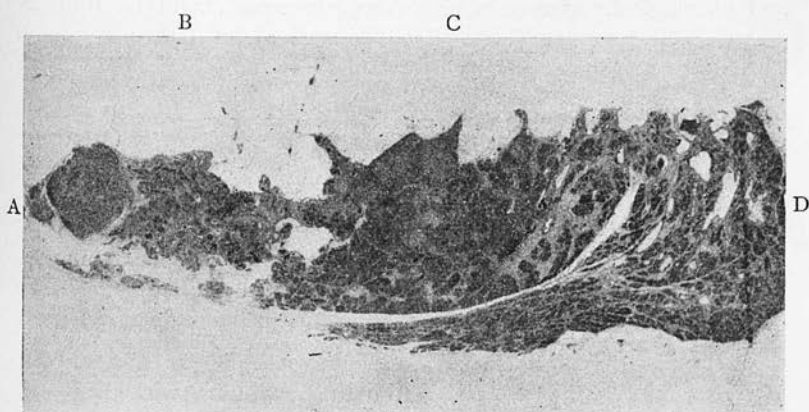


FIG. 57.—Case 2. Malignant growth removed 6 weeks after delivery. A, malignant papilloma (probably the 6-year tumour); B, area of duct cancer; C, area of lactating tissue, with extensive lymph vessel invasion; D, normal lactating tissue.

CASE 5, aged 40, 2-para; 8 months pregnant when treated. Pain in breast 3 months, lump 3 weeks, growing and nearer skin; tumour $5 \times 3\frac{1}{2}$ cm. in lower outer quadrant, hard enlarged axillary

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nodes and suspicious supraclavicular. Biopsy confirmed malignancy; breast and axilla treated with interstitial radium. Healthy child born a month later, when tumour smaller, whole breast shrunken and nodes not palpable, but mass in epigastrium and severe jaundice. Death 8 months after treatment.

CASE 6, aged 42, nursing child when examined. Lump present 2 to 3 months, small, hard, in upper outer quadrant; enlarged axillary lymph nodes. Radical amputation. Extensive recurrence in chest-wall, with œdema of arm; no physical signs of growth in thorax, but sudden death 18 months after operation (Figs. 87 and 88).

CASE 7, aged 29, 6-para, all nursed; last child 13 months old. At 4th month of pregnancy, breast painful with some nipple discharge; this breast gave no milk. Diagnosed inflammatory and breast incised; wound still discharging 18 months later. Radical amputation, axillary nodes extensively invaded. Death 18 months later, with local recurrence and metastases in liver.

CASE 8, aged 32, 3-para, youngest 11 months still being nursed when lump found 5 months before examination. This breast never filled out as the other did. Radical amputation, extensive axillary involvement. No later note.

CASE 9.—No clinical notes available, except that breast radically amputated during lactation. Axillary lymph nodes greatly enlarged and histologically showed almost complete replacement by tumour growth. No later note (Figs. 58, 66, 89 and 90).

CASE 10, aged 37, 2-para, aged 10 years and 15 months; second child not nursed. Tumour found in breast 3 months before examination; gradual growth, no pain, slight tenderness. Growth firm, circumscribed, movable, about 4 cm. diameter, no palpable axillary nodes. Diagnosed benign and segment of breast containing tumour removed. Radical amputation completed 12 days later as histological examination showed very malignant type of papillary adenocarcinoma; no tumour tissue found in mammary area of second operation and axillary nodes not invaded. No later note (Figs. 59 and 91).

CASE 11, aged 39, 4-para, still nursing child 15 months old when examined; lump found 5 months previously, with dragging pain, worse with nursing; gradual increase in size, slight nipple retraction. Tumour 5 cm. diameter, firm, irregular outline, skin and deep tissues slightly adherent; axillary nodes enlarged. X-ray of spine and pelvis showed no obvious deposits; radical amputation, axilla extensively involved. Death 14 months after treatment (Figs. 68 and 69).

CASE 12, aged 39; no note of previous pregnancies or lactation; radical amputation for malignant tumour of 6 months' duration,

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with axillary invasion; post-operative X-ray therapy. Patient became pregnant 3 months after operation and brought child to term. Death 10 months after delivery, with metastases in lung.

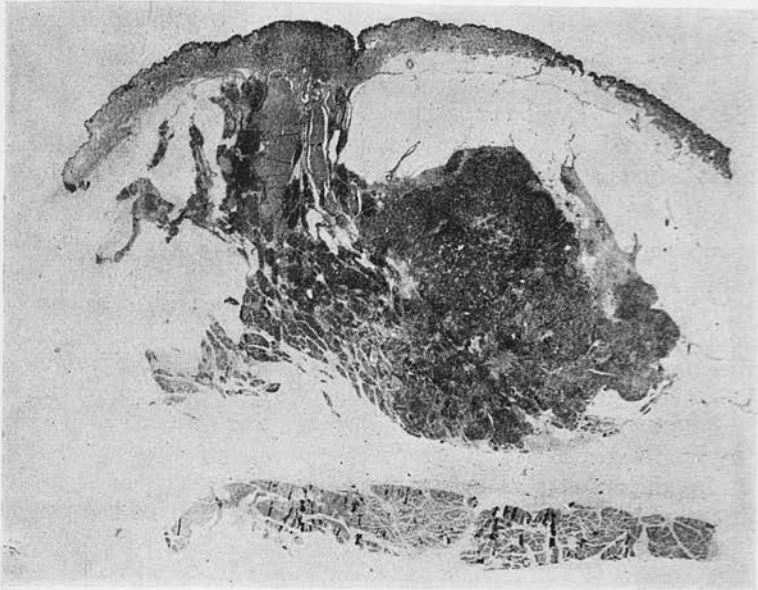


FIG. 58.—Case 9. Malignant tumour removed during lactation.



FIG. 59.—Case 10. Papillary adenocarcinoma, found 12 months post-partum. Malignant Mammary Growth during Pregnancy and Lactation (large sections).

CASE 13, aged 30, 4-para; two-stage operation, with 3 weeks' interval for a clinically benign tumour, which was hard but well-defined and freely movable; histologically, infiltrative malignant growth with invasion of axilla. Became pregnant 4 months later, and with the pregnancy, several firm, movable recurrent nodules

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appeared near scar ; these were dissected out and showed malignant growth of similar type. Two months later, when patient 4 months pregnant, more nodules in scar and scattered over thoracic wall. No later note (Fig. 67).

CASE 14, aged 31, primipara ; child 13 months old, nursed 8 months. Tumour found 3 months after lactation ceased ; hard, slightly tender nodule in upper outer quadrant. Radical amputation ; histologically, scirrhous carcinoma with marked malignant invasion of lymph vessels (Fig. 92) ; large axillary nodes almost replaced by tumour tissue. No later note.

CASE 15, aged 40, one child, still-born 16 months before examination. Ten months after delivery, patient felt whole of one breast hard ; fomented it ; recent severe pain in mammary area. Nipple retracted, entire breast hard, skin bluish with subcutaneous nodules ; skin and deep tissue fixation ; no palpable axillary or other lymph nodes. Radical amputation with insertion of radium ; small lymph nodes found adherent to axillary vein. Death 3 months later, with nodules in skin of breast and back, and metastases in spine, lung and abdomen.

Another case, a malignant mammary growth removed from a dog during lactation, is described on pp. 637-38 and illustrated on Plate VII.

