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

I.—Early Development to Maturity.

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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

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. Creighton[1] 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'Farland[2] 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

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] Cheatle 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

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.

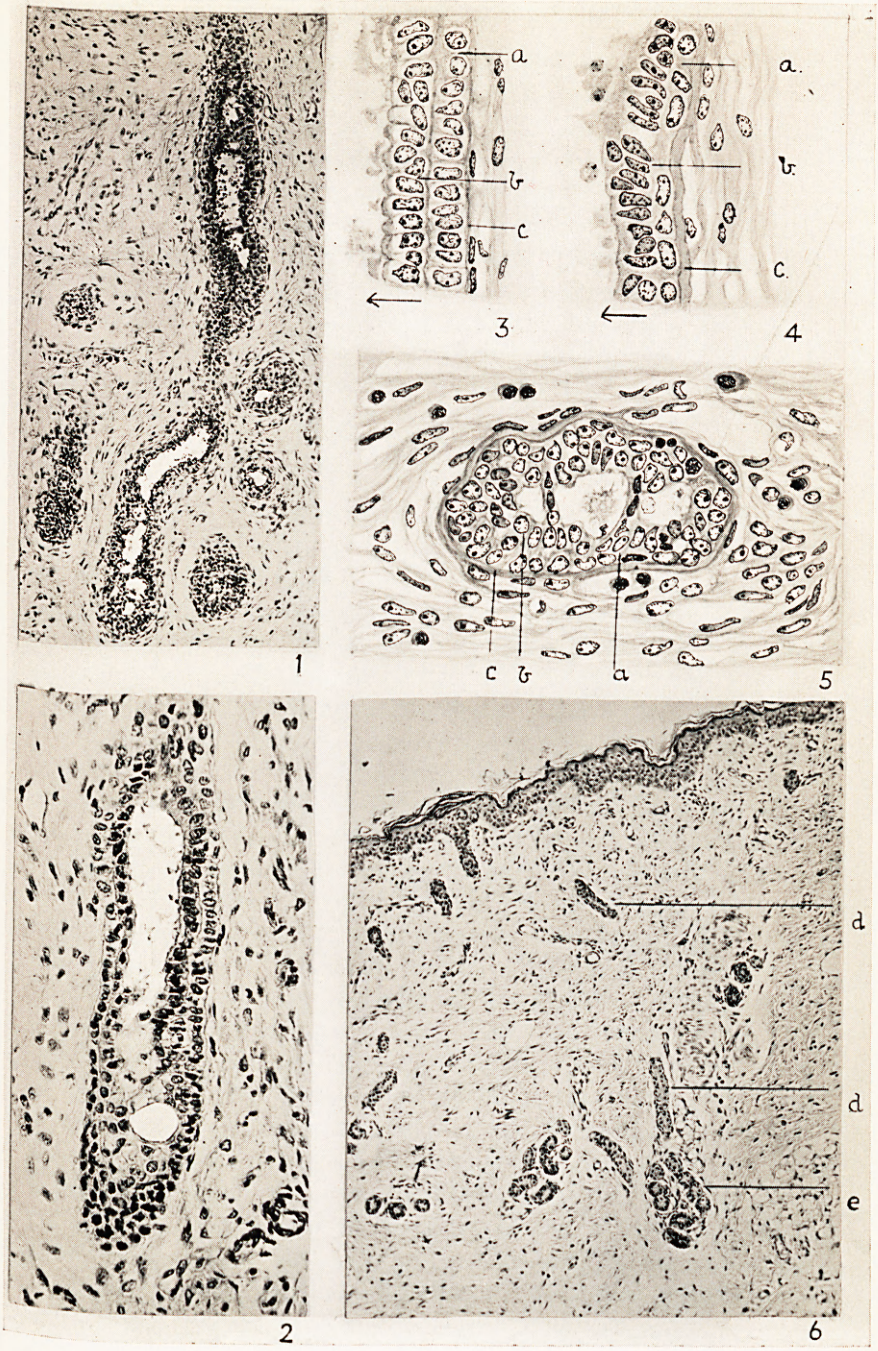
A. *In the Embryo.*

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 fœtal 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 fœtal 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 fœtal 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 fœtal



FŒTAL TISSUE.

