THE BREAST

STRUCTURE: FUNCTION: DISEASE

EDITED BY

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BRISTOL: JOHN WRIGHT AND SONS LTD.

LONDON: SIMPKIN MARSHALL LTD.

1950

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PRINTED IN GREAT BRITAIN BY
JOHN WRIGHT AND SONS LTD.,
AT THE STONEBRIDGE PRESS,
BRISTOL

ACKNOWLEDGEMENTS

As Editor of this book, it has been a very real privilege and pleasure to work with authors so keenly interested and helpful. I wish to express my sincere appreciation of all that they have done.

Many others have given valuable help in different ways, and particularly I thank: Members of the staff of the Morbid Anatomy Department of St. Mary's Hospital, Paddington, and of the Pathological Department of the Royal Northern Hospital for collection of material and help in many other ways; Miss G. Barry, M.S., F.R.C.S., for material and case-histories; Dr. E. K. Dawson for permission to make use of diagrams in published work and for the loan of a slide; Dr. Carnegie Dickson for the loan of reprints; Professor M. F. Lucas Keene for the use of his histological preparations of human embryos; Miss D. Knott, M.S., F.R.C.S., for material and case-histories; Drs. Gardener and Van Wagener for permission to make use of diagrams and extracts from published work.

The medical, pathological, and technical staff of the Radiotherapy Department of the Royal Northern Hospital have shared in the work of the various sections of the chapter on this subject. I thank Mr. A. W. Jennings (physics) and Miss E. V. Webb (technical) for their work, also Dr. Lionel Cohen for his collection of material from the literature from which data have been included in the text of this chapter and that on cancer. I am, too, most appreciative of the interesting contributions made by Dr. P. M. Peters of the Department of Pathology, Prince of Wales's General Hospital, to this and other chapters.

For the illustrations I am indebted to a number of artists and photographers: Miss Anna Zinkeisen for her coloured drawings made in the operating theatre of the Royal Northern Hospital either during an operative exposure or immediately after removal of the particular specimen; Miss Margaret McClarty for various drawings, including those of the operation of radical mastectomy and of dissections and anatomical material made in the Anatomical Department of the Royal Free Hospital School of Medicine; Mrs. Patrick Clarkson for her copies of photomicrographs in the section on Endocrine Control, and her illustrations—together with those drawn by its author—for the chapter on Plastic Surgery; Mr. Gilbert Purssey for his work in the chapter on Radiotherapy, made in the department at the Royal Northern Hospital, and other drawings, and Mrs. Neago for her contribution. I am indeed grateful for much time generously given to the work and for the skill in its execution.

I am, too, indebted to a number of my colleagues, also to Sir Harold Gillies, Mr. David Levi, Dr. Janet Maxwell, Professor Milnes-Walker, Sir Cecil Wakeley, and others for the use of photographs and illustrations of cases, to Mr. Valentine Swain for his help in the collection and arrangement of these, and lastly to the editors and publishers of a number of periodicals for permission to make use of their material.

Many of the photomicrographs and photographs of specimens have been taken by Mr. E. V. Willmott, F.R.P.S., of the British Post-graduate School of Medicine. Mr. J. S. Sheppard and Mr. L. W. Pettitt, of the Photographic Departments of the Royal Free Hospital School of Medicine and the Prince of Wales's General Hospital respectively, have also contributed to these. The results, I think, speak for themselves.

Invaluable help has, of course, been gained by the authors from the work and writings of others. This is recorded in the chapter references, but I should like to add my personal acknowledgement. Many of the statistical data used in the text have been taken from Dr. Janet Lane-Claypon's detailed investigations of cancer of the breast for the Ministry of Health, from that instructive book, Geschickter's *Diseases of the Breast*, and from reports issued by the Research Committee of the British Empire Cancer Campaign. Also in an Appendix a number of relevant statistical tables are included which have been extracted from many sources with much care by Mr. Anthony Green.

For her considerable work and care in the preparation of the script I am much indebted to Miss D. W. Hood, and to Miss Barbara Temperley, not only for its revision and many suggestions, but also for her constant endeavour to protect the English language from, at any rate, undue abuse!

Finally, I take this opportunity of expressing my most grateful thanks to the publishers, Messrs. John Wright & Sons Ltd., of Bristol, for their great care and always helpful advice and co-operation in the production of this book.

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*London, W.*1.
April, 1950.

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CONTENTS

FOREWORD

STRUCTURE and function, although influenced by heredity and individual circumstance, are pre-determined and interdependent and in mature living tissue their process is stable, resilient, and well balanced. A tissue incapacity to perfect its special purpose and disturbance of this balance would appear to cause structural change or reversion to structural immaturity, which may be revealed in manifestations specific in form though differing in extent and character.

The object of this book is to present from this point of view a general picture of the structure, function, and disease of the breast and to include suggestions for treatment. During its preparation, however, the authors have become increasingly, almost painfully, aware of how much yet remains to be learned and done.

F. D. S.

THE BREAST

CHAPTER I

THE STRUCTURE OF THE BREAST

By Lilian M. Dickson and Evelyn E. Hewer

I. GENERAL ANATOMY

The human breast is a cutaneous organ in the thoracic region present in both sexes but reaching full development only in the pregnant woman for the purpose of suckling.

A. THE FEMALE BREAST

1. Form and Gross Structure

The female breast forms a rounded elevation on the anterior thoracic wall. It consists of a glandular portion, the *mammary gland* proper ; a quantity of *fat*, which gives it its contour ; and a covering of *skin*. Near the summit, a small projection, the *nipple*, is surrounded by a disk-like pigmented area, the *areola*.

Beginning as a thickening and then an ingrowth of the surface epithelium, the breast undergoes changes, progressive and retrogressive, throughout life, and its appearance and structure depend on age and state of activity, as well as on individual variation. It is convenient to use the *young adult nulliparous* condition for a general description, and then to note *modifications at other ages and physiological states*, but it should be kept in mind that the fully developed organ is the breast of late pregnancy and lactation.

In the Young Adult Nullipara.—

1. *The Breast as a Whole.*—The breast is hemispherical, becoming slightly more conical towards the summit. It is soft enough to be compressible, firm enough to keep its contour, and is freely movable on the chest wall.

2. *The Mammary Gland Proper.*—The mammary gland is a multiple gland, comprising a variable number of independent ducts (10–20), each with its own system of smaller ducts and alveoli, and associated stroma ; and to each of these 10–20 entities the term *lobe* is applied. The gross appearance of the gland does not, however,

reflect the lobar plan; the parenchymatous parts are embedded in a stroma of connective tissue which gives no external evidence of the limits of the lobes. The whole gland forms a flattened cone with apex at the nipple and base on the chest wall (*Fig.* 1). The edge is irregular, and well-formed processes of varying size and position may be present, one such process, extending supero-laterally towards or into the axilla, forming the 'axillary tail'. Occasionally small detached portions are found on the periphery. The gland is tough, and somewhat nodular, qualities recognizable on palpation through skin and fat; it is greyish-white in colour.

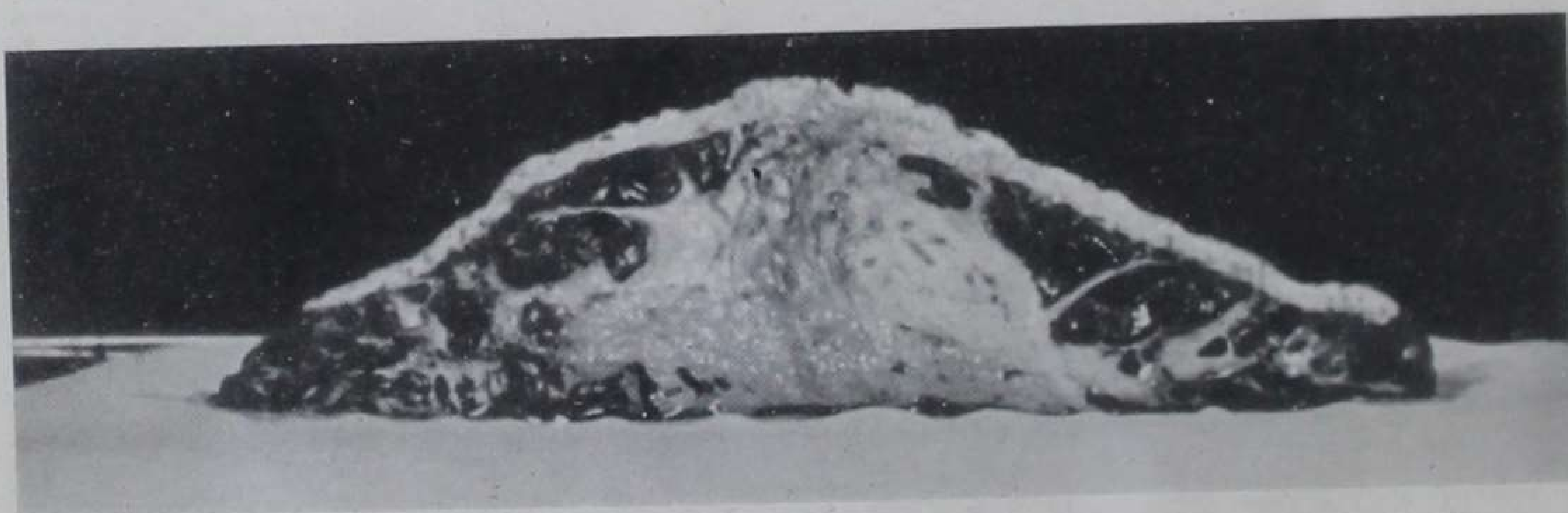

Fig. 1.—Hemisection of whole breast. Fat appears black in sharp contrast to the connective-tissue stroma of the mammary gland and the suspensory ligaments. Stained osmic acid vapour. (*Photograph.*)

The parenchyma of the nulliparous breast is small in amount and is scattered irregularly throughout the gland (*Fig.* 2). In each lobe it comprises a main lactiferous duct, a lactiferous sinus, branches of the main duct, and a number of lobular ducts. The *lactiferous duct* descends through the nipple from a small opening on the surface, and beneath the areola is dilated into a *lactiferous sinus*. Narrowing again, the duct undergoes division, partly dichotomously, partly by irregular branching, ultimately to give rise to a number of groups of small (*lobular*) ducts, from the terminal portions (*ductules*) of which, during pregnancy, the *secreting alveoli* develop. Each of these groups, with its associated stroma, constitutes a *lobule*.

The stroma is composed of connective tissue in which collagenous fibres predominate. Described as interlobar, interlobular, and intralobular (periductal), according to its relation to different parts of the parenchyma, it shows variations in character in the several regions, but its fibrous connective tissue elements are continuous throughout the gland, and moreover are continuous with the connective tissue of the underlying pectoral fascia and, by means of the suspensory ligaments (of Astley Cooper), with the connective tissue of the overlying skin (*see Figs.* 1, 2).

3. *Fat.*—The fat which contributes so largely to the external form of the breast is part of the general layer of subcutaneous tissue, and is found chiefly between the gland proper and the skin (*see Fig.* 1). The delicate connective-tissue septa which divide adipose tissue into partially discrete masses form, in the breast, the well-marked suspensory ligaments already described, which provide continuity between the stroma of the gland and the dermis. There is little if any fat beneath

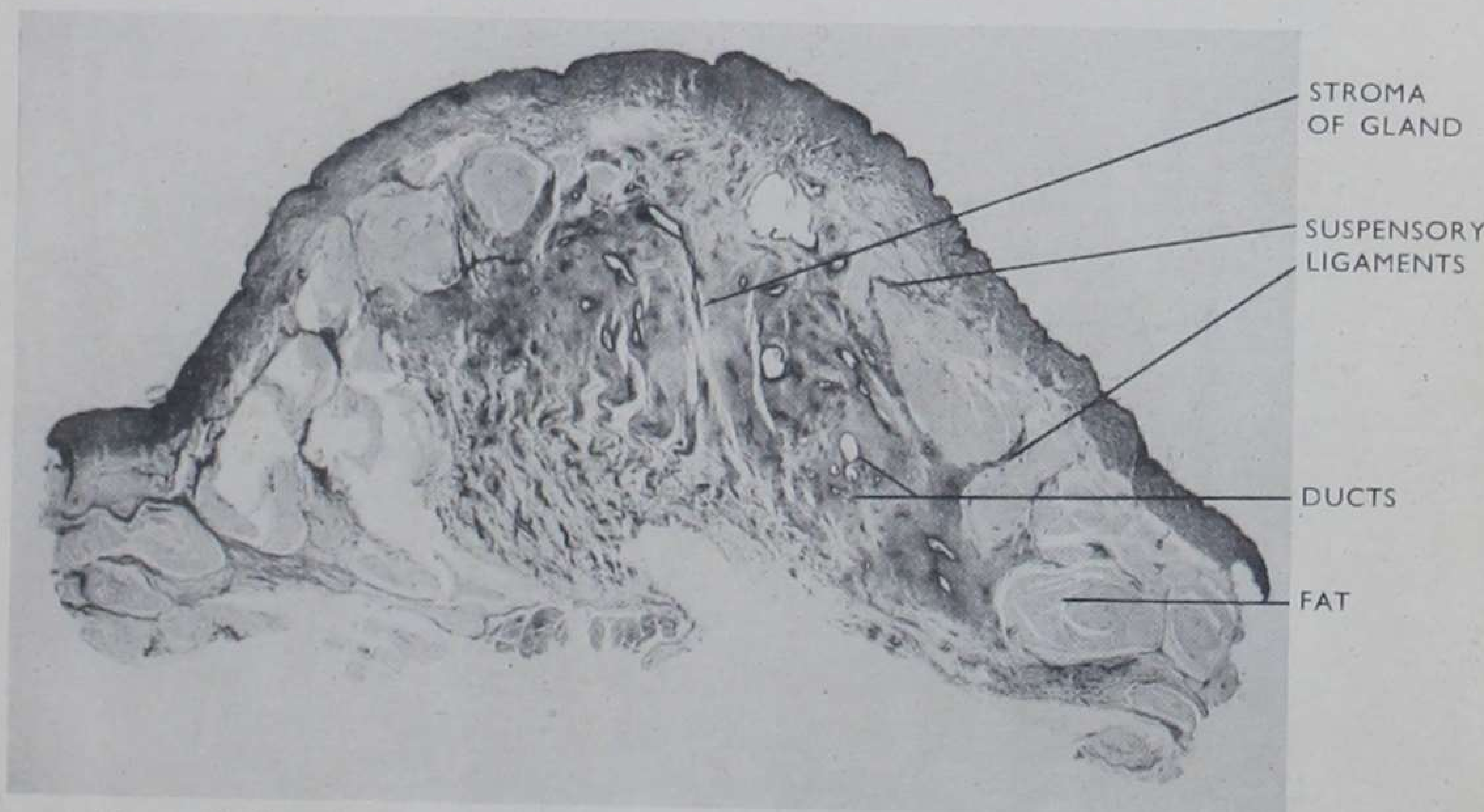

Fig. 2.—Section of whole breast. Same specimen as in *Fig.* 1. Shows irregular distribution of parenchyma throughout the gland. Duct epithelium stained dark. Stained hæmatoxylin and Biebrich scarlet. (*Photograph.*)

the nipple and areola, and usually only a thin layer on the deep surface of the gland. Fat may be present in the stroma of the gland itself, varying both in quantity and situation.