These histories, though lacking in detail, bring out a number of important points. The period at which the tumour was first noticed by the patient varied considerably in this series, and the data obtained throw little light on the genesis of the growth. A small pre-pregnancy growth may easily escape detection and later, its increase in size may be masked for some time by normal mammary enlargement during pregnancy and lactation. It is improbable that carcinoma emerges *per saltum* in any tissue of the body and a study of human mammary tumours makes improbable, in my opinion, the conception of cancer beginning in the pregnancy or lactation during which it is detected. I have included in my group two cancers removed in the post-lactation involution period and two cases where pregnancy in multiparæ was associated with the recurrence of a malignant tumour removed shortly before.

The clinical features were sometimes misleading. In four cases (Nos. 3, 5, 7 and 11), pain was the first symptom ; in three (Nos. 4, 10 and 13), a two-stage operation was performed for a clinically benign tumour, and in one (No. 7) the breast

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had been previously incised for a suspected inflammatory condition. Lactation was interfered with in three cases (Nos. 3, 7 and 8). The estimated duration of the tumour varied from two or three months (No. 4) to six years (No. 2), but it is important to note that histologically only 2 of the 15 cases were grade I. or early growths; in the remaining 13, malignant disease had already involved the axillary tissues before treatment. Of the two early cases, No. 10, treated by two-stage operation, showed clinically and histologically no malignant spread beyond the actual tumour area, but in Case 4, a recent case and also clinically benign and treated by a two-stage mastectomy, the extent of malignant spread is at present undetermined, for though no lymph nodes could be found in the axillary tissue, the larger lymph vessels in the fat of the mammary area and in the pectoral fascia adjacent to the deep muscle were extensively invaded. Because of tumour fixation and gross axillary involvement, 7 of these cases would probably be considered inoperable by many surgeons to-day, even apart from the association of tumour with pregnancy or lactation. Of the 15 patients, 8 are reported dead, one is dying with multiple skeletal metastases and in 4, where no follow-up notes are available, the condition when examined was so advanced that treatment gave little or no hope of eradicating the disease. The remaining 2 cases, one lost sight of, the other recent, were possibly early growths with a hopeful outlook. Of the 8 reported fatal cases, death occurred within eighteen months after treatment, and in 3 cases within six months.

(c) *Tumour Type and Histology.*—Carcinoma associated with pregnancy and lactation is usually described as "acute cancer," of a highly malignant, rapidly growing type. The end-results in this series, where known, support this opinion, but in the majority of the cases, neither the clinical features (misinterpreted in at least 4) nor the actual type of tumour indicated an especially malignant growth. "Acute cancer," as a clinical term, usually implies rapid growth, generalised enlargement and possibly hyperæmia of the mammary area with a rise of local temperature ("inflammatory carcinoma"), a description which might have applied to Cases 1 and 15; but only in Case 2 is rapid growth mentioned, after delivery, in a tumour of six years' standing; No. 4 showed no obvious increase in size, gradual growth is noted in Nos. 10 and 11

and in others, the interval between detection and treatment is considerable.

The descriptions of the clinical appearances and gross anatomy in these cases provide insufficient data for tumour classification; but where the whole mammary area is available for histological examination, the progressive stages of malignant origin, invasion and dissemination are apparent and the type of growth varies according to the area examined. Several of the tumours indicate an origin in a papillary formation which, with active proliferation of the epithelial cells covering the vascular cores and consequent filling of the dilated ducts, has produced the cellular type of growth usually called medullary or encephaloid carcinoma. The stages of this transition from benign to malignant papillary growth are seen in the animal tumour (Figs. 48-53, Plate VII.). The history and the appearance of the tissue in Case 2 provide further evidence in favour of this conception of a pre-existing benign papilloma, as one area (Fig. 57, A) was very defined macroscopically and of papillary structure—presumably the 6-year-old tumour—though malignant and beginning to infiltrate when removed (Fig. 63). Another area (Fig. 57, B) shows a generalised duct carcinoma with much central necrosis (Fig. 64), a type sometimes called "comedo carcinoma"; lactating tissue with extensive lymph vessel invasion is present (Fig. 57, C) while an area (Fig. 57, D) is of normal unaffected lactating tissue. A small area of connective tissue infiltration, scirrhus in type, is also present, but at this level of the whole breast section, the transition from duct (comedo) carcinoma to normal tissue with infiltrated lymph vessels is unusually abrupt. It would be difficult to place this tumour in any of the usual schemes of classification. Case 10 shows a much earlier stage of papillary adenocarcinoma (Fig. 59), with the malignant cells still almost entirely confined within the cyst-wall; Case 6 also shows, in parts, the structure of a malignant papillary growth (Fig. 87), with later spread as a cellular scirrhus carcinoma and extensive lymph vessel invasion, as well as cancerous emboli in veins (Fig. 88). The very defined edge of the malignant growth in Case 11 and its "peritheliomatous" structure (Fig. 69, *cf.* Fig. 52 from the animal tumour), also suggest to me the late stage of a tumour originating in a papillary type of proliferation; in Nos. 3 and 9 there is, in parts, a somewhat similar structure, at a later, more dis-

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organised stage, in addition to non-cystic small duct carcinoma (Fig. 89 from Case 9). Six of the 15 cases, as well as the animal growth, thus indicate or suggest stages of papillary tumour formation, which at one stage was benign, though apparently observed early in only one case, No. 2. Case 1 shows no evidence of papillary structure, but began as a multiple duct cancer (Figs. 60 and 61); when removed, the main tumour mass, clinically and macroscopically a medullary growth (Fig. 54), showed an infiltrating cellular scirrhus type (Fig. 62). In the remaining cases, small sections from biopsy or operation material show malignant cell genesis in small ducts with tissue infiltration as scirrhus carcinoma (Figs. 85, 86), or only scirrhus areas without indication of the genetic type.

The findings in these pregnancy and lactation tumours thus show malignant tumour types as varied as observed at other periods of pathological growth—papillary adenocarcinoma, which at a late stage forms a medullary tumour, “comedo carcinoma,” or small non-cystic duct cancer; all, if removed at a late stage, may show malignant dissemination in the mammary tissues of a scirrhus type. All intrinsic carcinoma of the breast is necessarily glandular carcinoma and is, in my findings, duct carcinoma in its initial stages, arising from cystic or non-cystic ducts.² When the many types of mammary cancer are analysed, especially when the whole tumour area is available for histological examination, these may be more reasonably regarded as *stages of growth* rather than as different *types of growth*, if the initial variation in the non-malignant mammary background be allowed for.⁴⁵ With the exception of Case 10 and the animal tumour, all these cases had reached an advanced stage of malignant growth before treatment, indicated by areas of infiltrating scirrhus structure, with extensive lymph vessel involvement and, in some cases, even blood vessel invasion.

The cytology in these tumours varies as greatly as their tumour type (Plates VIII., IX. and X.). Judged by criteria such as “differentiation,” nuclear hyper-chromatism, frequency of mitotic figures, etc., only in two cases, 10 (Fig. 91) and 11 (Fig. 68) would the histological type of growth be termed highly malignant; but if we assess the actual malignancy of mammary carcinoma by the facilities for and the evidence of extension of the cancer cells in microscopic section, rather

than merely by cellular type and architecture, all the tumours in the series, with two exceptions, Case 10 and the animal growth, fall into a highly malignant category. In Case 10, though the tumour was of an anaplastic type, with numerous mitoses, irregularity in size of cell and nucleus and giant cell forms (a small area is seen in Fig. 91), the growth was still almost entirely confined within a large cyst (Fig. 59), the axillary nodes examined were not invaded and the tumour had been excised locally as a clinically benign lesion.

