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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. Coen [11] 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 Bloodgood [44] 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. Kilgore [45] 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. Encapsuled 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

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, *l*, 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 fibro-adenomata 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

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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. ×20.

FIG. 49.—The benign stage of the papillary growth in a cyst, showing a lactating area (x). ×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). ×200.

FIG. 51.—An area of the papilloma seen in Fig. 49, showing basal cell proliferation without secretory activity. ×200.

FIG. 52.—A later stage of tumour cell proliferation, showing a papillary adeno-carcinoma, of basal cell type (*cf.* Fig. 48, y). ×200.

FIG. 53.—Another area of the same mammary tumour, showing invasion of tissues near the skin by malignant growth of squamoid cell type. ×200.

FIG. 48

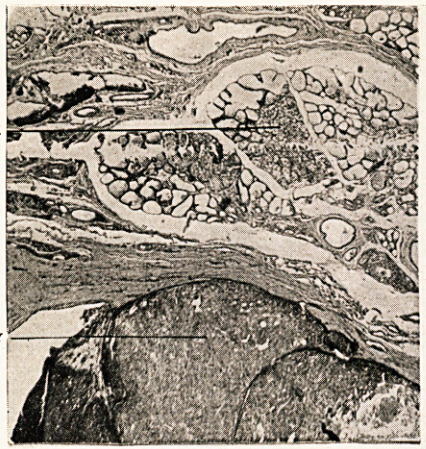


FIG. 49

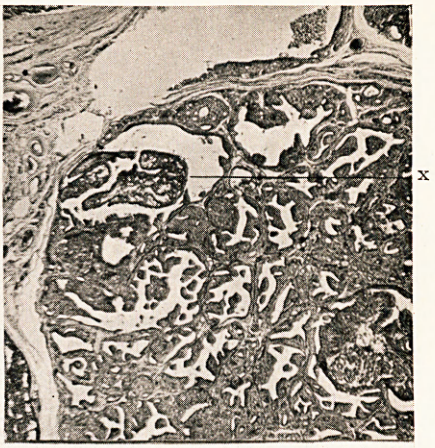


FIG. 50

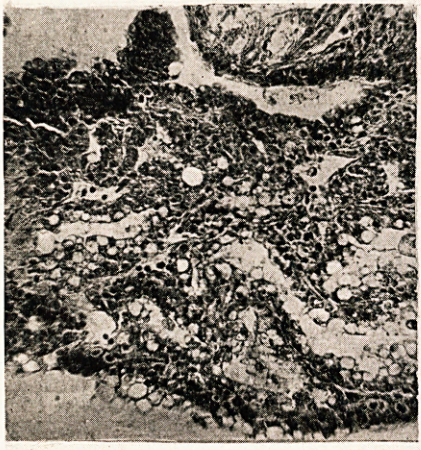


FIG. 51

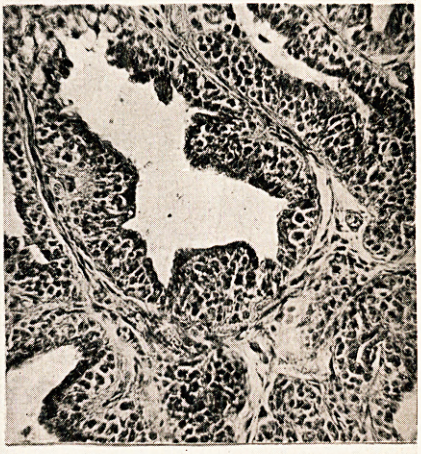


FIG. 52

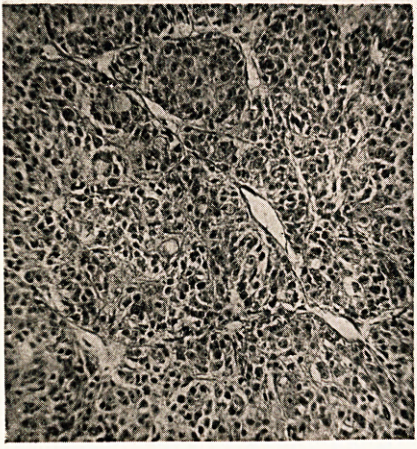
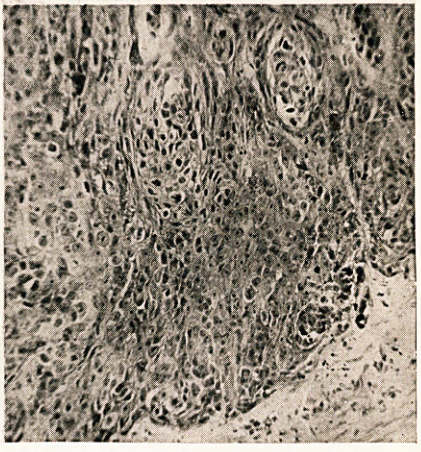


FIG. 53



Malignant Mammary Tumour in a Lactating Animal (Dog).