4. *Skin.*—Except in the nipple and the areola the skin of the breast presents no special features.

5. *The Nipple.*—The skin is dark pink, of rather hard consistency, corrugated, and contains the openings of the lactiferous ducts. Small sebaceous glands are present, but not sweat-glands nor hair follicles. The interior of the nipple is occupied by the lactiferous ducts and accompanying vessels, embedded in connective tissue which contains abundant smooth muscle-fibres (*see Fig.* 49).

6. *The Areola.*—This is lighter pink, soft, and contains large sebaceous glands, the *areolar glands* (of Montgomery), which arise

independently of hair follicles. Sweat-glands and hair follicles are present, mainly at the margin.

A layer of loose connective tissue separates the nipple and areola from the underlying mammary gland.

Features peculiar to Particular Ages and States of Functional Activity.—

1. *At Birth.*—In both sexes there may be slight prominence of the mammary region, which may persist for a few weeks after birth, due to activity in the duct epithelium during the last weeks of fœtal life. The nipple is slightly depressed below the surface. Within the gland the full number of lactiferous ducts is present and some branches have formed, but no lobules (*see Figs.* 22, 23).

2. *At Puberty.*—During childhood the "growth of the gland keeps pace with general body growth" (Dawson), but no other changes take place. Adolescent swelling begins to show with the onset of puberty, when, as the menstrual cycle is established, the breast rapidly increases in size. The enlargement is due in part to an increase of glandular tissue (both stroma and parenchyma; growth of existing ducts and now the formation of lobules taking place), and in part to the deposition of fat. Slight periodic enlargement may occur at certain stages of the menstrual cycle.

3. *In Pregnancy.*—The nipple and the areola are deeply pigmented, appearing dark brown or black, and the areolar glands are prominent. The breast rapidly enlarges, owing in part to increased vascularity and accumulation of tissue fluid but mainly to an increase of parenchyma, in which the most notable change is the formation of the alveolar epithelium. The presence of the additional tissue fluid renders the breast increasingly hard.

4. *During Lactation.*—The gland reaches its maximal size, owing to its secretory activity.

5. *In the Post-lactating Period.*—Retrogression is rapid; the gland is reduced in size and the parenchyma returns nearly to the nulliparous condition. The pigmentation of the nipple and the areola lessens, but never entirely disappears.

6. *Menopause and Old Age.*—The menopause does not noticeably modify form. Both in the parous and non-parous woman the organ becomes more pendulous with advancing age, but size and shape depend mainly on the individual's tendency to accumulate fat, and are little affected by the amount of true mammary tissue present. This also is subject to individual variation, and in some breasts a relatively considerable amount of parenchyma may be found in old age.

2. Position and Relations

The breast lies on the anterior wall of the thorax within an area limited by the 2nd and 6th ribs in the vertical plane and the edge of the sternum and the mid-axillary line horizontally. One or more of these limits may be reached by processes of the glandular portion of the breast which normally extends beyond the confines of the external swelling (*Fig.* 3).

The gland is superficial and covered only by fat and skin. Its posterior surface is separated by a little loose connective tissue and then by a layer of deep (pectoral) fascia from parts of three muscles: pectoralis major behind its medial two-thirds, serratus anterior behind its lateral third, and the external abdominal oblique overlapped by its lower edge. An inferomedial process of the gland may lie on the aponeurotic extension of the external oblique which forms the upper anterior part of the rectal sheath. If sufficiently well developed, the axillary tail pierces the deep fascia of the floor of the axilla and may reach as high as the 3rd rib deep to the outer border of pectoralis minor. Small projections from the deep surface of the gland occasionally pierce the underlying pectoral fascia and come into direct contact with pectoralis major.

Medial to the gland lie the perforating branches of the internal mammary vessels and the anterior cutaneous branches of the 2nd to 5th intercostal nerves (*Fig.* 3).

Lateral to the gland, in order from before backwards, are the vertically disposed external mammary branches of the lateral thoracic vessels; the lateral cutaneous branches of the 2nd to 5th intercostal nerves (the branch of the 2nd nerve, intercostobrachial, may be very closely related to the axillary tail); and the nerve to serratus anterior, lying vertically in the mid-axillary line (*see Fig.* 6).

3. The Blood-vessels and Nerves

Arteries.—The arterial supply of the breast is derived from the internal mammary and axillary arteries through branches which enter the medial, posterior, and lateral parts of the organ respectively. The internal mammary is the principal source of supply through its perforating (medial) and intercostal (posterior) branches. The axillary artery supplies the lateral group of branches through the external mammary branch of the lateral thoracic artery.

The *perforating* arteries which supply the breast are those of the 2nd, 3rd, 4th and sometimes the 5th intercostal spaces. They emerge with the anterior cutaneous branches of the intercostal nerves half

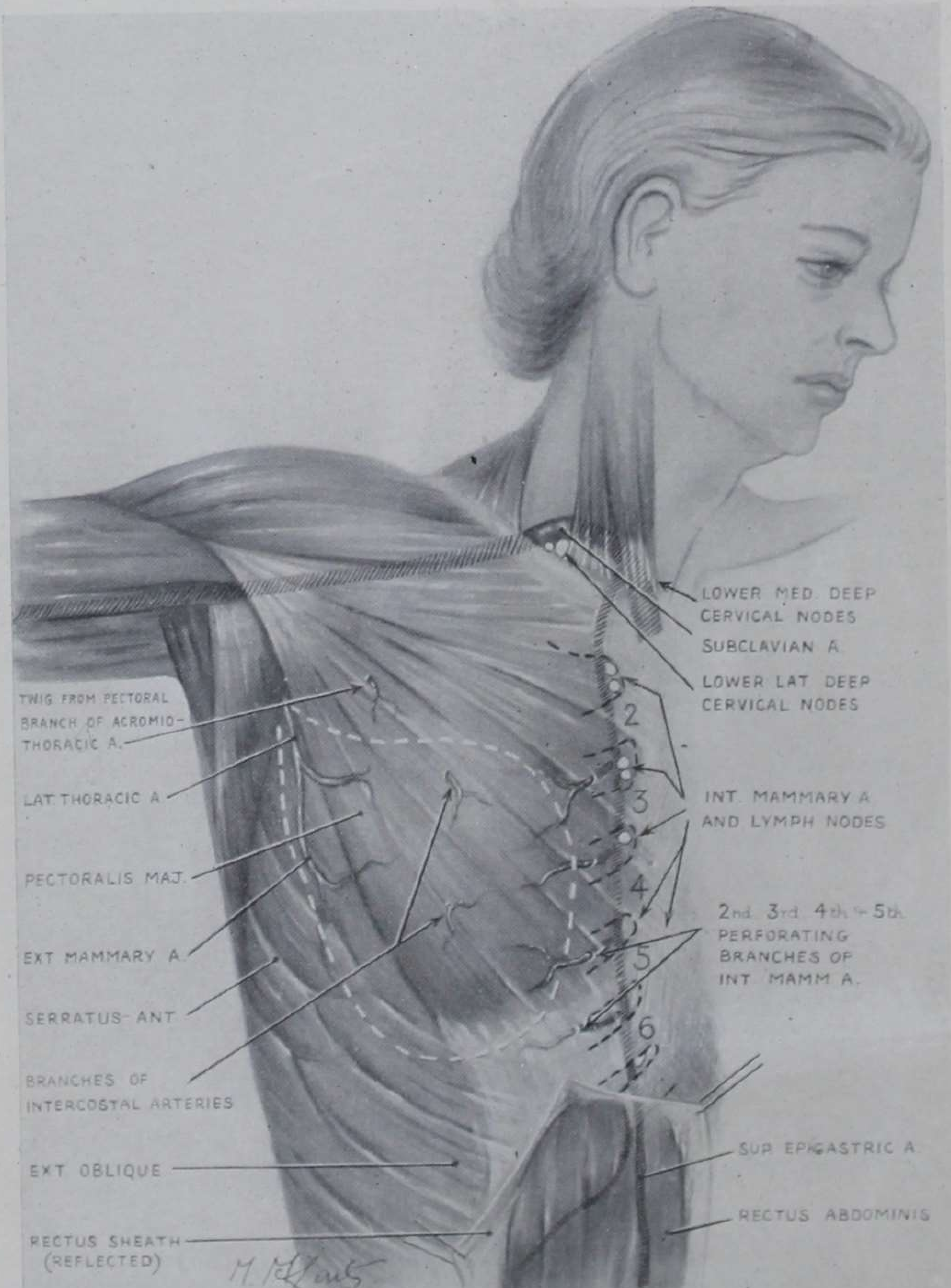

Fig. 3.—The anterior aspect of the neck and the upper part of the trunk of the right side. The dissection displays the muscular relations and the arterial supply of the breast, which lies within the area marked by the dotted line. Arteries deep to the plane of the dissection are shown cross-hatched.

an inch lateral to the sternum, and enter the breast on its medial side. They are its largest vessels (*Fig.* 3).

The *intercostal* arteries give small, inconstant branches to the posterior surface of the gland.

The *external mammary* artery arises from the lateral thoracic artery at the junction of the outer border of pectoralis minor with the chest wall (*see Fig.* 6). It descends nearly vertically, skirting the lateral edge of the breast and supplying it with branches usually of small size. The lateral thoracic artery may be small or absent, in

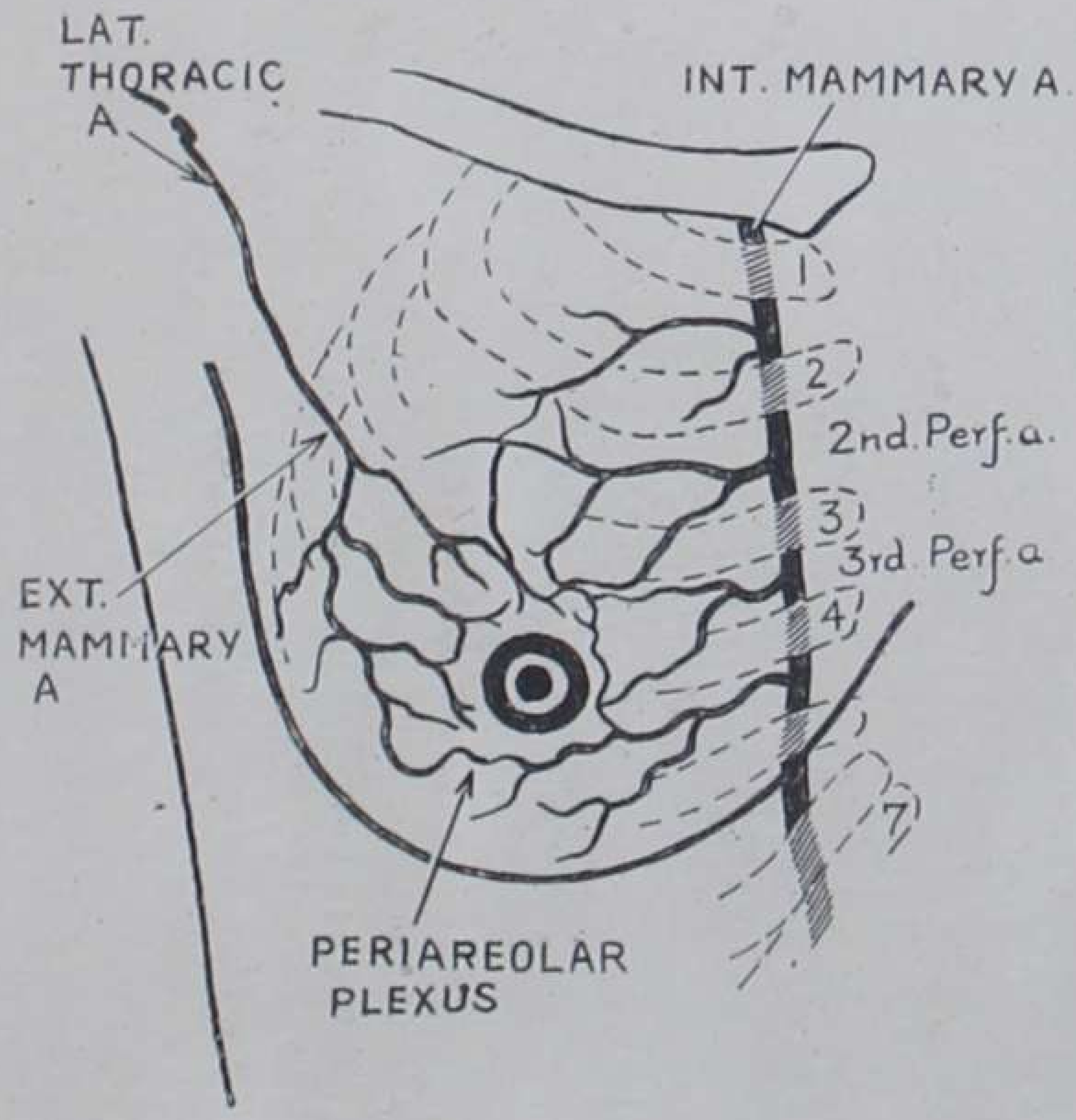

Fig. 4.—Diagram of the arterial supply of the nipple, showing a well-formed periareolar plexus derived from the second, third, and fourth perforating branches of the internal mammary artery and the external mammary branch of the lateral thoracic artery. (*After J. W. Maliniac.*)

which case the external mammary usually arises from the subscapular artery in the posterior wall of the axilla. Small twigs may reach the supero-lateral part of the breast from the *pectoral branch of the acromio-thoracic artery* (*Figs.* 3, 6).

The perforating and external mammary arteries ramify on both surfaces of the gland and, on the deep surface, anastomose with the branches of the intercostal arteries. On the superficial surface they anastomose with each other, send small branches to the skin and larger branches into the substance of the gland, and finally form a *periareolar anastomosis* or plexus (*Fig.* 4). From the plexus small branches arise which supply the areolar skin; others turn medially and at the base of the nipple form a second, very fine, plexus from which vessels ascend to the summit. The main contribution to the periareolar plexus, and consequently to the supply of the nipple, is usually made by the internal mammary artery through its 2nd, 3rd, and 4th perforating branches; but in a considerable number of cases, the external mammary artery appears to be of equal importance, and in some it is predominant.* The anastomosis is usually good, but may be poor or even fail to form, in which case the nipple is supplied by terminal twigs of the perforating and external mammary arteries (*see* Chapter XII, Plastic Surgery).