The facilities for malignant growth and dissemination are very evident in pregnancy and lactation tissue. The vascularity of the proliferating and secreting lobule has been noted and we may assume that malignant growth, if already present, would grow more rapidly on this account, as in all young and active tissues. More striking than this hyperæmia, however, and of more importance in cancerous spread in the earlier stages, is the abundant lymph drainage of breast tissue during reproduction. Whether already existing lymph vessels become more obvious because distended, or whether new ones are formed *pari passu* with the increased vascularity, would be difficult to demonstrate on a comparative basis, as in non-functioning mammary tissue lymph tracts are not easily recognised unless distended by malignant cells. The finding of Stiles⁴⁷ that new lymph germ centres develop in the axilla during reproduction suggests, however, that lymph vascularity in the mammary area is actually increased at this period. Lymph vessels in relation to normal ducts and lobules are shown at the fifth and ninth months of pregnancy in Figs. 24 and 11, at *x* respectively, in normal lactating tissue at ten weeks

PLATE VIII

Malignant Mammary Tumours in Pregnancy and Lactation

- FIG. 60.—Duct carcinoma (d) in late pregnancy, showing unaffected lobules (l) and spread into secreting tissue (s) (*cf.* Fig. 84). Case 1.
- FIG. 61.—Another area of tissue seen in Fig. 60 showing duct carcinoma, without secreting tissue. Case 1.
- FIG. 62.—An area of infiltrating growth from tumour shown in Figs. 60, 61. Case 1.
- FIG. 63.—Malignant mammary tumour, of papillary type, showing periphery with early invasion. The whole papillary area is seen in Fig. 57, at A. Case 2.
- FIG. 64.—An area of "comedo carcinoma" (duct cancer), without lobule formation in a lactation tumour. See Fig. 57, at B. Case 2.
- FIG. 65.—An area from the lactation tumour seen in Figs. 63, 64, showing lymph invasion (*cf.* Fig. 57, at C). Case 2.

FIG. 60

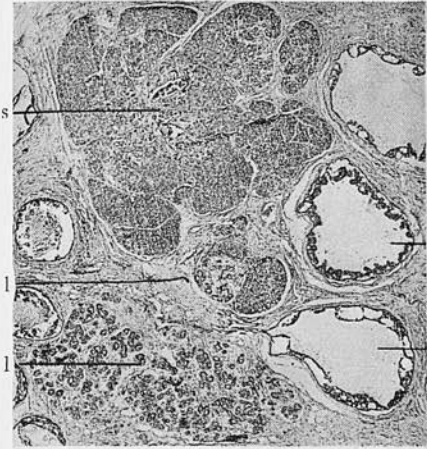


FIG. 61

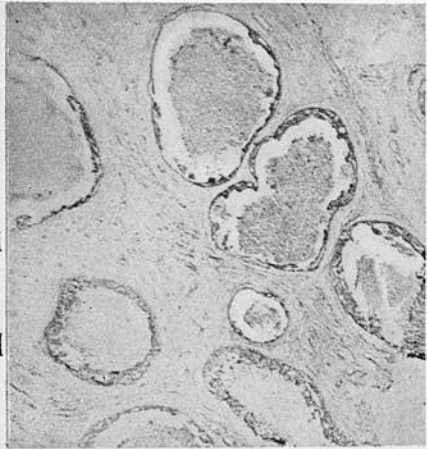


FIG. 62

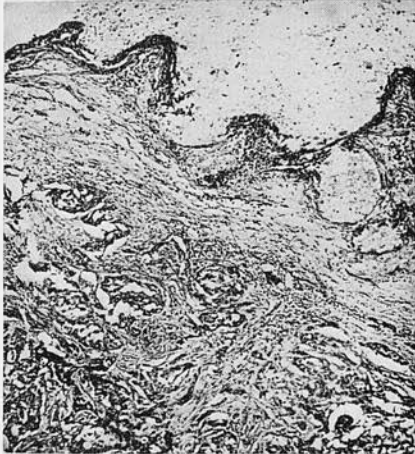


FIG. 63

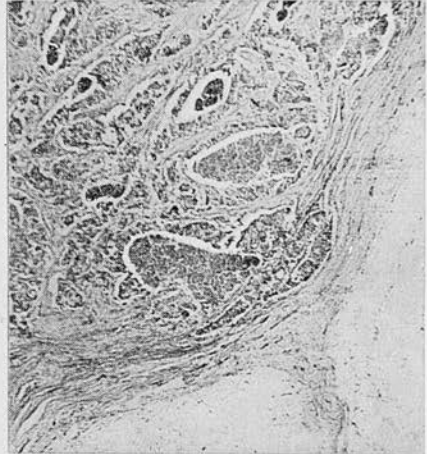


FIG. 64

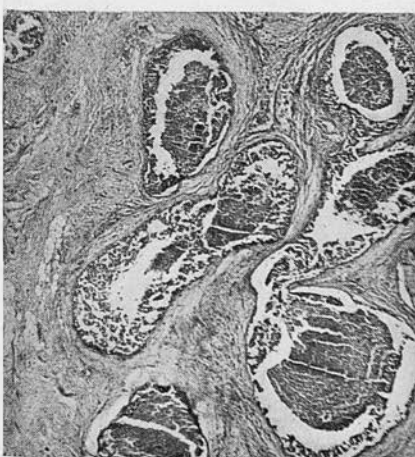


FIG. 65



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in Fig. 18, *x*, and entering an axillary lymph node removed during lactation in Fig. 25. Lymph vessels apparently return slowly to their normal distribution and calibre, as tissue examined three months after lactation had ceased shows them still widely distended (Fig. 26). This is not surprising when we consider the amount of proliferated lactating tissue which has to be removed by these channels when nursing ceases.

Evidence of the transport of malignant cells by lymph vessels, when cancer is associated with reproduction, is abundant. In my series, it was observed in all the tumours examined, except the two early cases (No. 10 and the animal growth); neither of these showed invasion of the axillary lymph nodes. In Case 4, as already noted, though no nodes were found in the axillary tissue, the lymph vessels were invaded to the deep layers of the pectoral fascia. Lymph vessel invasion is illustrated in Figs. 65, 67 (*l*), 69 and 92, in tissue from Cases 2, 11, 13 and 14 respectively; lymphatic permeation of the whole mammary area was observed eighteen months after lactation in a malignant case not included in this series (Fig. 71).