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 Kilgore [45] mentions two intracystic papillomata in a list of 96 mammary lesions first noticed during these periods. Bloodgood notes that papillomatous cysts are rare. My

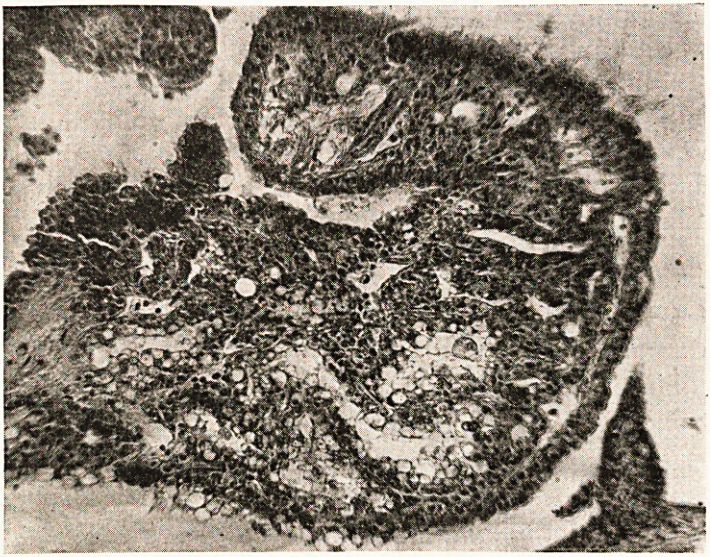


FIG. 50A.—Lactating papilloma (area *x* in Fig. 49, Plate VII.).

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

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).

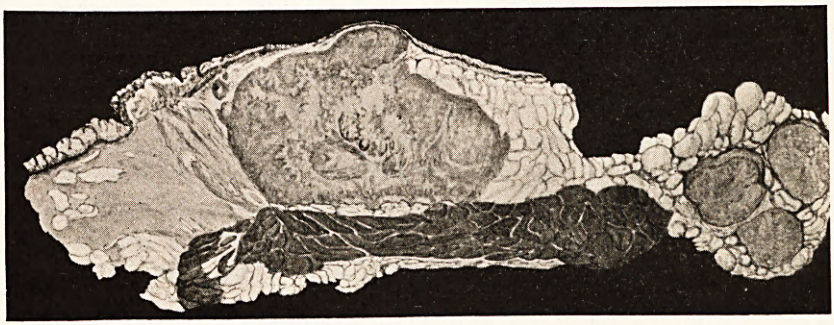


FIG. 54.—Case 1. Large mammary tumour with axillary invasion, in a patient 8½ months pregnant.

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 scirrhous carcinoma; radical amputation completed 3 weeks later. No enlarged lymph nodes found. This is a recent case and

the patient is well without sign of recurrence or metastases $5\frac{1}{2}$ months after treatment (Figs. 56 and 86).

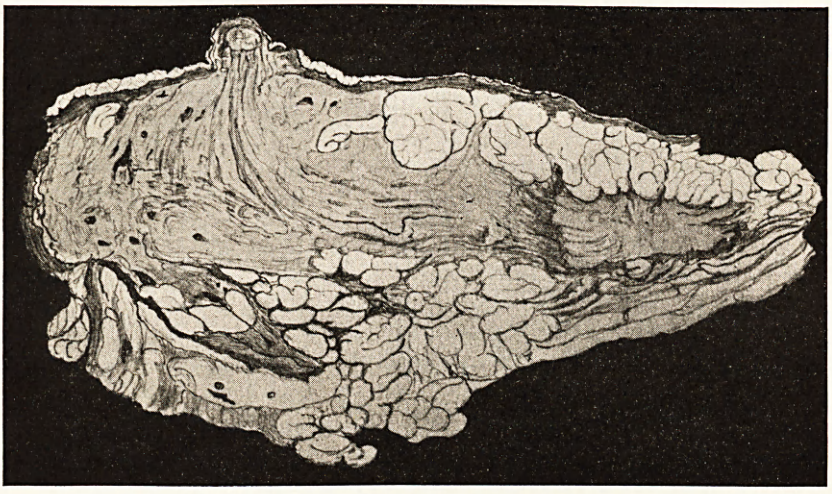


FIG. 56.—Case 4. Scirrhous carcinoma, discovered during lactation.