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

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

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 school[7] recognise two types of epithelial cells in the mamma, which they consider can be distinguished very readily at the fœtal 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. Ewing[8] is of the opinion that fœtal 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 fœtal tissue and to the presence of paccinian corpuscles in the *corpus mammæ*.

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

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 fœtus. 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 fœtus.

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 fœtal 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 mammæ*

is described by several writers and interpreted as a developmental anomaly or a metaplasic 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 Scharnagel [10] 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. Creighton [11] 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 mammæ* 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 fœtal 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 fœtal 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 mammæ*. 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

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 fœtal and puberal growth, in the small duct proliferation characteristic of early pregnancy and in other conditions where new glandular structure is being rapidly formed. Krompecher [12] 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 work [13] 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

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 fœtal growth, no smaller glandular elements, that is, no ductules arranged in lobules, have been observed.

When the fœtus 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 fœtal ducts is, however, a usual finding. In a case of maternal eclampsia with death of the fœtus at term, the fœtal 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

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. Keynes[14] considers the breast a gland which throughout life is exhibiting some secretory activity, and explains "infancy mastitis" as an abortive attempt

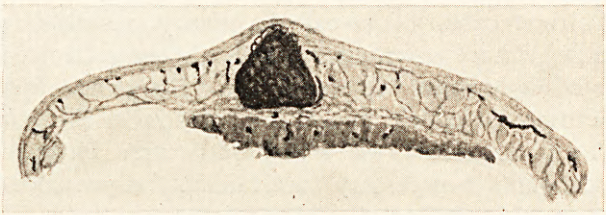


FIG. 8.—Full-time fœtal material (maternal eclampsia)—actual size.

of the gland at birth to fulfil its ultimate function of lactation. Berka[15] 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 Bremer[16] 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; Maximow[17] found it contained little but degenerating epithelial cells. Abraham's investigations[18] 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

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

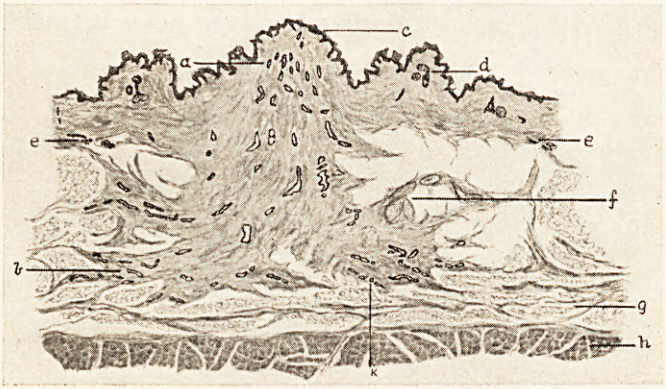


FIG. 9.—Normal breast tissue, child of 8 years.

a, large mammary ducts; *b*, small mammary ducts; *c*, nipple; *d*, sebaceous gland and hair-follicle; *e*, sweat glands; *f*, nerve with paccinian 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, Myers[19] found growth discontinuous during this period.