The highly malignant character of these tumours, as evidenced by extensive cancer cell dissemination by the lymph stream, is amply demonstrated by these histological findings; but a more ominous feature is also present which, in my opinion, throws light on the short post-operative duration of life in these cases. The increased vascularity and congestion of the tissue in which tumour has developed, associated with extensive malignant invasion of the perivascular lymph vessels, leads, as we should expect, to the possibility of malignant cells entering the blood stream. This was actually observed in 6 of the 14 cases which showed invasion of the lymph stream—Cases 1, 6, 9, 11, 13 and 15; two instances are illustrated (Figs. 69 and 88). The follow-up notes on these 6 cases, though incomplete and lacking autopsy findings, are instructive. Death occurred in Case 1 in six months, with metastases in the liver; suddenly, in Case 6, eighteen months after operation; in Case 11, fourteen months after treatment, but no clinical notes are available after leaving hospital; in Case 13 extensive malignant involvement of the thoracic wall developed; and in Case 15 death occurred three months after operation, with metastases in spine, lung and abdomen and subcutaneous nodules on the back. Case 9 was lost sight of. Invasion of the blood stream may have occurred in some of the

other cases, where only small areas of tumour tissue were available for examination. The discovery of such invasion, unless very widespread, is necessarily largely a matter of chance in the plane of the tissue examined, even in whole breast sections; but the later histories of Case 3 (multiple deposits in spine, pelvis and ribs seven months after operation), of Case 5 (tumour mass in epigastrium and severe jaundice, with death eight months after treatment), of Case 7 (metastases in liver with death eighteen months after operation) and of Case 12 (death with metastases in lung ten months after child-birth) suggest at least the possibility of blood stream dissemination. It is true that these distant deposits of malignant cells have been explained by lymph vessel permeation,⁴⁸ but the duration of life after operation was short in this series and Willis's autopsy examinations have shown that spread of cancer by the blood stream is more frequent than is usually supposed.⁴⁹

(d) *Sarcoma*.—My material provides no case of sarcoma associated with pregnancy or lactation, and I have found no record of a case in the literature. Kilgore⁴⁵ does not mention sarcoma in his series of mammary lesions of all types first noticed during lactation. The clinical data in cases of sarcomatous mammary growth in my tumour material are inadequate for any reliable conclusion as to association with reproduction. We should not expect sarcoma to arise or emerge in pregnancy or lactation, when mammary activity is directed towards epithelial proliferation and differentiation,

PLATE IX

Malignant Mammary Tumours in Pregnancy and Lactation

- FIG. 66.—Malignant mammary tissue showing discharge of secretion (c) into a duct partly filled with tumour cells (m). See also Figs. 89 and 90, Plate X. Case 9.
- FIG. 67.—Mammary tissue showing edge of malignant tumour, with lymph vessel invasion (l) beyond the edge. Tumour clinically well-defined and freely movable. Case 13.
- FIG. 68.—Malignant mammary growth removed during lactation, showing anaplastic type of tumour cell, with numerous mitoses (m) and monster cells (x). Case 11.
- FIG. 69.—Malignant mammary growth, removed during lactation, showing tumour cell emboli in a dilated blood capillary. Case 11.
- FIG. 70.—Mammary tissue in lactation showing elastic tissue (e) round a normal duct. No lactating lobules are seen in this area.
- FIG. 71.—Malignant mammary tumour removed 18 months after lactation, showing extensive malignant growth in lymph vessels (l) surrounding a normal duct (d).

FIG. 66

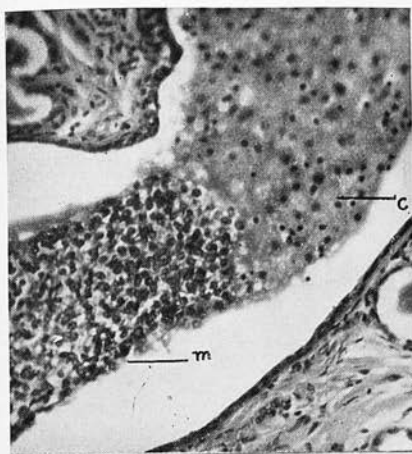


FIG. 67

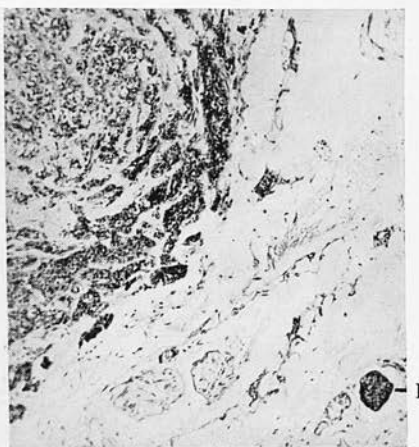


FIG. 68

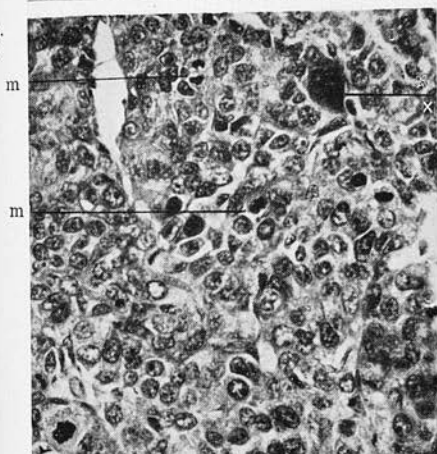


FIG. 69

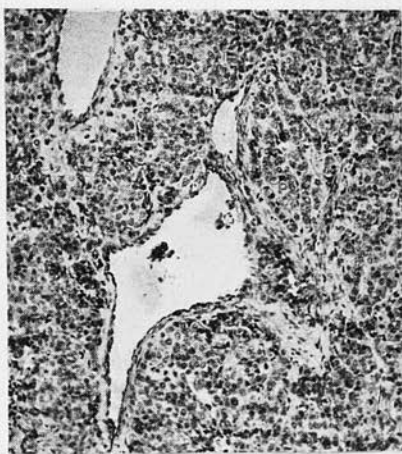


FIG. 70

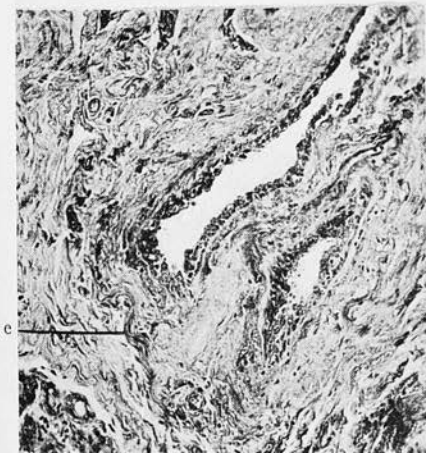
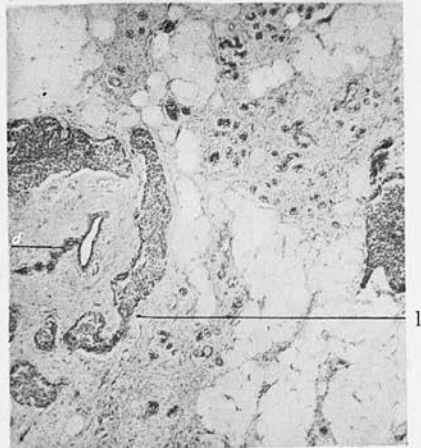


FIG. 71



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with a temporary decrease of the connective tissues. Kon⁵⁰ reports the case of a woman, aged 40, with a swelling in the breast since the last child-birth eight years previously and some bleeding from the nipple for one month. Radical operation was performed and the tumour found to be a polymorphous-cell sarcoma; the axillary lymph nodes, though enlarged, were not invaded and the patient was well three years later. This suggests a fibro-adenoma arising in post-lactation involution, as described earlier in this paper, with excessive fibrosis and later sarcomatous transformation.