Within the substance of the gland the arteries run an irregular course through the stroma; small vessels accompany the lactiferous ducts; and capillaries lie very close to the ductules and alveoli.

Veins.—The veins of the breast for the most part follow the arteries, but a certain number of fair-sized vessels run independently in the subcutaneous tissue and, enlarged, give a characteristic blue-veined appearance during pregnancy and lactation.

Nerves.—The breast is supplied by the anterior and lateral cutaneous branches of the 2nd to 5th intercostal nerves. They carry afferent fibres from the skin and mammary gland, and non-medullated autonomic fibres from thoracic sympathetic ganglia to the organ. The latter include fibres to blood-vessels, to the sweat-glands and hair follicles of the skin, and to the smooth muscle of the walls of the ducts and of the nipple and areola. The presence of secreto-motor fibres to the mammary parenchyma is not established, and the physiological evidence is against their existence (*see* p. 65).

4. Lymphatic Drainage

From the clinical point of view, the lymphatic drainage of the breast is probably the most important feature of the anatomical picture, and demands some detail in its consideration. In addition to the normal pathways of lymph drainage, consideration must be given to the more remote nodes and vessels which may be implicated in the spread of malignant cells.

The account that follows is based on the findings of many workers, which are collated in the major British text-books and in Rouvière's monograph. Particular references are for the most part omitted in the text, but a bibliography is appended.

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* J. W. Maliniac, 1948, also quoting Rouvière and Salmon, gives the following figures: external and internal mammary arteries of equal importance in 55 per cent of cases, external mammary predominant in 13 per cent; anastomosis good in over 70 per cent, fails to form in about 10 per cent of cases.

The description includes: (1) The position of the lymph-nodes that may take part in the drainage of the breast; (2) The arrangement of lymph-vessels within the breast, and their relation to the general pattern of cutaneous and subcutaneous lymph-vessels; (3) The course of the collecting vessels and the normal direction of lymph-flow from the breast; (4) The pathways that may be opened up under abnormal conditions.

1. The Lymph-nodes.*—Lymph-nodes of three regions share in the drainage of the breast: axillary, thoracic, and cervical.

a. Axillary Nodes (including interpectoral) (*Figs.* 5, 6).—The axillary nodes lie on the course of the axillary artery and its branches.

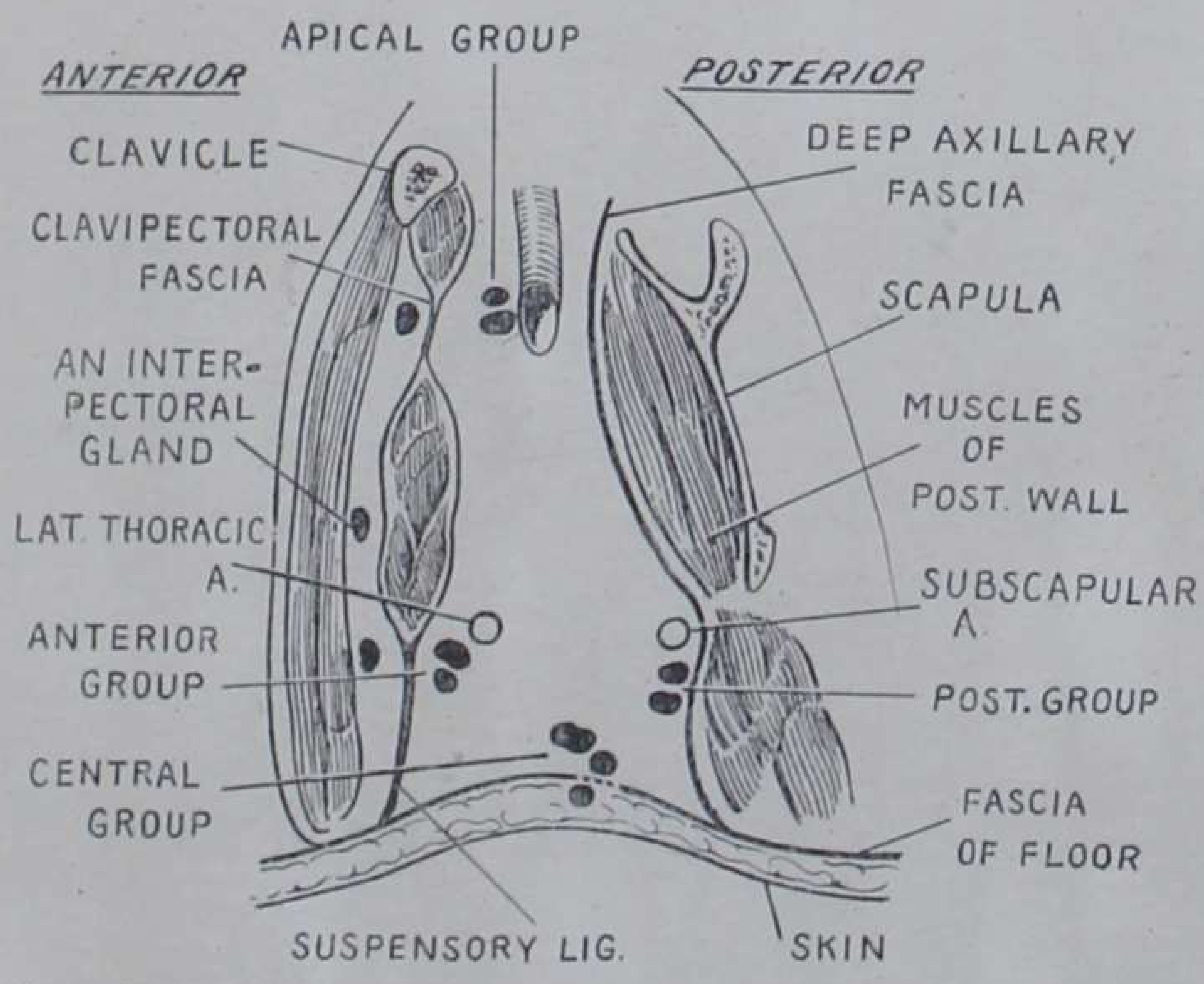

Fig. 5.—Schematic anteroposterior section through the axilla viewed from the lateral side. To show position of the axillary lymph-nodes (except the lateral group) in relation to the walls, floor, and blood-vessels of the axilla.

The axillary artery runs from the medial wall of the axilla above to the lateral wall below, and the branches related to lymph-nodes pass to the thoracic wall along the anterior and posterior axillary walls respectively. The nodes are *deep*, that is, they lie inside the deep fascial lining of the walls and floor (base) of the space. They form five groups, of which Groups I–IV are roughly basal, and Group V

* A minor problem in the study of lymph drainage of the breast is presented by the great variation in nomenclature that besets lymph-nodes, and which in some instances gives rise to apparent discrepancies in the findings of different workers. In the account that follows, the terminology employed is that of the Birmingham Revision of Anatomical Nomenclature, adopted by the Anatomical Society of Great Britain and Ireland in 1933 and now used in most British text-books of anatomy; but where other names have been widely used, they are given in brackets.

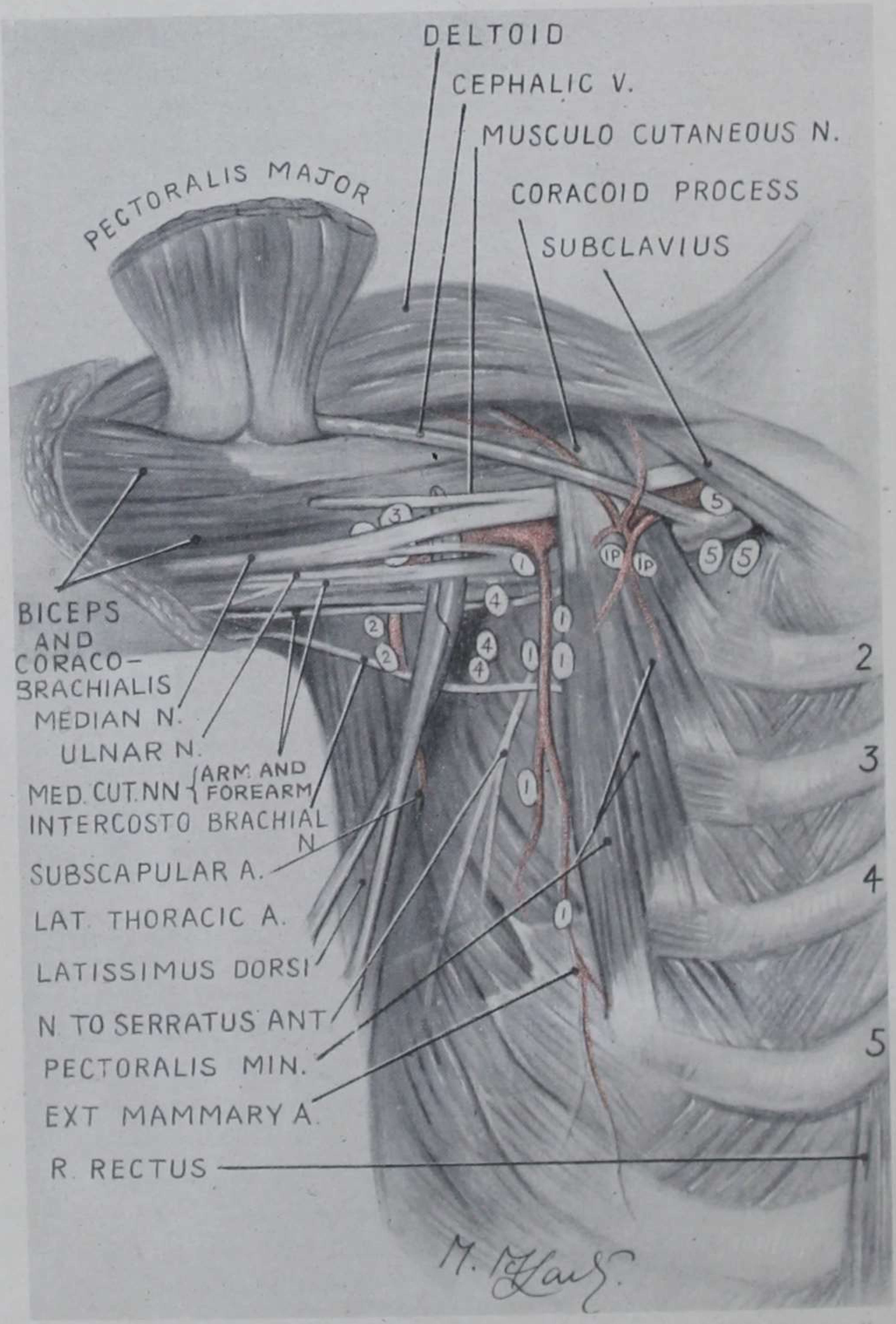

Fig. 6.—The anterior aspect of the axilla and thoracic wall after reflection of pectoralis major. The axillary lymph-nodes are numbered 1–5 (*see* text); IP = Interpectoral. Of the lateral cutaneous branches of intercostal nerves, only the second (intercostobrachial) is shown. The third, fourth, fifth, and sixth emerge in line with the second. The acromiothoracic artery (unnamed) is seen ramifying on pectoralis minor.

apical, but there is no sharp division between one group and another, and all are very freely linked by vessels. The number of nodes is variable: the apical group is usually the largest and may contain as many as a dozen nodes.

Group I: *The anterior* (or pectoral) nodes are related to the lateral thoracic artery and its external mammary branch. They lie in the anterior wall of the axilla below or just behind the outer border of pectoralis minor and under cover of pectoralis major; and may extend a short distance down the chest wall.

Group II: *The posterior* (also called subscapular) nodes lie on the posterior wall of the axilla along the subscapular artery in the groove between the subscapularis and teres major muscles, a little proximal to the posterior axillary fold.

Group III: *The lateral* (variously named humeral, brachial, axillary) nodes are related to the third part of the axillary artery lying on the upper third of the shaft of the humerus, medial to the muscular bellies of the short head of biceps and coracobrachialis.

Group IV: *The central* nodes lie in the fat on the floor of the axilla. Leaf described one or more members of this group as superficial, lying immediately on the skin below an opening in the fascial floor comparable with the saphenous opening in the anterior wall of the femoral triangle. It is doubtful whether such an opening is always present, but any marked thinning of the fascia would render the nodes more palpable.

Group V: *Apical* (variously named infraclavicular, subclavicular, subclavian). The nodes lie at the apex of the axilla on the proximal part of the axillary vessels deep to clavipectoral fascia (costocoracoid membrane) and the upper fibres of pectoralis minor.

Interpectoral: In addition to the five groups within the axilla, a few small, inconstant nodes are found between the two musculofascial strata which compose the anterior axillary wall. The largest and most constant of the nodes lie on the clavipectoral fascia; others may be found on pectoralis minor or on the suspensory ligament of the axilla. They are covered by pectoralis major. 'Interpectoral' is a convenient name for these nodes, and avoids confusion with other groups. The names infraclavicular and subclavicular are applied to the more cranial nodes by some authors.

The relation of mammary drainage to the above groups will be discussed later. At this stage it is convenient to note that the basal Groups I–IV freely intercommunicate and all send lymph-vessels to group V (apical); that the interpectoral nodes send efferent vessels through clavipectoral fascia (mainly) into Group V (apical); and that from the apical nodes a large *subclavian lymph-trunk* passes with the subclavian blood-vessels to open into the junction of the internal jugular and subclavian veins at the root of the neck either directly or after joining the jugular lymphatic trunk, and a few efferent vessels pass to deep cervical nodes.

b. Thoracic and Associated Nodes (*see Fig.* 3).—The thoracic nodes concerned are principally those which lie on the course of the internal mammary artery and its branches. Posterior intercostal nodes may be of some importance.

i. *Internal mammary* (also called sternal). One or two small nodes are nearly constant in the anterior ends of the upper three intercostal spaces. They lie on the internal mammary artery separated from the pleura by fat and by the aponeurotic extension of the transversus thoracic muscle. Nodes are infrequent in the 4th and 5th spaces, but one is usually found behind the 6th costal cartilage at the bifurcation of the artery. In an examination of 60 cadavers of different age and sex, Stibbe* found a 97, 98, and 82 per cent incidence of nodes in the 1st, 2nd, and 3rd spaces respectively, 9 and 12 per cent in the 4th and 5th. He found no sex differences, and no age difference between 20 and 60 years, but the nodes were more numerous before 20, and rather less after 60.

ii. Small *anterior diaphragmatic* nodes lie behind the xiphisternal junction and form part of the internal mammary chain.

iii. Small inconstant nodes lie on the course of the terminal branches of the internal mammary artery, one or more accompanying the superior epigastric artery behind the rectus abdominis muscle in the *rectal sheath*.