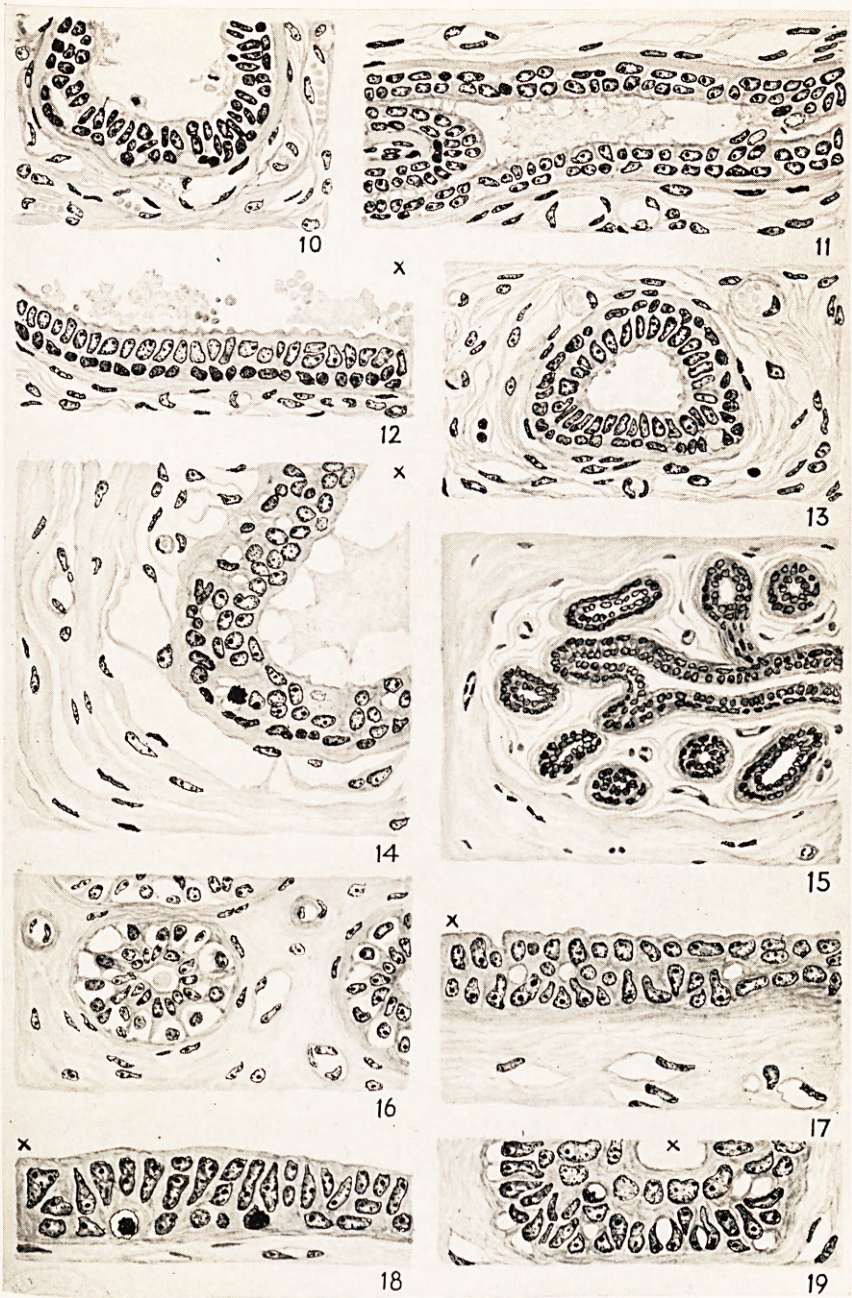
The whole mammary area from the normal breast of a child of 8 years is illustrated in Fig. 9. It shows considerable expansion of the *corpus mammæ* in comparison with the development pictured in Fig. 7, but no complex branching of small ducts to form lobules, even in the peripheral areas. The two-layered 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

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. (× indicates lumen of duct.)

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. Semb[20] 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

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

observed at an earlier stage of development. Gruber's description[21] 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