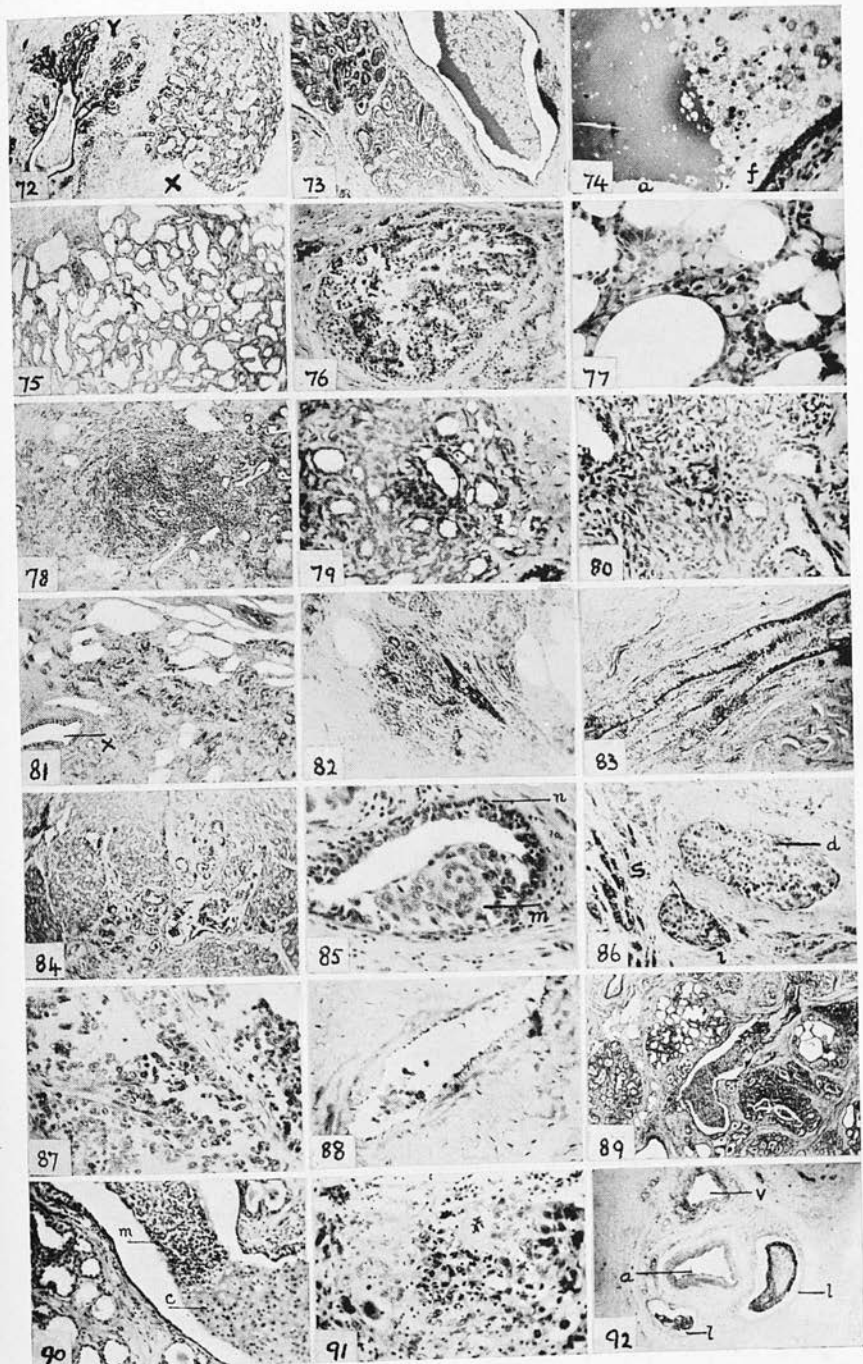
(e) *Discussion.*—Carcinoma emerging during pregnancy and lactation raises questions which, in my opinion, are fundamental to an understanding of the problem of malignant growth in mammary tissue.

i. *The Relation of Malignant Mammary Tumour to Reproduction.*—These tumours are usually described as “arising during pregnancy and lactation,” but it is difficult to say when they originate, as mammary enlargement associated with physiological hyperplasia and function is likely to conceal the early stages of malignant development, and the growth, in some cases, becomes apparent only with post-lactation glandular involution. A small benign tumour may have been present for a considerable time undetected, and the histological structure of the malignant area in several of the tumours examined indicates or suggests that the epithelial proliferation was of papillary type. I find it difficult to accept the possibility of papillary growth arising during reproduction in a tissue whose activity is directed towards the formation of secreting glandular structures. It seems probable that where a carcinoma of papillary type emerges at this period, there was a pre-existing benign tumour, which may or may not have already undergone malignant transformation before pregnancy supervened. The rarity of breast cancer in lactation—1·5 per cent. of mammary cancer at all ages in the 3-year figures already noted—and its frequency in older and in nulliparous subjects, suggest that where there is no pre-existing growth, malignancy does not emerge during reproduction. This position is supported by Ewing's opinion that lactation is more or less a safeguard against mammary cancer.⁵¹ The genesis of malignant tumour which histologically shows no papillary structure, presents greater difficulty, but even here a pre-existing lesion is suggested, evident as a benign or malignant epithelial hyperplasia

(epitheliosis) in the ducts, which inhibited their response to physiological stimuli. This would explain the absence of secreting tissue in the primary tumour area. Had pathological growth developed subsequent to the onset of physiological proliferation, it is unlikely that all traces of secreting tissue would have been destroyed by a malignant process which tends to spread rapidly along the lymph channels rather than by destroying and replacing the structures in its path. The complete absence of secreting tissue in the tumour area even before invasion from the malignant ducts had occurred, is seen in Figs. 61 and 64 (Cases 1 and 2 respectively); Fig. 60 from Case 1 shows a similar picture, combined with normal secreting lobules produced from the unaffected intralobular ducts of the area. In this case, however, malignant growth from the ducts was extending into the normal lobules and destroying the lining cells of the secreting structures (Fig. 84).

PLATE X

- FIG. 72.—Lactating lobule (x) and undifferentiated ("virginal") lobule (y) in a breast of 15 months' lactation.
- FIG. 73.—Lactating lobules and duct with secretion.
- FIG. 74.—Secretion in duct (albuminoid (a) and fatty (f) elements).
- FIG. 75.—Mammary lobule one month post-lactation (*cf.* Fig. 28).
- FIG. 76.—Mammary lobule 3 months' post-lactation (*cf.* Fig. 29), showing acinar collapse and disintegration.
- FIG. 77.—New fat formation—5 months' post-lactation.
- FIG. 78.—Delayed post-lactation mammary involution, after failure to nurse.
- FIG. 79.—The same, high power.
- FIG. 80.—The same, a more fibrous area.
- FIG. 81.—Breast tissue, 12-para, no lactation (*n.b.* unaffected duct, x).
- FIG. 82.—Another area from same tissue as Fig. 81.
- FIG. 83.—Two patent mammary ducts uniting to open on nipple surface.
- FIG. 84.—Malignant tissue spreading into and replacing lactating acini (Case 1). *Cf.* Fig. 60.
- FIG. 85.—Origin of malignant growth in small duct—lactation tumour—m, malignant area; n, normal duct wall. Case 3.
- FIG. 86.—Origin of malignant growth in lactation tumour (Case 4). d, small duct; l, invaded lymph vessel; s, scirrhous area.
- FIG. 87.—Malignant papillary growth in lactation tumour. Case 6.
- FIG. 88.—Malignant cells in vein. Case 6.
- FIG. 89.—Normal lactating lobules emptying into malignant duct (centre). Case 9.
- FIG. 90.—Duct of Fig. 89, showing malignant cells (m) and secretion (c). *Cf.* Fig. 66. Case 9.
- FIG. 91.—Anaplastic malignant tissue lining the cyst in a papillary growth—lactation tumour, Fig. 59. Case 10.
- FIG. 92.—Invasion of lymph vessels (l) in lactation tumour (Case 14); v, vein; a, artery.



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The coincidence of malignant ducts and normal secreting lobules in the same area is also seen in Figs. 66, 89 and 90, which show the same duct containing secretion and cancer cells.