Vessels from the smaller groups pass to the internal mammary nodes from which the collectors enter the thoracic or right lymphatic duct, or open directly into the subclavian vein. The internal mammary nodes may communicate directly with the corresponding nodes of the opposite side, with mediastinal nodes, and with the lower medial deep cervical nodes.

iv. *The posterior intercostal* nodes are small nodes lying near the heads of the ribs at the posterior end of each intercostal space. They drain adjacent vertebræ as well as the thoracic wall.

c. Cervical Nodes (*see Fig.* 3).—The deep nodes alone of the neck are concerned, and of these only the two lower groups :—

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* Stibbe, E. P. (1918), *J. Anat., Lond.*, 52.

Lower lateral deep cervical nodes (variously named subclavian, supraclavicular, posterior inferior deep cervical) lie on the third part of the subclavian artery in the supraclavicular triangle.

Lower medial deep cervical nodes, lying behind the sternomastoid at the root of the neck, are of importance only because of their communications with the lateral group and with the internal mammary nodes.

Collecting vessels from the cervical nodes join the jugular trunk or open directly into the jugulo-subclavian venous junction.

2. The Lymph-vessels.—

a. General Plan of Superficial Lymph Drainage.—The cutaneous origin of the breast is reflected in the arrangement of its lymph-vessels,

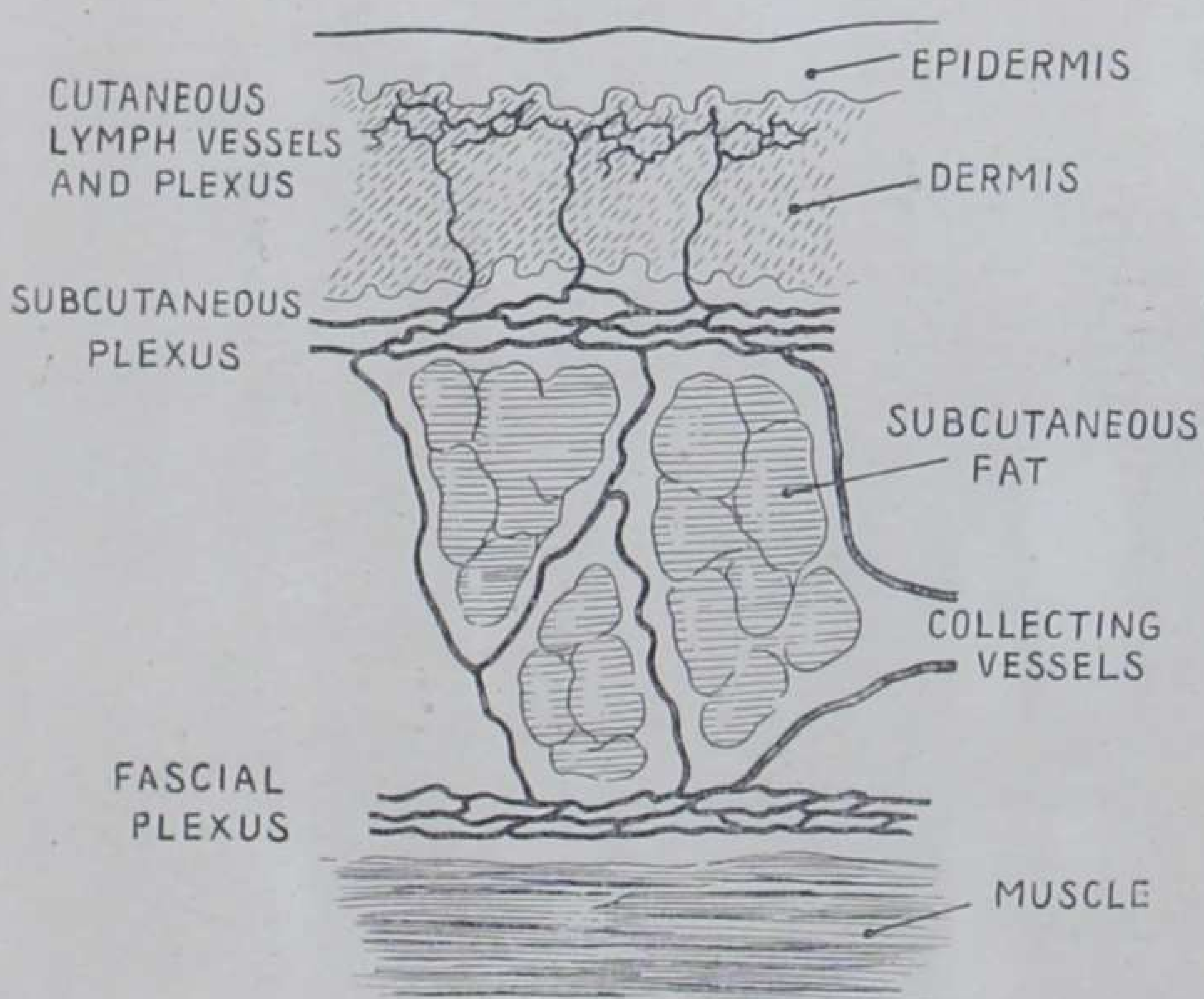

Fig. 7.—Diagram of the general plan of arrangement of the lymph-vessels of the skin and subcutaneous tissue. The cutaneous plexus may be less continuous than is depicted.

which follows the general pattern for the skin and subcutaneous tissue. This general pattern includes cutaneous (subepidermal and dermal), subcutaneous, and fascial plexuses, and is as follows (*Fig.* 7):—

Blindly ending capillaries lie in the dermal papillæ and open into a fine subepidermal capillary plexus " which is probably not continuous over large areas but forms more or less discrete patches ".* A second and in places a third intradermal plexus have been described. All these are *cutaneous*. From the cutaneous plexuses vessels pass to a

* Brash, J. C. (1948), *Cunningham's Text-Book of Anatomy*.

subcutaneous plexus of wider vessels lying at the cutaneous-subcutaneous junction. The subcutaneous plexus is separated by subcutaneous fat from the *fascial* plexus, also of large calibre, which lies in the loose connective tissue between the fat and the deep fascia. Fascial and subcutaneous plexuses are linked by vessels in the connective-tissue septa of the adipose layer. The subcutaneous and fascial plexuses, and, to a lesser extent, the cutaneous plexus, are continuous

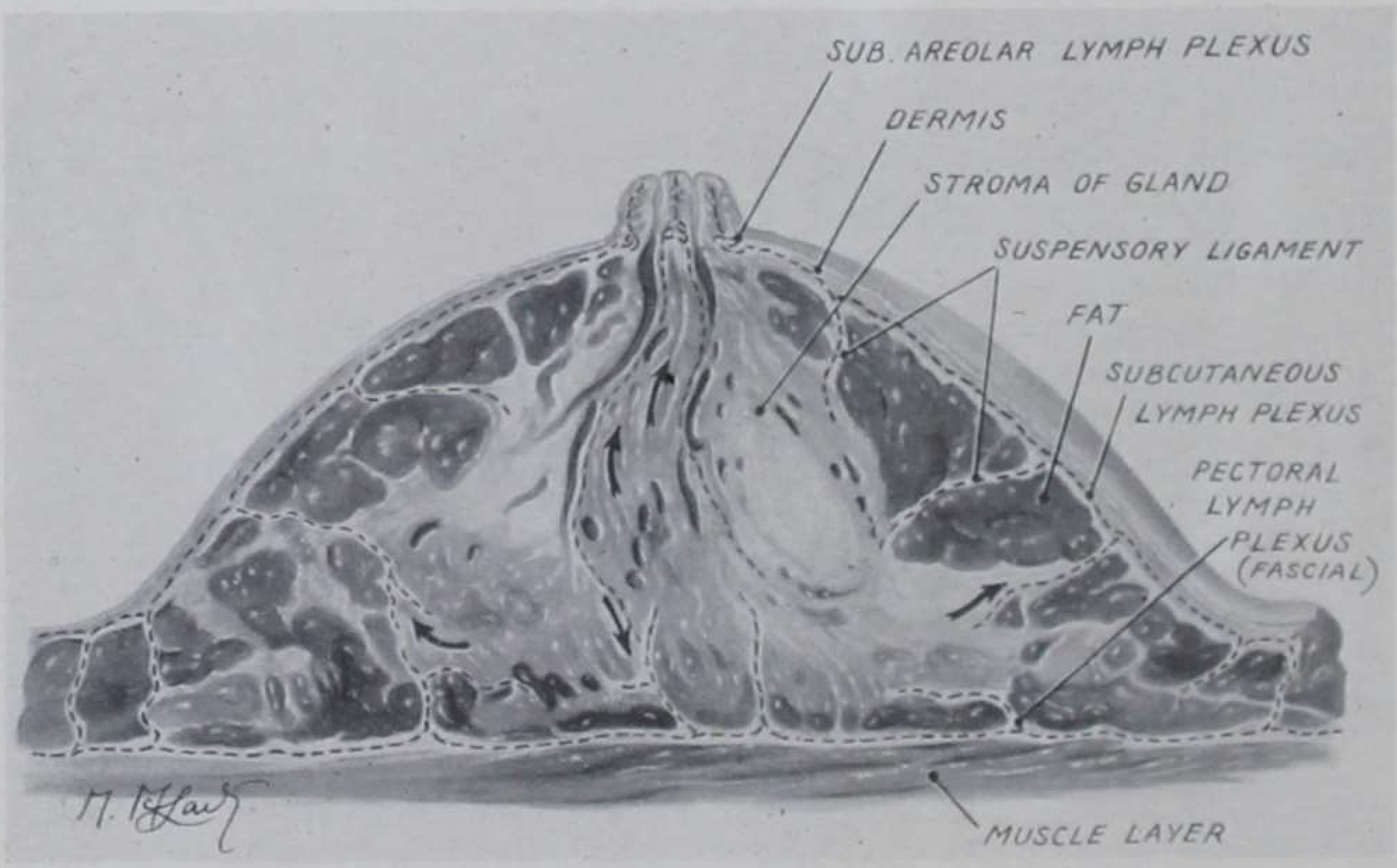

Fig. 8.—Schematic drawing of *Fig.* 1 to show the arrangement of the lymph-plexuses in the breast. The arrows indicate the direction of lymph-flow to the plexuses.

across the 'lymph sheds' or junctional lines of lymph territories: namely, the middle line, the umbilical plane, and the horizontal plane of the clavicles.

From both the subcutaneous and the fascial plexuses large efferent or collecting vessels (the superficial lymph-vessels of descriptive anatomy) pass to lymph-nodes. Between the umbilical and clavicular planes, the majority of the collecting vessels pass to axillary lymph-nodes of the same side, but from near the middle line, a few pass to contralateral nodes.

Both the collecting vessels and the vessels of the larger plexuses are valved, and the valves are so arranged that the lymph is directed away from the sheds.

b. Arrangement of Lymph-vessels in the Breast.—The skin contains a fine *cutaneous* plexus which opens into the subcutaneous plexus between the skin and the subcutaneous fat. Beneath the nipple and areola the subcutaneous plexus forms the well-marked *subareolar* *plexus* (of Sappey). A fascial plexus lies behind the breast in the pectoral fascia. The mammary gland, penetrating the subcutaneous fat, lies in the plane between the subcutaneous and fascial (pectoral) plexuses which, therefore, become widely separated but remain in communication by means of the vessels which traverse the gland and the suspensory ligaments (*Fig.* 8).

Within the mammary gland proper, vessels lie in the main on the periphery of the lobules but closely accompany the ducts. Most of the larger vessels converge with the ducts towards the nipple to end in the subareolar plexus. Some, however, pass to the surface of the gland from which they may join the pectoral plexus or be carried by the suspensory ligaments to the general subcutaneous plexus, or pass directly to lymph-nodes.

3. Normal Direction of Lymph-flow from the Breast (*Fig.* 9).—No hard-and-fast line can be drawn between the drainage of

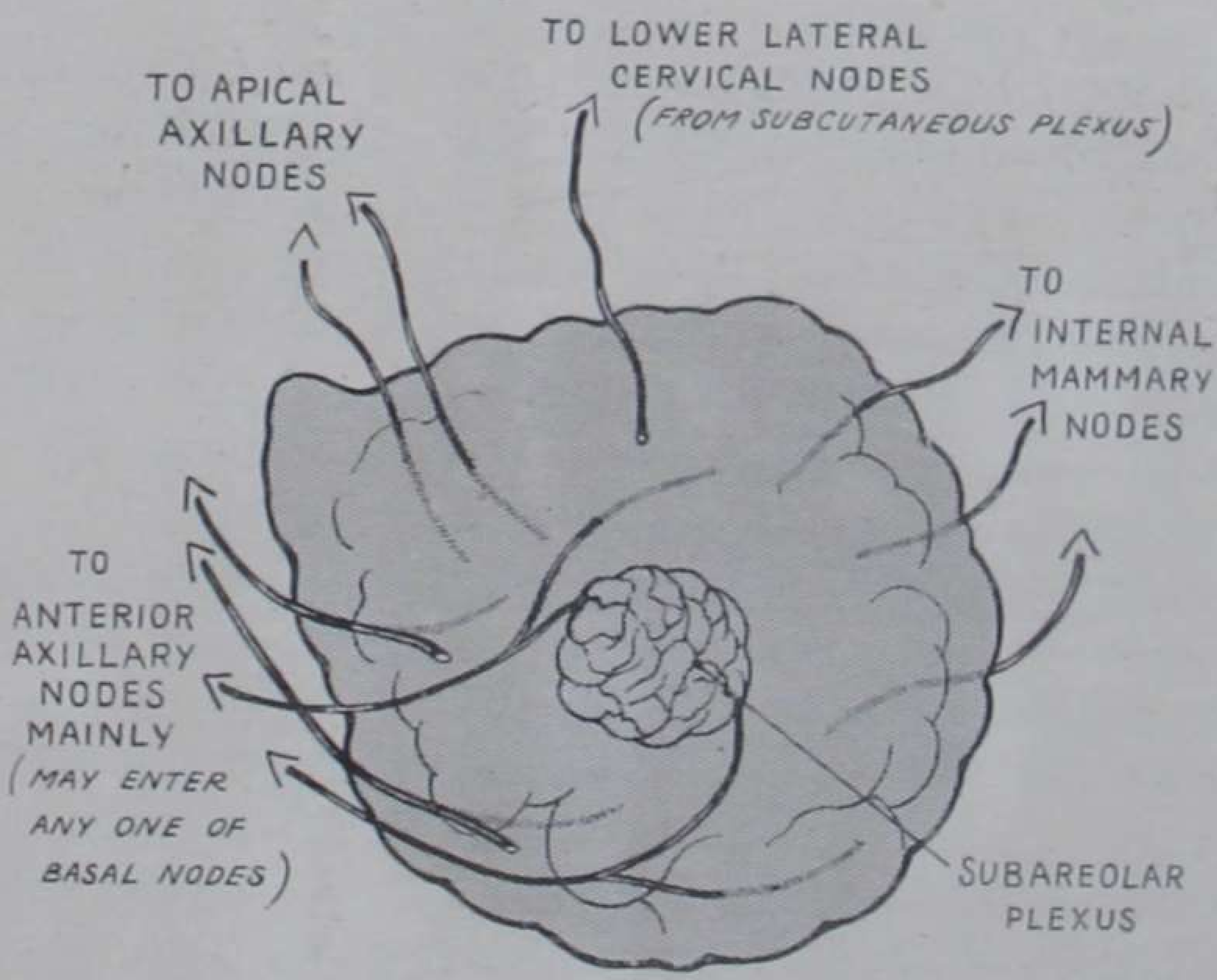

Fig. 9.—Diagram of the anterior surface of the right mammary gland to show the direction of the principal collecting vessels. Dotted lines indicate an origin mainly from the pectoral plexus and the surface of the gland, lines with open ends an origin mainly from the subcutaneous plexus. The position of the vessels does not imply that drainage is restricted to the neighbouring area.

the skin and the drainage of the glandular tissue because both are in free communication with all the plexuses from which the main collecting vessels arise. For the same reason it is not possible to relate a particular group of collecting vessels to a particular area of the skin or the gland.