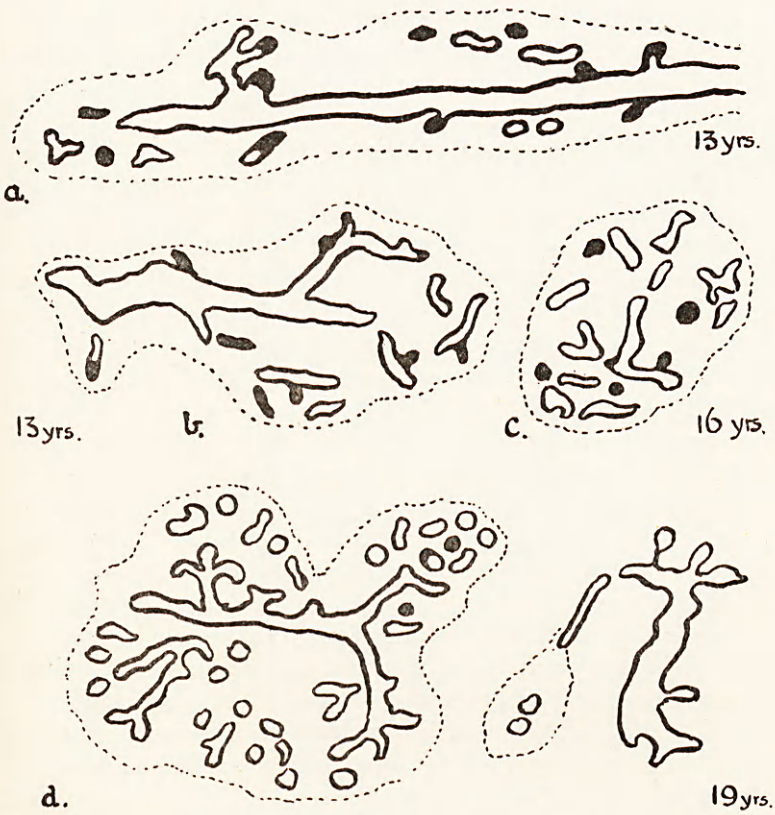


FIG. 22.—The developing lobule—the dotted line indicates the limit of loose lobular connective tissue.

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

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).

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 Rosenberg[23] 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 Centano[24] Ingleby[25] 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