Both these types of malignant growth, the papillary and the lining cell proliferation without vascular cores, suggest epithelial activity antecedent to the onset of physiological mammary hyperplasia in pregnancy, but the possibility of pregnancy itself producing malignant epithelial growth must be considered. Does the increase of glandular tissue—adenosis—characteristic of reproduction ever lead to carcinoma in the breast? Adenomatous hyperplasia is considered in the literature of the subject as a possible origin of malignant tumour and the question has been discussed in an earlier paper.² Ewing⁵² describes types of "acinar carcinoma" characterized by multiplication of acini, with later invasion of the surrounding mammary tissues. He does not associate this glandular proliferation with reproduction, though in one type—"primary acinar carcinoma"—there is "an extensive multiplication of acini in rather well-defined lobules . . . the structure somewhat resembling the lactating breast." Adami⁵³ described adenocarcinoma as characterized by "numerical increase of ducts," the proliferation which leads to malignancy "usually starting in lobules as an acinous arrangement recognisable in older parts of the growth." MacCallum⁵⁴ also describes adenocarcinoma originating from adenomatous nodules; he considers that malignant growth may arise from mammary adenoma, if the cells burst through the basement membrane and lie loose in connective tissue spaces, though he observes that it is difficult to show this transition histologically. There is, on the other hand, much opinion against the view that malignant tumour in the breast originates from glandular overgrowth, whether associated with pregnancy or not. Charteris⁵⁵ finds that the epithelial activity which is of consequence in pathological mammary hypertrophy is not concerned with the formation of new acini, but with cellular proliferation within glandular structures,—that is, with epitheliosis. McFarland³⁵ considers "the carcinomatous development of an adenomatous growth the rarest event," and finds there are almost no cases in which it is clinically confirmed. Crile, Telkes and Rowland⁵⁶ state that "cancer cannot attack the cells of a hyperplastic gland," while Cheatele⁸ has been unable to trace any microscopical indication of a

transformation of mazoplasia, "an almost physiological condition with an increased number of acini," into carcinoma. Experimental work suggests that the œstrogenic principle may produce adenomata or fibro-adenomata of the breast,⁵⁷ but it does not appear that it is capable of producing carcinoma.⁵⁸ My studies, based on the examination of over 1000 malignant mammary tumours cut in large or small sections which, in almost all cases, show the genesis of cancerous proliferation, have provided no evidence that carcinoma in the breast develops from adenomatous proliferation, still less from proliferated glandular tissue which has undergone secretory changes. Bloodgood⁵⁹ considers that no tumours of the breast give histological pictures similar to lactation hypertrophy, and Berka¹⁴ was of the same opinion. The type of epithelial proliferation produced by pregnancy—adenosis—is, in my opinion, essentially physiological and different in kind from the epithelial activity—epitheliosis—which may lead to malignant growth. This in itself may explain the rarity of cancer emerging during this period; it also suggests that possibly all the cancerous tumours which become apparent during gestation or lactation were already active, though undetected and not necessarily already malignant, before the stimulus of pregnancy affected them.

I have found no evidence that cancer cells originate in the secreting acini. Growth in the lobule would appear finally checked by the differentiation of ductules to form secreting structures; these are lined by only one layer of epithelial cells, differentiated for secretory function and apparently incapable of reverting to proliferative activity. One would hardly expect to find progressive vegetative growth arising in a tissue so specialised for function that it does not normally survive beyond the period which called for its formation, but disappears after the cessation of lactation. In the tumours associated with reproduction which I have studied, the cancer cells in all cases originated in the ducts, which do not form part of the secreting surface of the gland. Malignant growth along the ducts may later involve the lobules, when it destroys and replaces the secreting cells, but more usually, tumour extension occurs by the connective tissues and the lymph stream.

ii. *Diagnosis of Malignancy in Lactation.*—The clinical diagnosis of pathological growth in the breast associated with

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pregnancy or lactation may present difficulty, especially in the early stages of tumour formation ; the histological diagnosis, even from biopsy tissue, should not do so, if the distinction between adenositis and epitheliosis be accepted. In this and earlier studies, I have laid emphasis on the finding that *adenositis as such is not the starting point for malignant development in the breast*. It is possible that epitheliosis may be a later and secondary activity within the hyperplastic glandular elements and by continued cell proliferation, lead to actual carcinoma, but I have not yet observed this as, in my findings, malignancy originates in the ducts and adenositis mainly affects the ductules. The significance of glandular overgrowth, if normal in type, is rarely misinterpreted, but when the proliferated structures are distorted by fibrosis, or occur in association with conditions such as acute or subacute inflammation or a thick-walled cyst, all of which clinically may suggest tumour formation, the histological picture has been not infrequently erroneously considered malignant. Bloodgood has followed and re-studied a series of such cases, called by him "border-line lesions," and although histologists disagreed as to the nature of the epithelial proliferation and diagnosed it as cancer or "suspicious of cancer" or adenocarcinoma, he found that in none of the cases did malignancy subsequently develop, even after limited resection.^{43, 60} Some of Bloodgood's histological illustrations are very similar to those presented in this paper and here regarded as normal or delayed post-lactation mammary involution, without any suggestion of malignant development (see Figs. 31, 32, 38, 41-45 and 78-80). In these involution pictures, I have observed that the epithelial cells disintegrate before the disappearance of the basement membrane, an important diagnostic point which receives confirmation with a high power lens. Malignant epithelial cell incursions are not ringed in this way. Bloodgood urges study of these "border-line lesions" which, in his opinion, have always exaggerated the operative cures of cancer of the breast ; but it is also helpful in diagnosis to learn to recognise the physiological mammary picture of pregnancy and lactation and the variability of the post-lactation involution process. A more adequate lactation history than is usually available for the pathologist would also be of assistance.

The conception of "differentiation" in malignant mammary growth may be, in part, responsible for the histological diagnosis

of the lactation or post-lactation involution picture as adenocarcinoma. Differentiation, as a descriptive term in the literature, may imply "adenomatous arrangement" ⁶¹ or "tubule formation" ⁶² of the epithelial cells, or an adult cell morphology, ⁶³ or evidence of secretory activity. ⁶³ The pregnancy and lactation tumours in my series show no such "differentiated" characters. The malignant growth before invasion is a duct carcinoma, papillary or without vascular cores; after invasion, all the tumours show a more or less cellular infiltration of the connective tissues with a scirrhous reaction and without adenomatous or tubular architecture or "secretory vacuoles"—I do not include tubular growth in a pre-formed channel such as a lymph vessel. This is in keeping with the highly malignant character of mammary tumour in gestation, but it makes obscure the bearing of "differentiation" as an inhibitory factor on cancerous cells.

iii. *Prognosis and Treatment in Lactation Cancer.*—The prognosis and treatment of mammary cancer in pregnancy and lactation is outside the scope of this study, apart from the light thrown on both questions by the histological characters. These give evidence of rapid growth and early dissemination, by the lymph and also possibly by the blood stream, of tumour which, it is suggested, ante-dated the onset of pregnancy. Early cases (grade I., without axillary involvement) are therefore rare and prognosis, except in these, is extremely grave. All the isolated cases I have found in the literature, unless reported soon after treatment, proved rapidly fatal, with skeletal, thoracic or abdominal metastases. Odermatt, ⁶⁴ Wolff, ²⁴ Lee ⁶⁵ and Sistrunk and MacCarty ⁶⁶ have reported series of cases, with very similar results. With regard to treatment, Hueper, ⁶⁷ Hertzler ⁶⁸ and indeed most clinicians regard these tumours as surgically inoperable. Kilgore, ⁴⁵ however, considers that "the prognosis of cancer of the breast in connection with pregnancy and lactation is anything but hopeless, and the benefit of immediate complete operation should be given in each case." He found, in the series of 49 malignant cases already referred to (p. 639), that 8 patients were well four and a half to twenty-one years after operation, a survival rate of 17 per cent. These cases were "all definite medullary or scirrhous carcinoma," none being of the "border-line or adenocarcinoma type." The condition of the axillary lymph nodes is indicated in only 33 of the 49 cases (7 not invaded, 26 invaded); 5 of the