Lymph is carried from the breast by collecting vessels which arise mainly in the plexuses—subareolar, general subcutaneous, pectoral—with a few passing directly from the surface of the gland. The collecting vessels pass to *axillary, internal mammary, and lower lateral deep cervical lymph-nodes* in the following manner :—

a. To Axillary Nodes of the Same Side.—

i. Two or more large collecting vessels leave the subareolar plexus, and curving round the lower border of pectoralis major (or, occasionally, piercing the muscle) join the *anterior axillary lymph-nodes.* One of these vessels may miss the anterior nodes and go straight to one of the other basal groups.

ii. One or more vessels, usually from the deep surface of the gland, pass directly to the *apical lymph-nodes.* They may traverse pectoralis major or turn up under its lower border ; and then pierce clavipectoral fascia, passing through one or more interpectoral nodes on their way.

iii. Smaller collecting vessels from the general subcutaneous plexus and variably from the pectoral plexus and from the surface of the gland may pass to any or all of the nodes in the lower part of the axilla.

b. To Internal Mammary Nodes.—Collecting vessels mainly from the pectoral plexus and from the surface of the gland accompany the perforating branches of the internal mammary and intercostal arteries to the internal mammary lymph-nodes in the upper three (usually) intercostal spaces. These vessels pierce the pectoral muscles. It is possible, though probably unusual, for one or more to turn backwards to the posterior intercostal nodes.

c. To Lower Lateral Deep Cervical Nodes.—At least one collecting vessel is frequently found to leave the subcutaneous plexus of the upper part of the breast, cross the clavicle superficially, and end in the lower lateral deep cervical nodes. Mornard describes a vessel from the surface of the gland itself passing deep to the clavicle to one of these nodes in 3 per cent of cases examined.

d. To Contralateral Axillary Nodes.—These occasionally receive a vessel from the subcutaneous plexus of the medial part of the breast (Oelsner).*

The above may be summarized thus :—

i. Most of the lymph from the breast, including the nipple, drains into ipsilateral axillary lymph-nodes, of which the *anterior*

* Quoted by Rouvière.

group receives the major part direct, the *apical* group always some direct, and any of the other basal groups may receive some direct.

2. Some lymph always passes direct to the internal mammary nodes and some probably to lower lateral deep cervical nodes.

3. Rarely lymph passes to contralateral axillary nodes and to posterior intercostal nodes.

4. Pathways that may be opened up under Abnormal Conditions.*—Clinical and post-mortem findings have established that, in addition to dissemination along normal lymph pathways from the breast, cancer cells may travel by lymphatic routes to other parts of the body, among which may be cited the opposite breast; contralateral axillary, lower cervical, and internal mammary lymph-nodes, and the lymph-nodes in the rectal sheath; viscera, notably the lungs, pleura, and liver; and the skeleton, especially the vertebral column.

In these cases, if spread is by lymphatic channels, it must be either with the lymph-stream by aberrant collector vessels or retrograde.

The presence of aberrant collector vessels from the mammary subcutaneous plexus of one side to the axillary nodes of the opposite side has been mentioned, and doubtless aberrant vessels to other contralateral groups of nodes account for a certain number of cases of unusual spread to lymph-nodes. The communications that frequently exist between the right and left internal mammary nodes are sufficient to account for contralateral involvement of that group. It is probable, however, that in a majority of cases spread is retrograde, whether by reversal of the lymph-flow or by the passage of cancer cells against the flow or by permeation.

The causes and nature of retrograde spread are outside the scope of this section, but mention may be made of some of the anatomical features of lymph-vessels which facilitate it. The vessels of the subcutaneous and fascial lymph-plexuses are relatively large, and the plexuses are continuous over large areas, and across the sheds, and are in communication with each other. The vessels of the plexuses and all collecting vessels are highly distensible, and the smaller collectors show irregularity but little gradation in size. All these features facilitate flow in either direction, and that there is a 'normal' direction depends mainly on the arrangement of the valves, which face opposite ways on the two sides of a lymph-shed. Lymph-flow

* "Lymphatic spread of cancer is more extensive than the normal anatomical channels would indicate. When the normal lymph-flow becomes obstructed by invading neoplasm, the stream may be deviated or reversed, new channels opened, and malignant cells widely dispersed beyond the zone of physiological drainage" (S. Handley).

can be reversed if the vessels are dilated to a point at which the valves are inactive.

In most of the examples of unusual spread quoted above, the subcutaneous and fascial plexuses can provide the channels for retrograde spread and probably do provide the main channels for involvement of the opposite breast, although the communications between the right and left internal mammary nodes already described give an alternative route. Spread to the nodes of the rectal sheath and to the liver is retrograde, either by the superficial plexuses to the surface of the sheath and then by perforating and para-umbilical vessels to nodes and liver respectively ; or, on a deeper plane, along the internal mammary chain and then along superior epigastric vessels to the nodes, or through the diaphragm to the bare area of the liver. The parietal pleura may be involved through vessels which accompany the branches of the intercostal arteries from the deep surface of the mammary gland. Spread to the lungs, apart from direct extension from the pleura, is probably retrograde from sternal nodes through mediastinal nodes. The intercostal vessels provide the link between the breast and the vertebral column, through the posterior intercostal nodes lying on the heads of the ribs into which lymph from the thoracic vertebræ drains. Caudally the intercostal nodes communicate with the para-aortic chain and so with the external iliac and femoral nodes.

The dissemination of cancer cells within the skin is not facilitated by the anatomical conditions which play a part in abnormal spread elsewhere. The vessels of the subepidermal plexus and the papillary vessels which enter it are very fine, and it has been denied that any continuous cutaneous plexus exists. That it is at least very restricted in extent is generally held ; although some experimental work* suggests that it may be more extensive than has been supposed.

B. THE MALE BREAST

The male breast (*see Figs.* 28–30) presents no differences from the female at birth. Some growth of the mammary gland takes place during childhood and may be more marked at puberty, after which retrogression occurs. In the adult male, the gland measures about 25 mm. in diameter, hardly extending beyond the areola. Ducts are usually well developed, but no lobules form. Fat is present in the stroma ; its virtual absence between gland and skin preserves an external flat contour.

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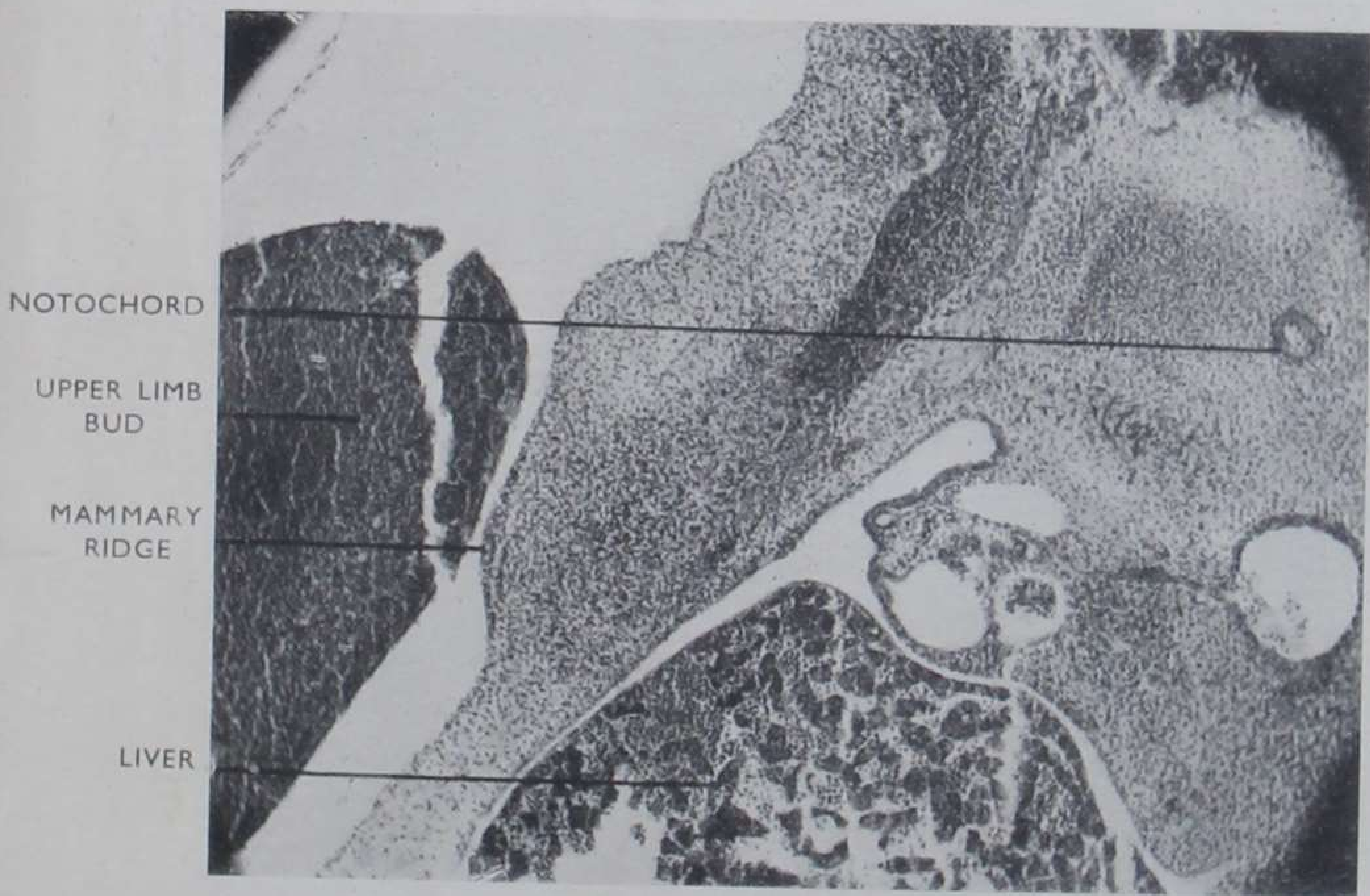
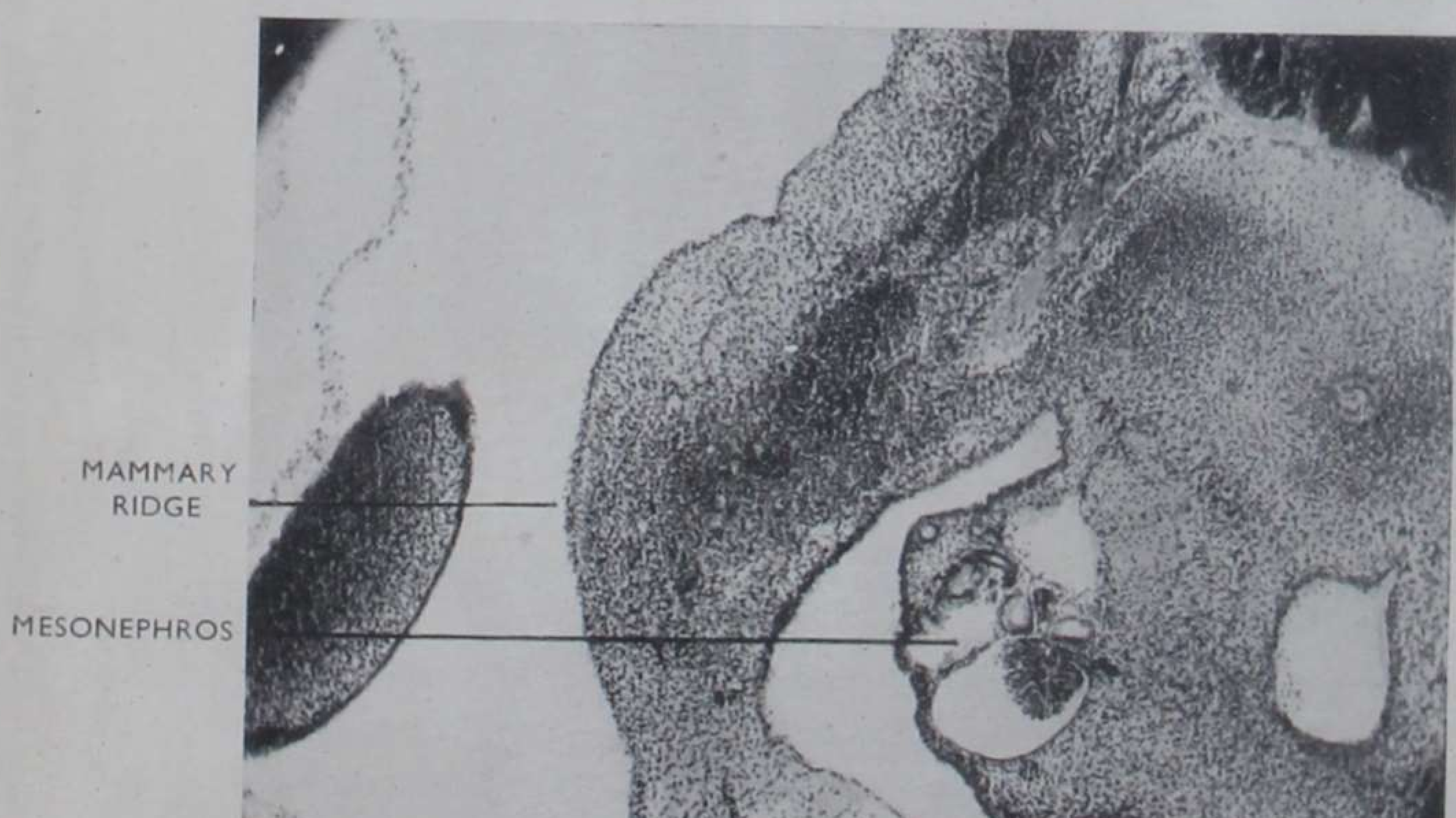
* Forbes, G. (1938), *J. Anat., Lond.*, **72**.