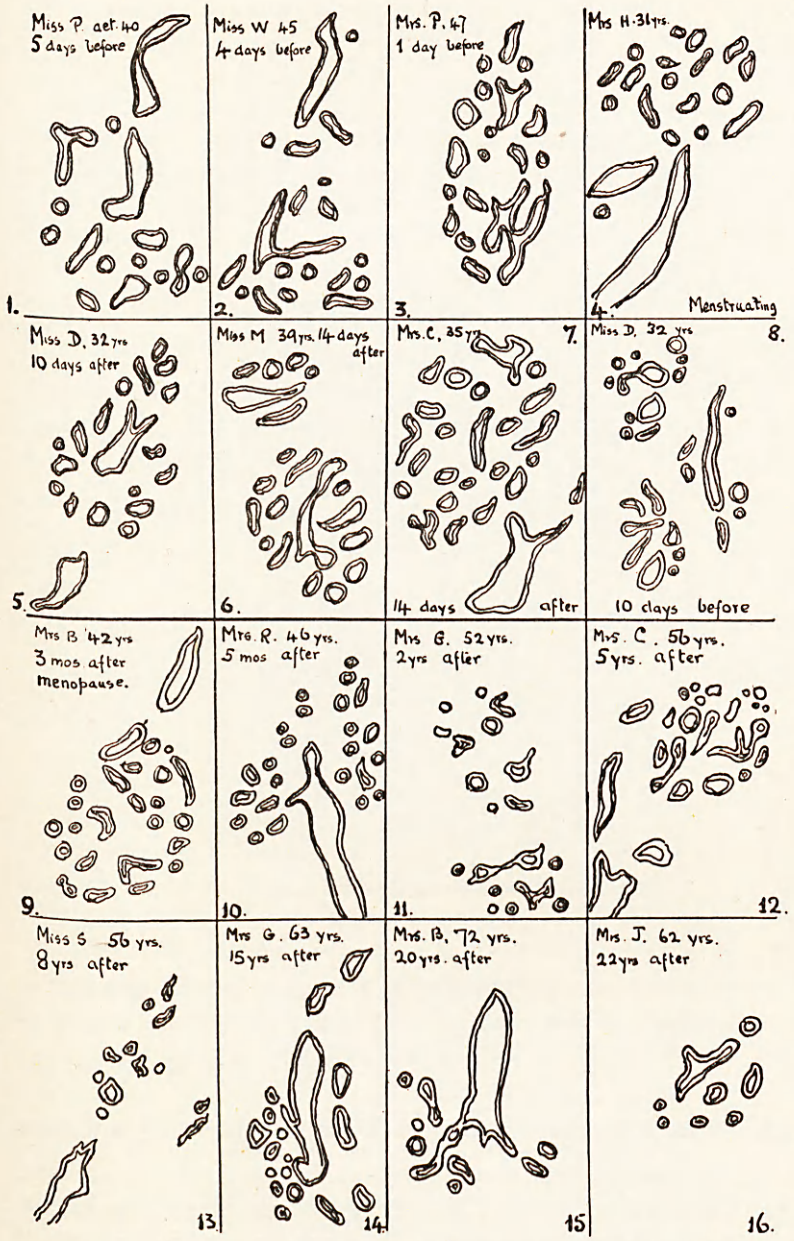


FIG. 25.—Normal mammary tissue, showing menstrual phases (1 to 8) and post-menopausal phases (9 to 16).

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

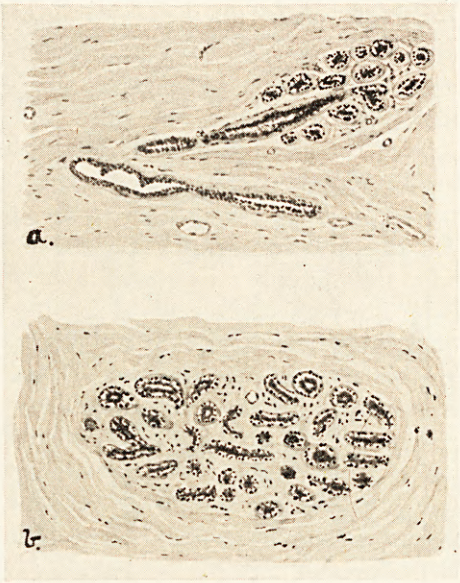


FIG. 26.—Mammary tissue – intermenstrual picture.
a, aged 39; *b*, aged 20.

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

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.*

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

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.

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

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. Wevill[27] 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

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 paper[29]; 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. Wainwright[30] 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; White[31] 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

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.

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,

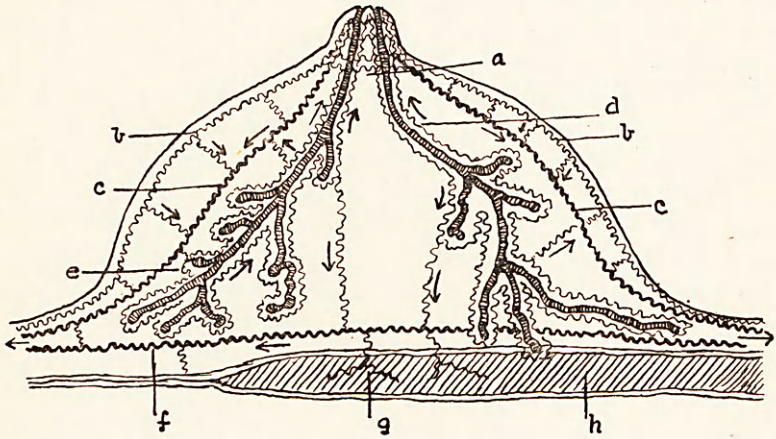


FIG. 28.—Diagram of lymph vessels in the mamma (simplified, from Keith's *Embryology*).

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 fœtal 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

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

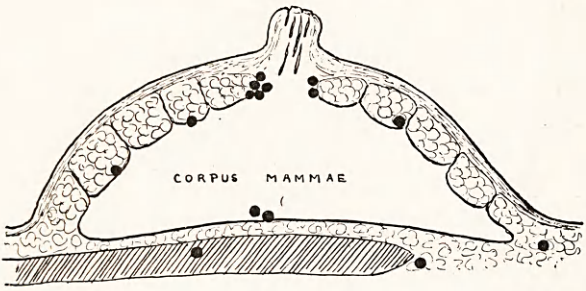


FIG. 29.—Positions where paccinian corpuscles have been observed in the breast.

observed scattered groups of fine elastic fibres in the loose intralobular connective tissue, but Maximow failed to find them in this position. Cheatle 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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