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

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,

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).

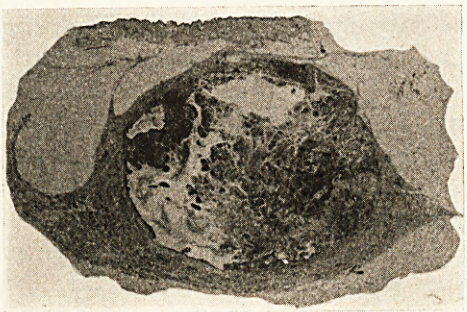


FIG. 59.—Case 10. Papillary adenocarcinoma, found 12 months post-partum.
Malignant Mammary Growth during Pregnancy and Lactation (large sections)

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

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

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, scirrhous 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 scirrhous 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-

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 scirrhous 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 scirrhous carcinoma (Figs. 85, 86), or only scirrhous 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 adeno-carcinoma, 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 scirrhous 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 scirrhous 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 anaplasic 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 Stiles [47] 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

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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

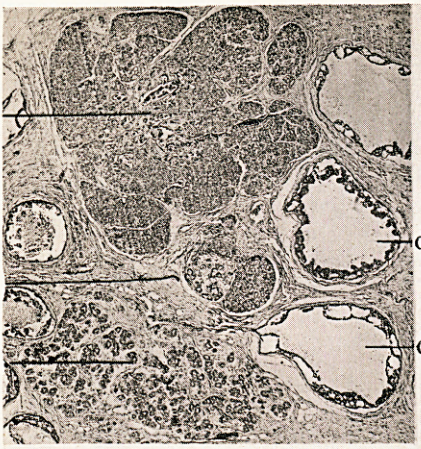


FIG. 61

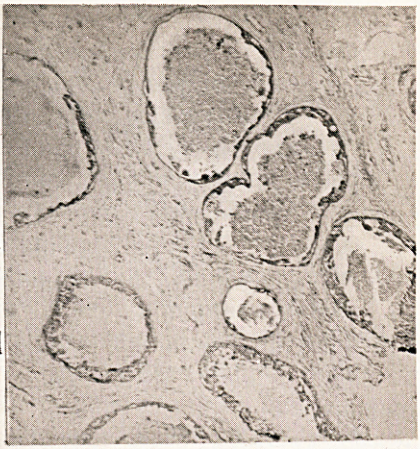


FIG. 62

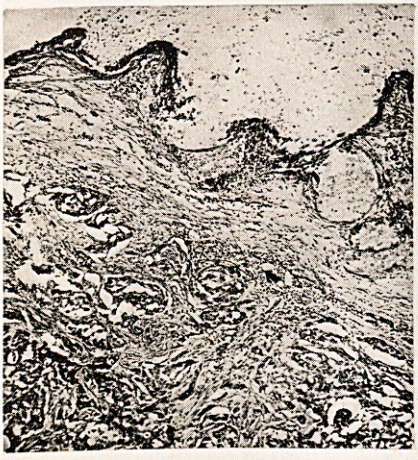


FIG. 63

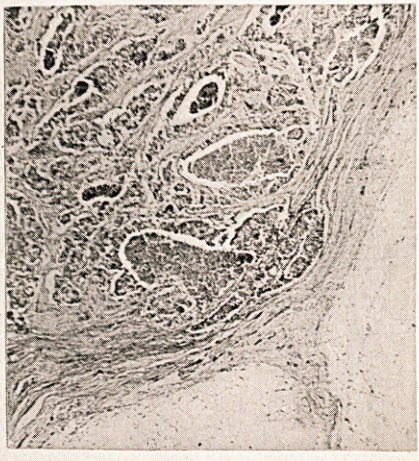


FIG. 64

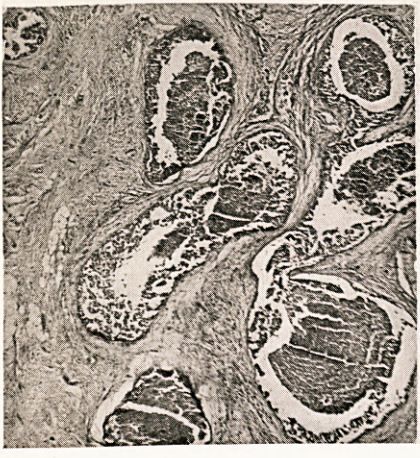
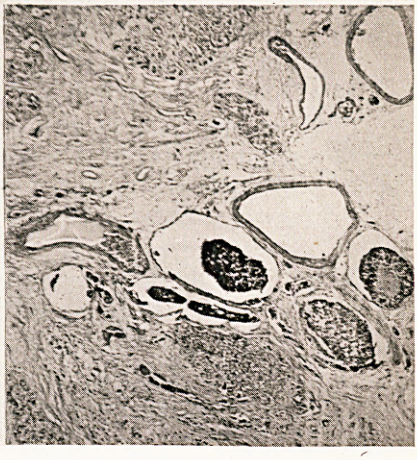


FIG. 65



Malignant Mammary Tumours in Pregnancy and Lactation.

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. Kilgore [45] 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,

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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 anaplasic 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

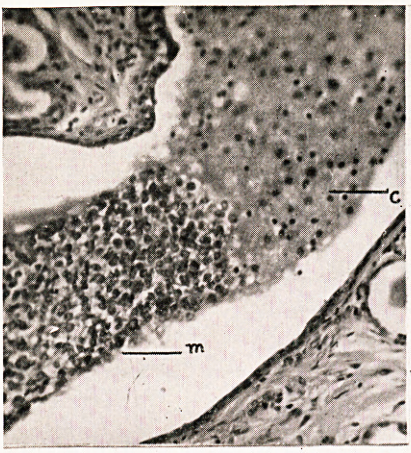


FIG. 67

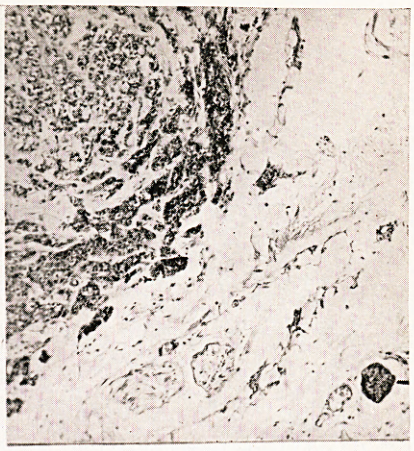


FIG. 68

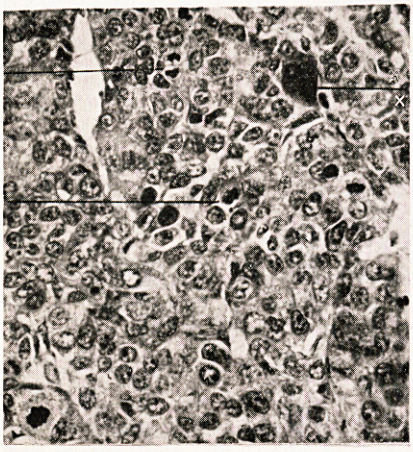


FIG. 69

FIG. 70

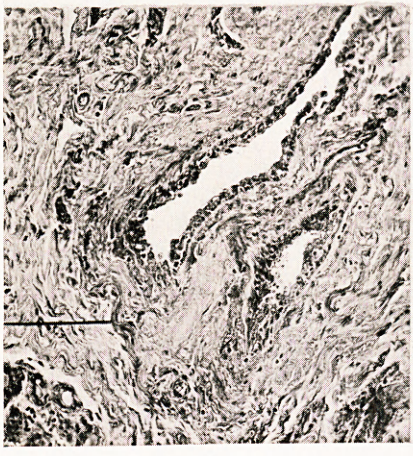
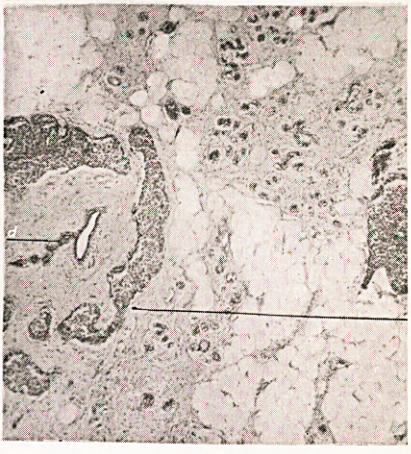


FIG. 71



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with a temporary decrease of the connective tissues. Kon [50] 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.