II. DEVELOPMENT

The mammary gland arises from the surface epithelium of the anterolateral aspect of the chest wall; epithelial processes invade the





Figs. 10, 11.—Transverse sections through the same 10-mm. human embryo (30–35 days). (*Lucas Keene*, No. 2387.) *Fig.* 10 is the more cranial section; the mammary ridge is well defined opposite the upper limb bud. *Fig.* 11 is caudal to the above; the ridge is visible opposite the distal part of the limb but is less well defined. Stained hæmatoxylin and Biebrich scarlet. (*Photograph.*) (× 48.)

underlying connective tissue, which provides the stroma and vascular elements of the gland.

The first indication of mammary growth is a strip of high epithelial cells extending from the axilla to the groin. In many mammals, breasts are developed along the length of this 'milk line' or mammary ridge ; in others, further mammary development is restricted to a single area, the usual size of the litter being apparently the determining factor. In man the greater part of the ridge disappears, leaving the definitive mammary anlage as a circumscribed area in the thoracic region.

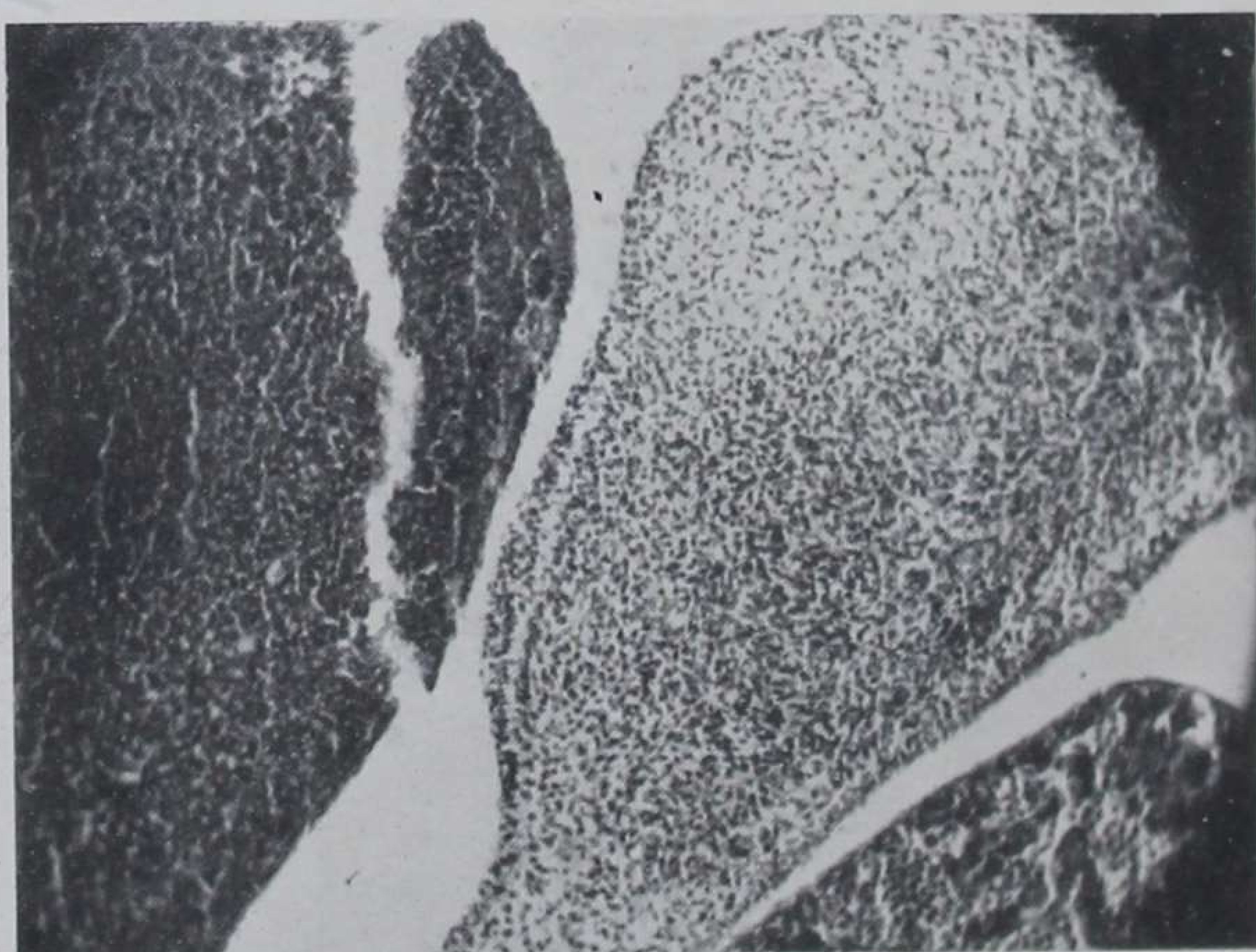


Fig. 12.—Same section as *Fig.* 10 more highly magnified. High epithelial cells of ridge show clearly. (*Photograph.*) × 90.)

In the human embryo the age of appearance and the extent of the ridge are variously given. Frazer, from his extensive collection, described the ridge in 7-mm. embryos, and as "extending from the axilla towards the groin". Earlier appearances have been stated. In the series of embryos examined by the author (Lucas Keene collection) including 5-mm., 6-mm. (two), 9-mm. (two), and 10-mm. (three), as well as older specimens, only a doubtful indication of the ridge is visible at the 9-mm. stage and in no earlier ones. It is well defined in all three 10-mm. embryos ; in the cranial portion of the ridge the cells stand out in strong contrast with the surrounding epithelium ; caudally the ridge is less conspicuous and does not reach the groin (*Figs.* 10–12).

In these young embryos a certain heightening of the epithelium is found in many parts of the surface, with cells closely resembling those of the less differentiated parts of the mammary ridge. The appearance suggests that embryonic surface epithelium generally may retain for a time potentialities which might include the formation of mammary gland anlagen. This would explain the occurrence of supernumerary mammæ in so-called aberrant positions.

In 12–18-mm. embryos (about 35 to 45 days) the mammary anlage is restricted to the thoracic region, and may conveniently be called

Fig. 13.—Transverse section of 12·5-mm. human embryo (*Lucas Keene* No. 2325). Shows cup-like nipple area and continuity of the columnar epithelium lining the cup with the epithelium of the adjacent surface. Stained hæmatoxylin and Biebrich scarlet. (*Photograph.*) (× 90.)

the nipple area. Its cells have proliferated inwards forming a hemispherical mass in which a cup-like outer layer of columnar cells continuous with the surface epithelium is filled with oval and irregularly shaped cells (*Figs.* 13, 14).

During the next 10 or 12 weeks the surface of the nipple area becomes relatively less extensive, but further cell division expands the 'cup' into an irregular sphere (*Fig.* 15). Before the 20th week (embryos of about 150 mm.) solid processes begin to grow from the periphery of the sphere and burrow into the surrounding connective tissue (*Figs.* 16, 17). They have an outer layer of columnar cells

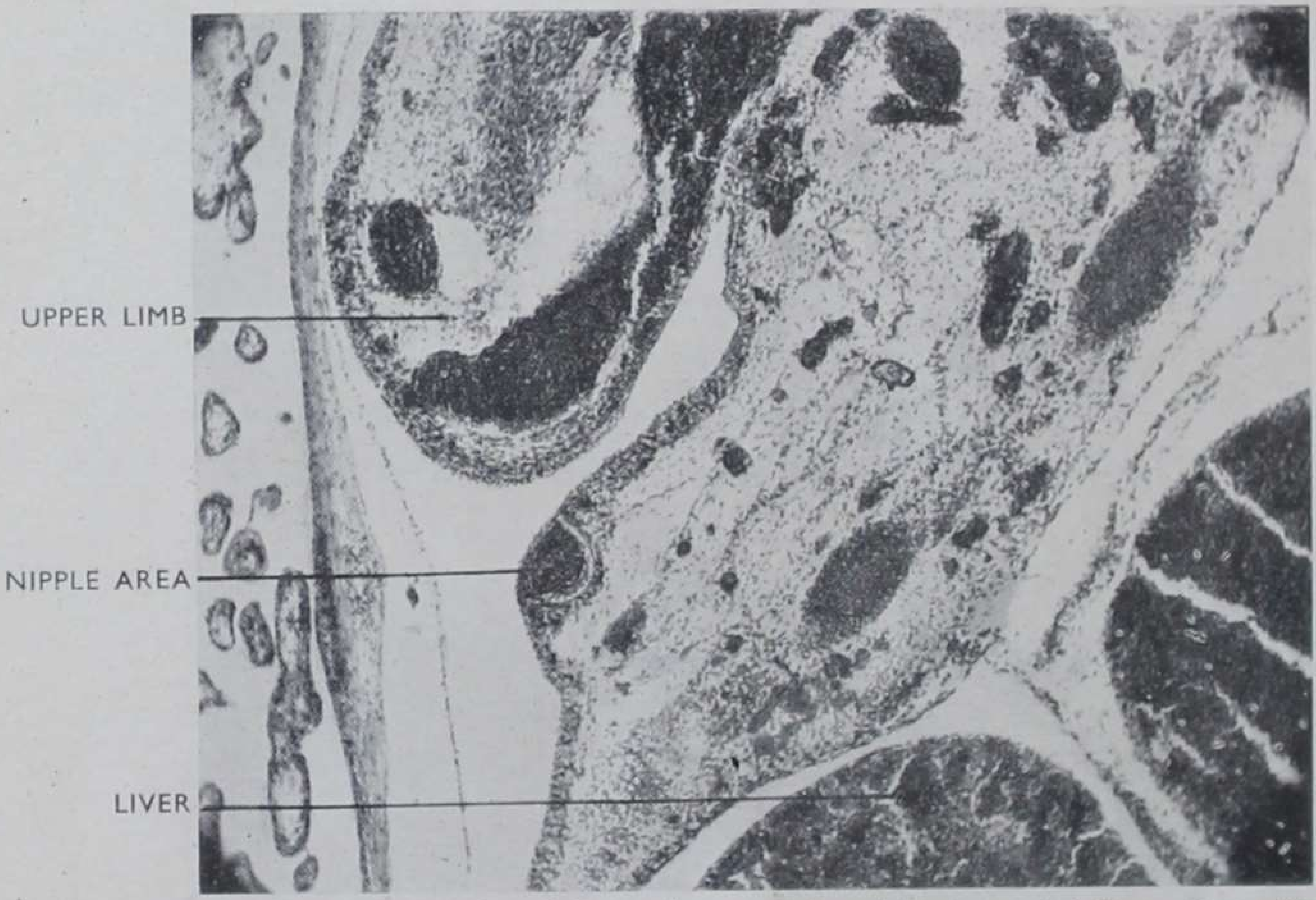


Fig. 14.—Transverse section of 18-mm. human embryo (about 7 weeks) (*Lucas Keene*, No. 2432). Shows no advance in complexity on the 12-mm. stage. Stained as *Fig.* 13. (*Photograph.*) (× 48.)

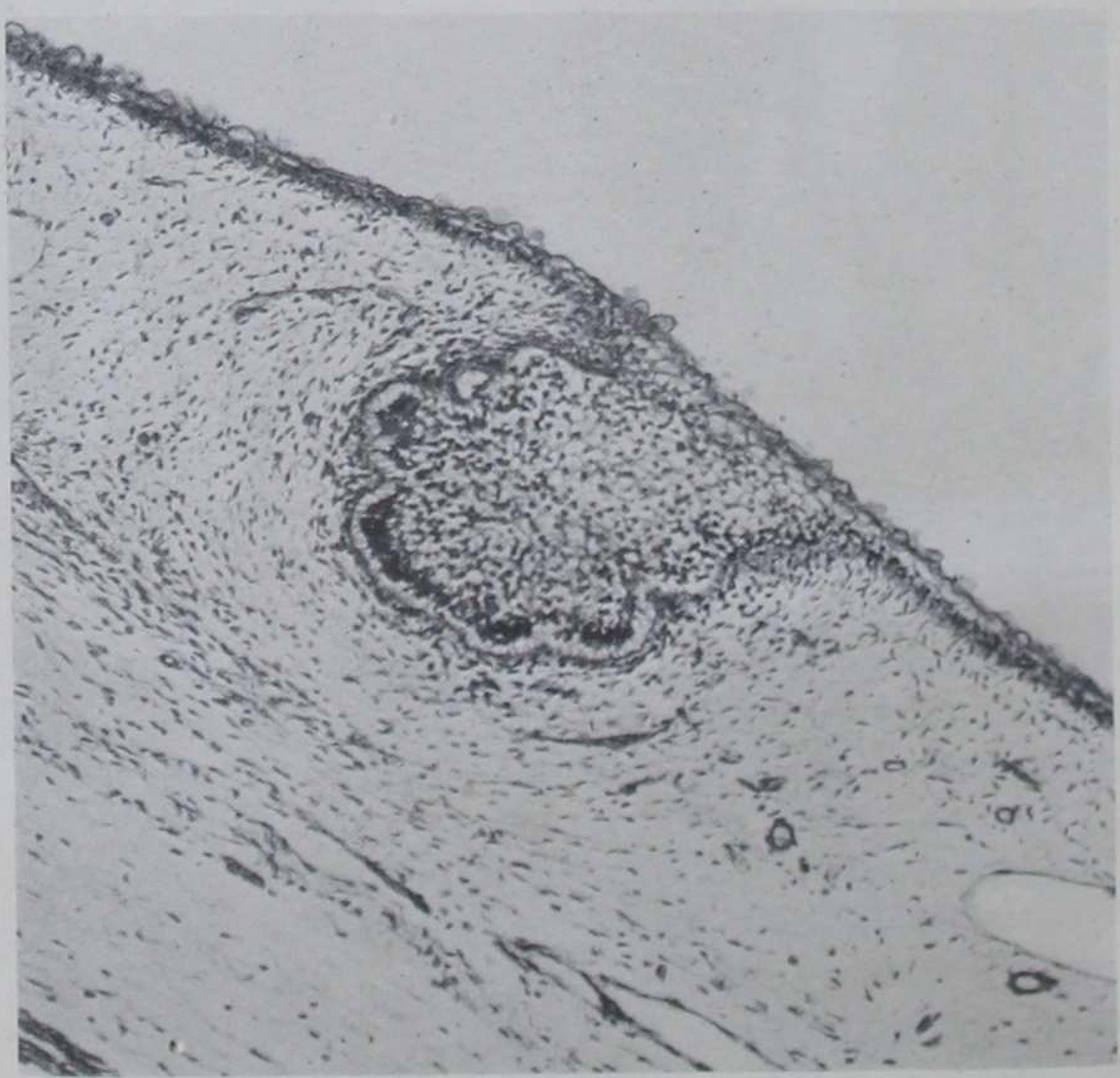


Fig. 15.—Human fœtus of about 17–18 weeks (*E. E. Hewer* No. 142). Shows the nipple area as an irregular sphere and, reaction in the surrounding connective tissue. Stained Ransom's silver nitrate method. (*Photograph.*) (× 116.)