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8 "cures" are in the early non-invaded (grade I.) group. Although MacCarty, discussing these results, described them as "extremely unusual" (he found all the pregnancy and lactation cancers treated at the Mayo Clinic fatal within five years), one might accept the survival of the 3 grade II. or III. tumours in the remaining 44 cases (6.8 per cent.), were adequate illustration presented. Unfortunately for an argument which is contrary to general experience, only one "cancer in lactating breast" is shown in microscopical section; this tumour was discovered at the seventh month of pregnancy, the child was nursed for a year before operation and the patient was well twenty-one years later. An area from this tumour chosen for illustration does not, in my opinion, show any malignant growth, but only milk ducts and lactating lobules. Any "cured carcinoma" associated with pregnancy or lactation is so unusual as to demand convincing histological illustration.

In a number of reported cases where the patient became pregnant after mastectomy for mammary carcinoma, malignant growth appeared in the remaining breast and proved rapidly fatal.^{21, 60} The short interval between the detection of carcinoma in both mammæ, in some of these cases, suggests that the second tumour was a metastatic rather than a primary formation. My material provides no case of pregnancy after mastectomy associated with the emergence of tumour in the other breast. Castration by radiotherapy of married women treated for mammary carcinoma before the menopause⁷⁰ or the interruption, at an early stage, of a subsequent pregnancy^{64, 65} has been advocated in these circumstances. In this connection, Keynes⁷¹ records a case which, in my knowledge of the literature, is sufficiently unusual to demand notice. The patient, aged 44, was treated for mammary carcinoma (confirmed by biopsy) with interstitial radium; fourteen months later she became pregnant, and as, at the fifth month, there was no sign of tumour recurrence, the pregnancy was allowed to proceed to term. The infant was nursed at both breasts, the treated one lactating normally; three years and ten months after treatment, *i.e.* two years after parturition, there was no sign of trouble and the patient was well. Writing in 1932, this was the only such case which Keynes had encountered; in two other cases he advised termination of pregnancy.

Writing in this journal twenty years ago, Barbour and

Ballantyne⁷² asked three pertinent questions regarding the subject-matter of this study—Why is breast cancer so rarely associated with gestation? Why does the association lead to rapid growth of the cancer? and, What is the bearing of the association on the nature of pregnancy and the origin of cancer in the breast? This paper is an effort, from the histological side, to throw a little light on these problems.

9. Summary

1. Mammary growth and function in pregnancy and lactation are described and illustrated.

2. The pregnancy stage shows glandular proliferation—adenosis—with progressive differentiation which eventually checks growth in the lobule; the lactation stage shows functioning of the differentiated, *i.e.* secreting cells, side by side with some degree of continued adenosis.

3. After lactation, the newly-formed secreting glandular structures degenerate and eventually disappear and the mamma reverts to an inactive condition.

4. This post-lactational involution is a variable process and is possibly delayed or prolonged by such conditions as infection, absence of lactation, etc.

5. Abnormal post-lactational involution may give rise to benign tumour formation (fibro-adenoma or fibro-adenomatosis). No association with malignant development has been traced in the tissue examined.

6. Benign mammary tumours—adenomata—emerging during pregnancy and lactation are discussed and illustrated. It is suggested that they are pre-existing formations.

7. A mammary papilloma in a lactating animal, showing secretory activity side by side with progressive stages of epithelial proliferation to malignant growth, is described and illustrated.

8. A study of malignant mammary growth associated with pregnancy or lactation is based on the detailed histological examination of 15 cases. The clinical picture and the tumour type and histology are described and various problems raised by the coincidence of malignant growth in the mamma with gestation are briefly dealt with.

Histological Study of Normal Mamma

10. Conclusions

1. No evidence has been found to suggest that mammary proliferation and function during pregnancy and lactation are associated with the genesis of benign or malignant tumour. The new epithelial tissue produced during gestation is essentially physiological in kind and different from that which may lead to carcinomatous development.

2. It seems therefore justifiable to assume that the benign and malignant tumours which become apparent during pregnancy and lactation are pre-existing formations.

[A third and concluding study in this series will appear in due course.]

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CARCINOMA OF THE BREAST

SURVIVAL FOR 24 YEARS WITH LOCAL RECURRENCES AND METASTASES IN THE OPPOSITE BREAST AND AXILLA

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ALTHOUGH the survival for many years of patients who have been subjected to radical operation for carcinoma of the breast is comparatively common, the successful treatment of a metastatic growth in the opposite breast and secondary invasion of lymph nodes in the opposite axilla appears to be sufficiently rare to warrant the publication of the case.

In 1910 the patient, a married female aged 47 years, primipara, was admitted to the Edinburgh Hospital for Women and Children, where Dr. Elsie Inglis performed a radical operation for scirrhus carcinoma of the right breast. The pectoral muscles were removed and the axilla cleared.

In 1921, the patient, aged 58 years, was re-admitted to undergo an operation for uterine prolapse. The menopause had been complete since the age of 50 and her health had been excellent. On examination, the operation scar was noted to be sound and healthy except for a small scab at the lower end which had persisted since the operation.

In 1922, she reported with a small lump at the lower end of the scar noticed 10 days previously and increasing in size with redness of the skin. Examination showed a hard lump the size of a florin, disc-shaped and lying in the thin tissue over the fifth intercostal space. It was movable on the chest wall, but the overlying skin was fixed, red and glazed. One and one-half inches lateral to it was a second nodule the size of a pea.

At operation both nodules were removed with a sufficient ellipse of skin and subcutaneous fat. Histological examination revealed that the nodules showed scirrhus carcinoma with tumor cells present near the skin margins (Fig. 1, the larger nodule, and Fig. 2).

In 1931, the patient reported with a swelling in the left (opposite) axilla, present for 12 months and gradually increasing in size, with occasional ulceration and the discharge of an offensive yellow fluid. Examination showed a small mass in the left axilla which appeared to consist of several lymph nodes matted together, about the size of a golf ball and adherent to the underlying tissues. The skin overlying was inflamed and fixed, and serous fluid exuded on pressure. At the same time, the scar on the right side showed three separate, flat, reddish nodules fixed to the underlying tissues about the midclavicular line. No clinical lesion was found at this time in the left breast. The left axilla was treated by one of us (M.C.T.) with 100 milligrams of radium at 2 centimeters and the three nodules in the original scar with 25 milligrams at 1 centimeter on surface applicators, each application delivering one skin erythema dose (600,000 ergs per cubic centimeter).

Three months later there was still a tumor the size of a walnut in the left axilla; it was scabbed and still fixed to the skin but was now movable over the deeper tissues. The left nipple now showed a slightly reddened area on its lateral aspect and was scaly; on palpation, the discolored area felt thickened. The thickened area in the left breast was excised locally, with the nipple (Figs. 3 and 4). The

nodes in the left axilla with the surrounding fat and the overlying skin were dissected away (Figs. 5-7).