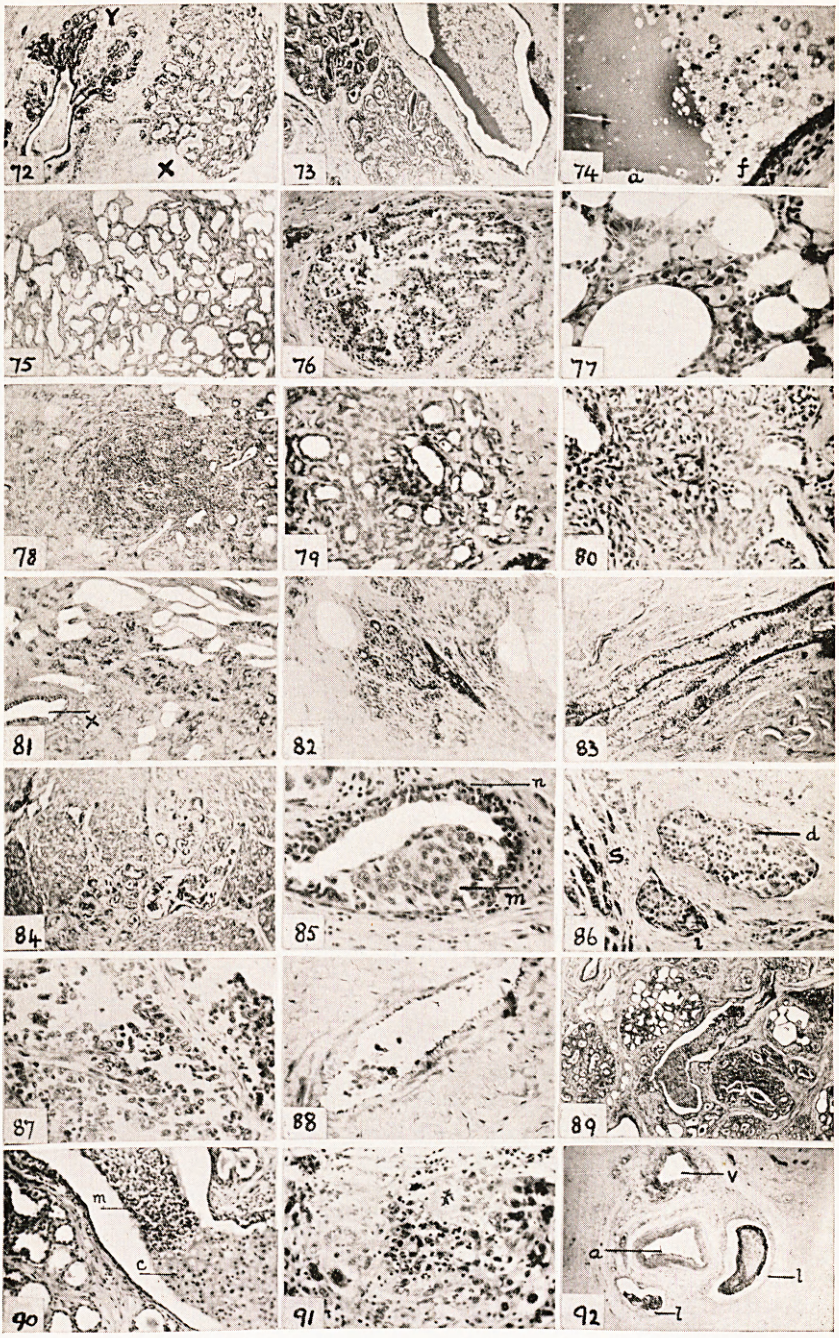
FIG. 88.—Malignant cells in vein. Case 6.

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.—Anaplasic malignant tissue lining the cyst in a papillary growth—lacation tumour, Fig. 59. Case 10.

FIG. 92.—Invasion of lymph vessels (l) in lactation tumour (Case 14); v, vein; a, artery.


72
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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] Ewing [52] 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." Adami [53] 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." MacCallum [54] 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. Charteris [55] 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. McFarland [35] 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 Rowland [56] state that "cancer cannot attack the cells of a hyperplasic gland," while Cheatle [8] 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. Bloodgood [59] considers that no tumours of the breast give histological pictures similar to lactation hypertrophy, and Berka [14] 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

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 adenosis and epitheliosis be accepted. In this and earlier studies, I have laid emphasis on the finding that *adenosis 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 hyperplasic 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 adenosis 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,[33] 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

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, 69] 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 menopause [70] or the interruption, at an early stage, of a subsequent pregnancy [64, 65] has been advocated in these circumstances. In this connection, Keynes [71] 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

Ballantyne [72] 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.

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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