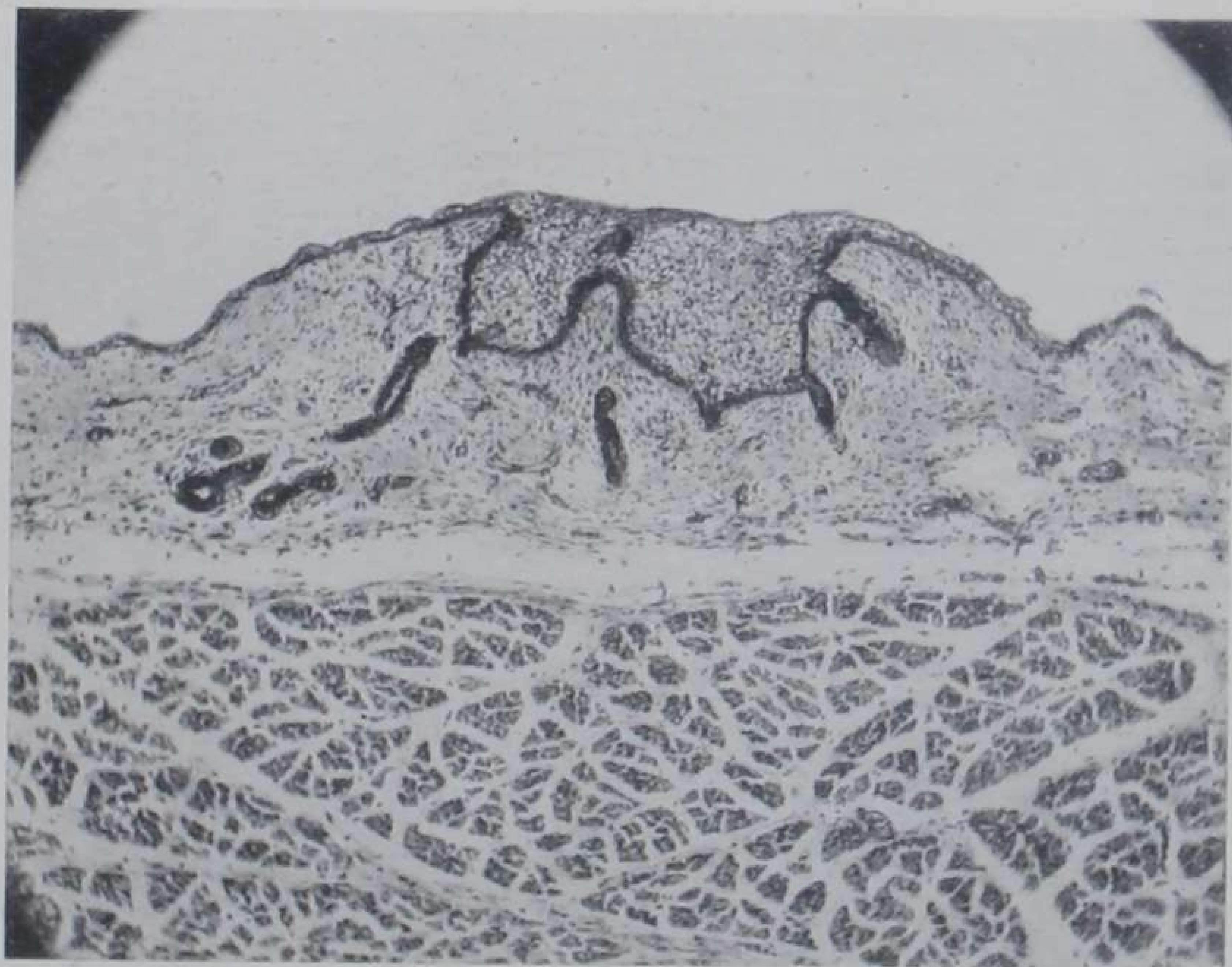


Fig. 16.—200-mm. human fœtus aged about 24 weeks. Section at right angles to the surface of the skin. Mammary area shows outgrowth of several processes, some partly canalized into ducts. Also reaction in connective tissue. Stained as *Fig.* 15. (*Photograph.*) (× 48.)

Fig. 17.—210-mm. human fœtus. Section at right angles to the skin surface. Shows stratification and shedding of the epithelium of the cup. The single process in the field is not yet canalized. Marked connective-tissue reaction. (*Photograph.*) (× 90.)

continuous with the columnar lining of the cup (*Fig.* 18) and an inner core of rather large, eosinophilic, oval cells.

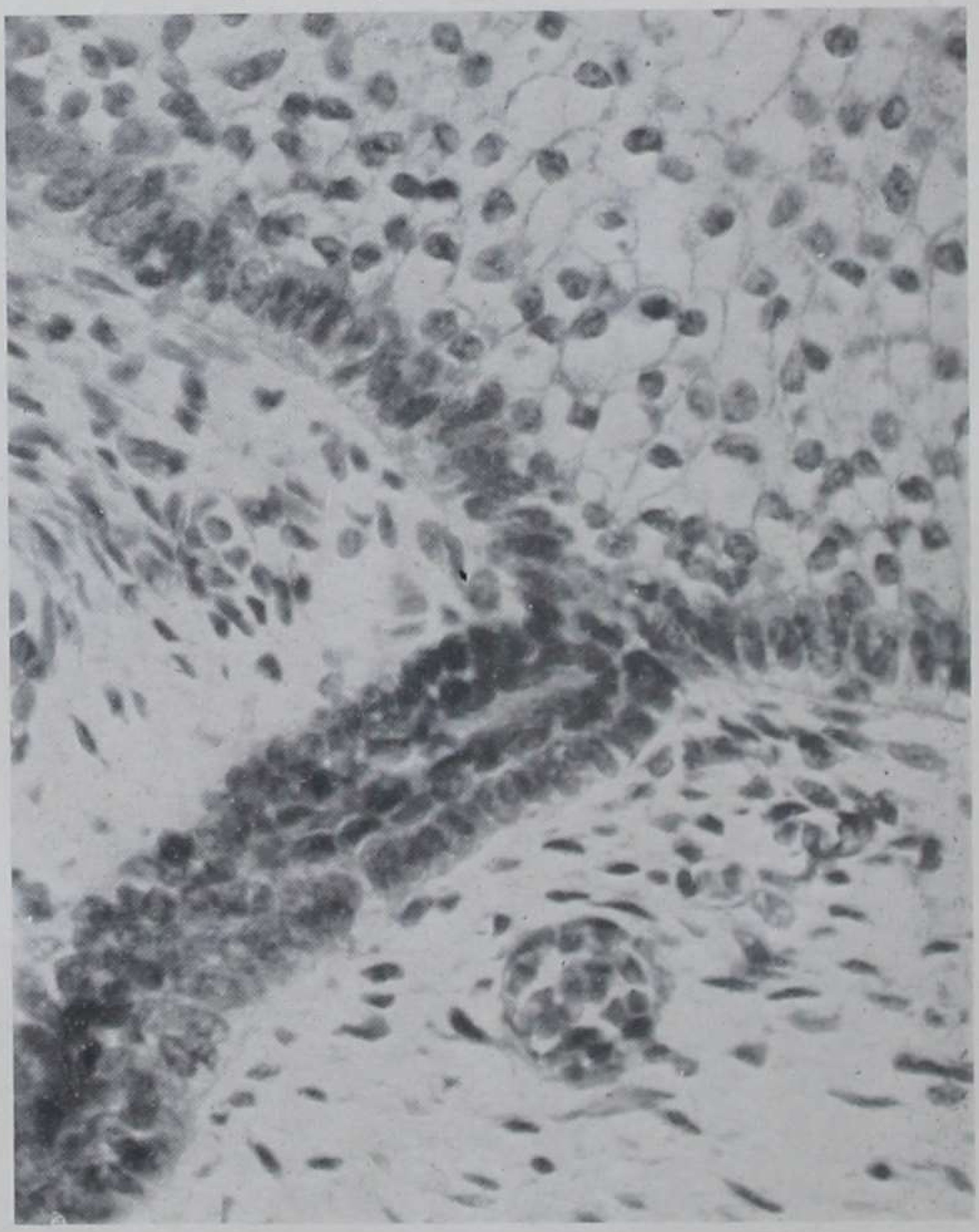


Fig. 18.—Same section as *Fig.* 17 more highly magnified. Shows columnar-cell lining of cup continued as outer layer of the process, and more oval cells forming central core. (*Photograph.*) (× 465.)

From 20 to 24 weeks onwards, canalization of the processes to form ducts proceeds. At first a lumen forms between cells of the central core, which become flattened against the outer columnar layer, producing a two-layered epithelium. Gradually, however, the inner cells disintegrate and disappear, widening the lumen, but a bilaminar duct wall persists, composed of an inner columnar layer and an outer layer of flatter cells, both layers probably derived from the original outer layer. The ends of the ducts remain solid, and further growth takes place by proliferation of the terminal cells (*Figs.* 15, 19, 20).

During the 8th and still more in the 9th fœtal months there is great activity of the ducts, which grow and branch, and the increase

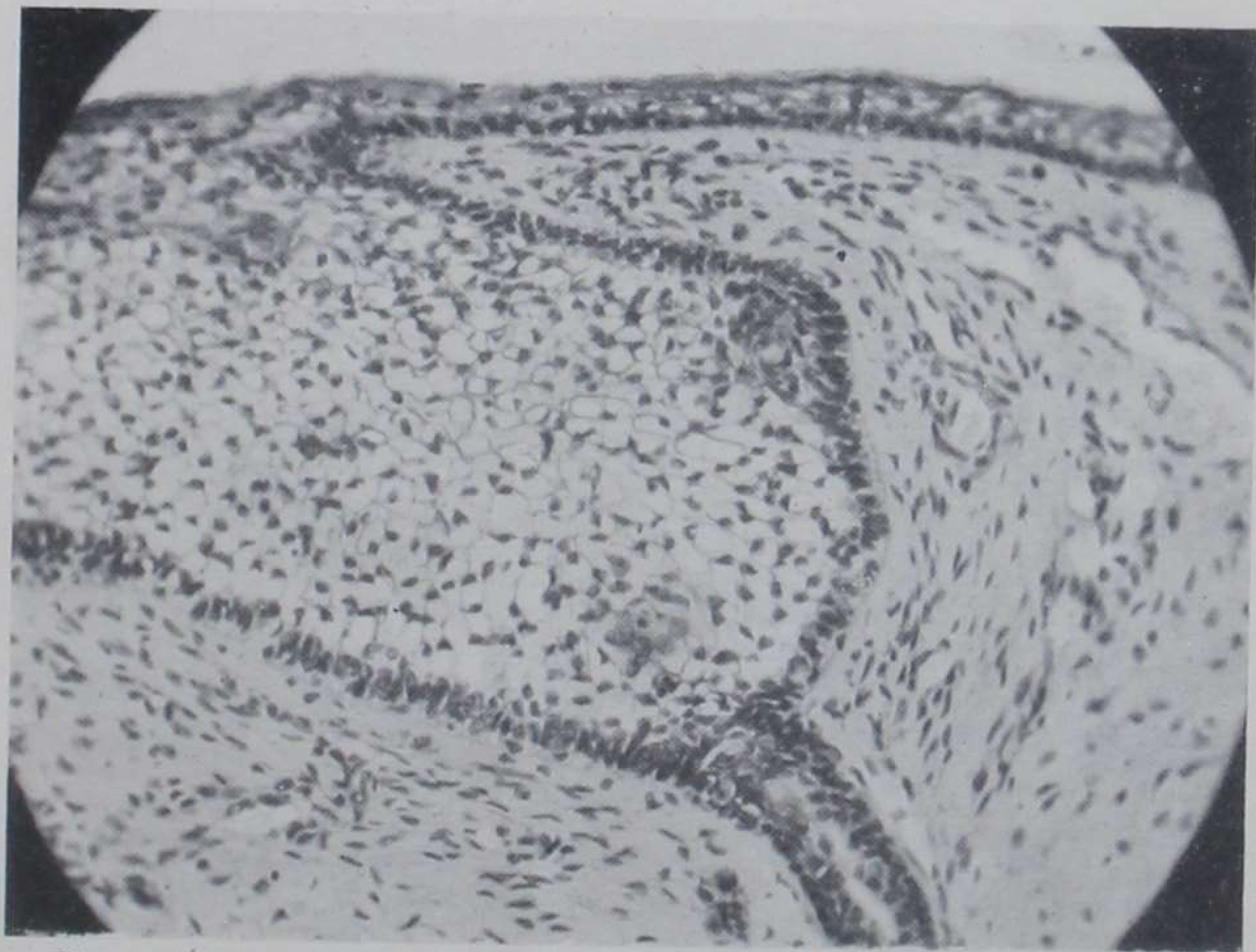


Fig. 19.—160-mm. human fœtus (about 20–24 weeks). Shows formation of lumen in the single process visible, and commencing disintegration of some of the central cells. (*Photograph.*) (× 200.)