Since this last treatment early in 1931, the patient has remained under supervision and has been very well. She was employed as a cook in an Institution since the first operation in 1910 until 1933, when she regretfully retired on her old age pension.

She was examined and photographed in September, 1934 (Fig. 8). At the age of 71, she feels well and able to do her own housework and to help to nurse an invalid. The scar of the primary operation (right side) shows an area of very dark pigmentation with some hyperkeratosis, but no sign of active disease. The left breast shows a linear scar in place of the nipple but is soft, movable, and appears normal for a woman of this age. There is a scar in the left axilla but it is perfectly movable and there are no palpable nodes. No nodes are palpable in either supraclavicular region. There is no cough, no shortness of breath, no swelling of the abdomen. Sometimes she feels a little stiff but has no pain anywhere.

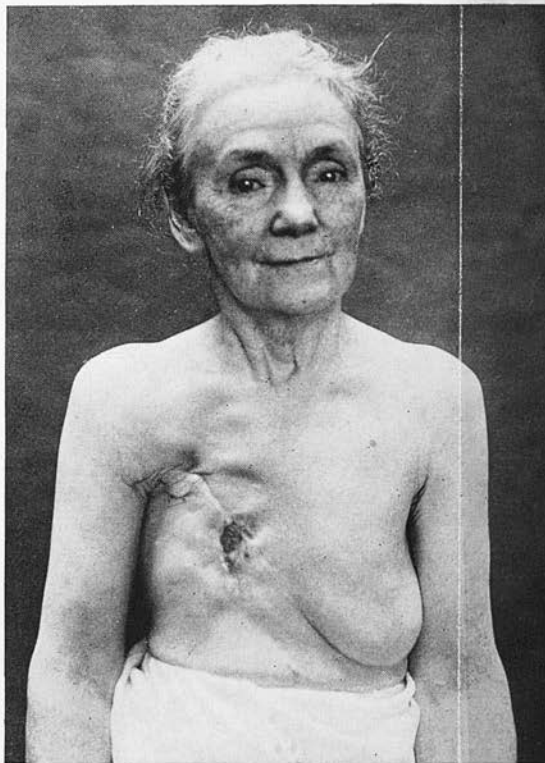


Fig. 8. The patient in September, 1934, aged 71 years, 24 years after primary radical operation (the darkened area in the scar is largely pigmentation).

¹Carnegie Research Fellow.



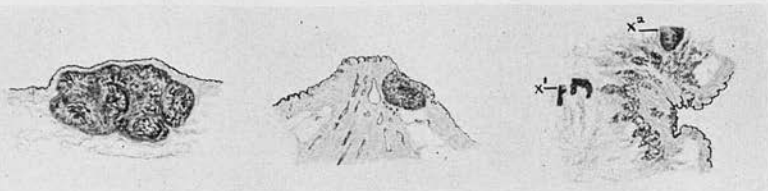


Fig. 1.

Fig. 3.

Fig. 5.

Fig. 1. First recurrence in scar, right side. Reduced $\frac{1}{6}$.
 Fig. 3. Metastatic nodule, left breast. Reduced $\frac{1}{6}$.
 Fig. 5. Tumor, left axilla, skin, nodes, *x*. Reduced $\frac{1}{6}$.



Fig. 2. Scirrhous carcinoma, peripheral area of first recurrence, Figure 1. $\times 70$.



Fig. 4. Nodule of scirrhous carcinoma, metastatic in left nipple. (cf. Figure 3.) $\times 70$.

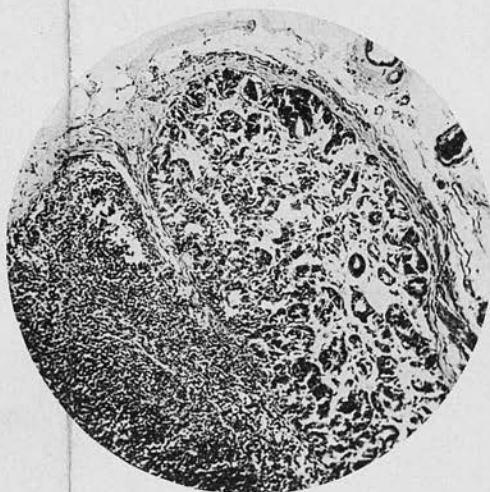


Fig. 6. Lymph node left axilla with malignant invasion. cf. Fig. 5, *x'*. $\times 70$.

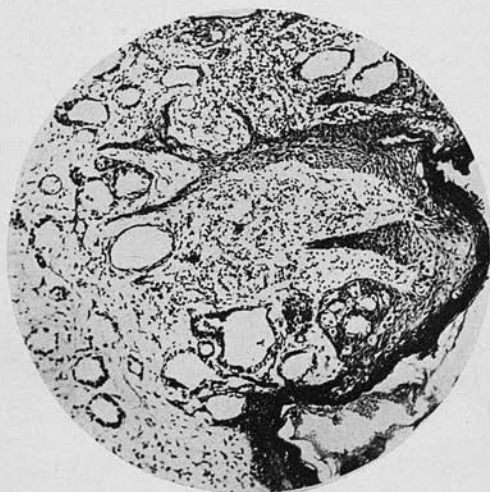


Fig. 7. Skin of left axilla (irradiated) with Paget-like changes and malignant cysts. (cf. Fig. 5.) $\times 70$.

Histology of the different areas examined. The original operation tissue is not available. The first recurrence in the scar shows glandular carcinoma, a typical scirrhous growth (Fig. 2). The nodule from the left breast shows a similar histological structure (Fig. 4) though somewhat more cellular. In our opinion, the position of the nodule (Fig. 3), the nature of the growth, and the absence of involvement of the mammary gland tissue suggests a metastatic tumor rather than a new and independent neoplasm in this opposite breast. The axillary tissue on this side shows malignant infiltration reaching to the skin and two small nodes invaded by cancer cells (Figs. 5, at x, 6, and 7). The cells are active in spite of irradiation. The Paget-like changes in the axillary skin and the small cystic areas with partially necrotic tumor cells may be due to radium treatment (Fig. 7). This left axillary area of carcinoma may be an independent metastasis but, more probably, is a secondary spread from the skin nodule in the left nipple, though the latter became evident clinically at a later stage.

It is not suggested that there is any special interest in the method of treatment, which merely followed the manifestations of the disease. The unusual feature is the extraordinary degree of resistance shown by this patient to the malignant

growth. The survival is not exceptional. At the Clinical Congress of the American College of Surgeons in 1932, where special emphasis was laid on the curability of cancer, Wainwright reported 3 cases well and apparently cancer free for over 20 years, though none showed recurrence or metastasis; Guthrie reported 1 case well for 16 years and McLean 9 cases well for 15 to 25 years. Pfahler and Parry¹ reported 22 cases alive 20 to 22 years after treatment; 6 of these had recurrences treated, none had metastases. Our patient had malignant tumors of the opposite breast and axilla which, from the clinical course and result of treatment, we consider are probably metastatic; a primary growth in the second breast and axilla is unlikely to have remained clinically cured for nearly 4 years after local excision of superficial nodules. The mode of involvement of the second breast is obscure in the absence of any clinical evidence of spread across the sternum.

¹Ann. Surg., 1931, 93: 412.

STUDIES IN THE NORMAL AND PATHOLOGICAL HISTOLOGY
OF MAMMARY TISSUES.

(with illustrations by the writer.)

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