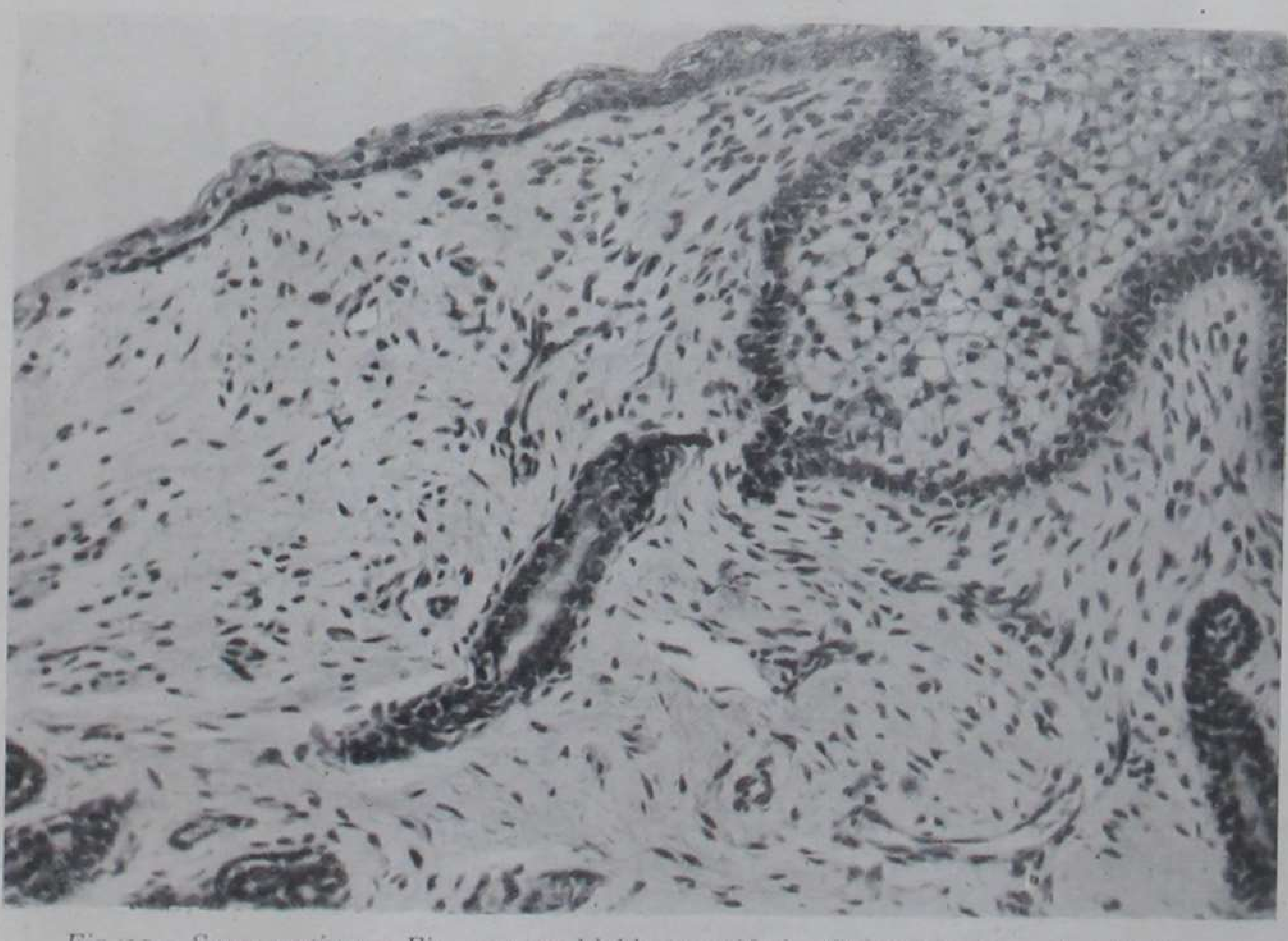


Fig. 20.—Same section as *Fig.* 15 more highly magnified. Shows two-layered epithelium of the duct. (*Photograph.*) (× 176.)

in the total amount of duct epithelium is very striking (*Fig.* 21). The cells enlarge and appear slightly swollen, in marked contrast with the compact cells of the sweat-glands at this stage. A basement membrane

Fig. 21.—8-months human fœtus. Section at right angles to surface of skin. Nipple area depressed below the surface. Ducts show considerable growth and some branching. (*Photograph.*) (× 41.) (Slide lent by *Dr. E. K. Dawson.*)

is well defined. The presence of myo-epithelial cells within the basement membrane is doubtful (although they have been described), again in contrast with the sweat-glands, in which they are well developed before the 7th month.

Reaction in the connective tissue adjacent to the nipple area precedes the first budding out of the solid processes, but becomes marked by increasing density and the formation of blood-vessels as the processes grow (*see Figs.* 15 et seq.). In the last few weeks of fœtal life the stroma shows a greatly increased vascularity, much cellular activity, and some differentiation of its fibrous elements.

At birth the nipple area is still depressed below the surface and shows a typical stratified squamous epithelium. The definitive number of milk ducts is present, and canalization through the nipple is complete; some branching of the ducts has occurred but no lobules have formed. The stroma shows some specialization. (*See Figs.* 22, 23.) (For a more detailed account *see* pp. 28–30).

The mammary anlage appears earlier than other derivatives of the surface epithelium although it lags behind them in further development. Hair follicles begin to form at about 12 to 13 weeks and sebaceous glands by 14 weeks. Sweat-glands begin to show at 14 to 15 weeks and are well developed by 20 weeks. The specimens examined confirmed Dawson's finding that no sweat-glands develop from the nipple area.

III. THE MINUTE STRUCTURE OF THE MAMMARY GLAND AFTER BIRTH

Introduction.—The fully developed gland consists of about 20 irregularly-shaped *lobes*, which are separated by dense interlobar connective tissue containing a varying amount of fat. Each lobe is an independent, compound, alveolar gland, and has one *excretory* (*lactiferous, lobar*) *duct* which opens on the *nipple*: before its opening there is a local dilatation (*sinus lactiferus, ampulla*).

Each lobe is composed of *lobules** of various orders: these consist of branching, lobular *ducts* (*parenchyma*) embedded in periductal connective tissue (*stroma*). The smallest ducts give rise to actual secreting tissue (*see below*).

The glands first appear as solid branching downgrowths from the epidermis into the underlying connective tissue and fat (*see* p. 21). These downgrowths rapidly canalize, and the *parenchyma* of the gland comes to consist of a system of epithelial ducts whose "degree of ramification varies according to the character of the inner

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* Some writers use the term 'lobule' to denote the ducts with all their ramifications, applying the word to the parenchyma only. As the periductal connective tissue is closely bound up functionally with the parenchyma, it seems better to include both stroma and parenchyma in the term 'lobule'.

environment " (Loeb). The ultimate branches of these ducts finally become secretory in character, chiefly through the spherical outpouchings (*alveoli*) with which they become covered.* The *stroma*, at first the ordinary fœtal subcutaneous tissue, is soon differentiated into (1) a dense, fibrous type of tissue round the excretory ducts (interlobar and interlobular connective tissue), and (2) a cellular type of tissue within the lobules and round the smallest ducts (intralobular or periductal connective tissue).

The nipple, lactiferous ducts, and larger lobular ducts are not subject to marked seasonal variation, and are therefore always surrounded by dense fibrous tissue. But during the life cycle, very marked changes occur in the parenchyma of the gland, and proliferation and activity of the epithelial elements is associated with a corresponding activity of the periductal connective tissue and fat of the stroma. For the purpose of description the following stages are considered :—

1. At birth.
2. From birth to puberty, i.e., during development of sexual maturity.
3. Adult, i.e., sexually mature :—
    a. Male.
    b. Female—throughout the menstrual cycle, including the ordinary ' resting ' phase.
    c. Female—throughout pregnancy and lactation, including the subsequent retrogression.
4. At the menopause, or shortly after cessation of reproductive activity.
5. In senility.

In this account it should be borne in mind that " there is no uniform standard of normal structure and function . . . 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 " (Creighton).

1. At Birth.—The glands have the same structure in both sexes. The whole mass is less than 1 cm. in diameter, and is surrounded by connective tissue that blends with the dermal and subdermal tissue : the nipple is not elevated.

a. Parenchyma.—The lactiferous ducts, grown down from the surface, have, repeatedly branched dichotomously (*Figs.* 22, 23) :

* The secretory part of the terminal duct together with its secretory alveoli is sometimes spoken of as an *acinus*.

Fig. 22.—Section of mammary gland area of full-term human fœtus (female). Note branching ducts, some dilated with debris. All the stroma appears cellular, and there is some lymphocytic infiltration. Stained with hæmatoxylin and Biebrich scarlet. (*Photograph.*) (× 14.)

originally solid, the branches are mostly canalized by birth. These are lined by two epithelial cell layers (*see* p. 32), the normal structure

Fig. 23.—Section of mammary gland area of full-term human fœtus (female). Note depressed nipple, and groups of lymphocytes. Stained with hæmatoxylin and eosin. (*Photograph.*) (× 36.)

of non-secreting glandular tissue. The basal cells are spherical or cuboidal, while the inner layer is usually more columnar: at the growing tips there are frequently swellings and additional basal cells, as provision for further growth; outside the layer of basal cells is a well-marked basement membrane. There are no alveoli. There is a tendency for the inner layer of cells to desquamate, a condition frequently associated with differentiation: such debris may fill some of the ducts and actually give rise to 'witch's milk'.

b. Stroma.—The bulk of the organ consists of dense *interlobar* connective tissue: the collagen fibres are thick, there are many elastic fibres, and the usual fibroblasts and histiocytes are fairly numerous (as is common in young tissues). The *intralobular* or *periductal* connective tissue, between the groups of ducts and their branches, is considerably less dense and more cellular: there are numerous fine elastic fibres. The small collections of lymphocytes commonly found near the growing ducts are the usual response to the presence of degenerating epithelial cells, in this case associated with canalization.

2. Birth to Puberty.—

i. MALE.—The gland remains rudimentary throughout life. There are never any alveoli, but only a series of ducts; these ducts are lined by the usual two-layered epithelium, but in many there is a breaking down of the inner layer with accumulation of debris in the lumen, which may be much dilated. This change is associated with a round-cell infiltration. At puberty there is sometimes a temporary congestion or inflammation.

ii. FEMALE.—A slow growth of the mamma continues, keeping pace with the general growth of the body, without differentiation of secretory tissue. The adolescent organ still contains only ducts, although showing considerable growth activity of both glandular tissue and surrounding stroma.

a. Parenchyma.—The ducts become elongated and a few new, lateral, branches form (*Fig.* 24). As puberty approaches there is considerable branching of the smaller ducts. Solid epithelial buds arise from a considerable length of the terminal part of the ducts; these become canalized very early, and thus groups of ductules are formed, surrounded by loose stroma: such a group will eventually give rise to a lobule (*Figs.* 25, 26). The budding ducts are usually spherical at first, and give the appearance of "toy balloons on a thick stalk" (Ingleby), like a bunch of cysts. The distal end of the duct is the most rapidly growing point: at first the stubby branches are

Fig. 24.—Section of breast tissue of girl aged 7 months. Stained with hæmatoxylin and Biebrich scarlet. (*Photograph.*) × 60.)

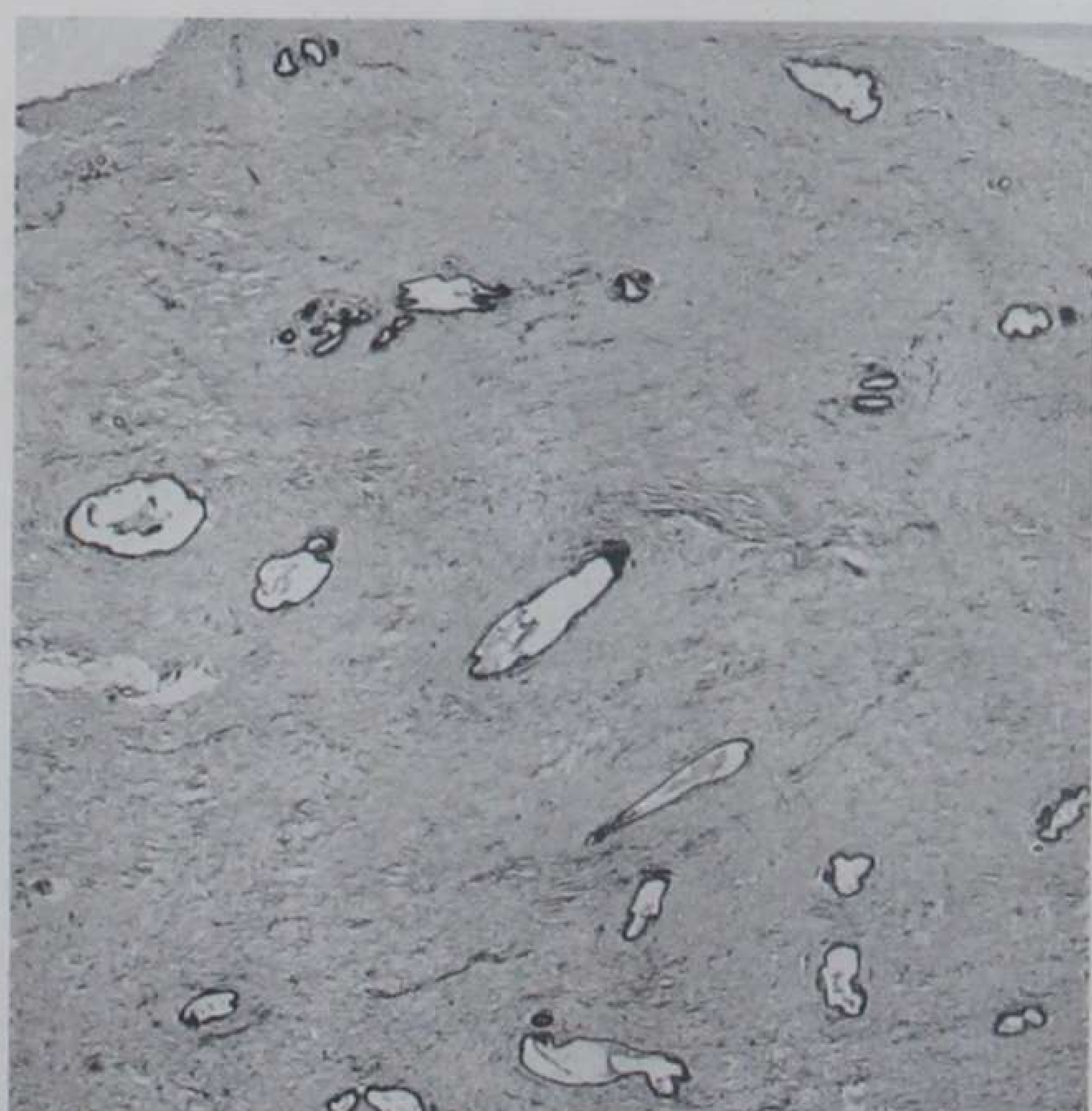

Fig. 25.—Section of the mammary gland of a girl aged 11 years. Note the beginning differentiation of lobules (upper centre). Stained with iron hæmatoxylin and van Gieson's stain. (*Photograph.*) (× 14.)

close together, but later the ducts are pulled out and the branches are further apart. The part of the duct nearest the epidermis is lined by a stratified epithelium: the rest of the duct has two rows of cells,

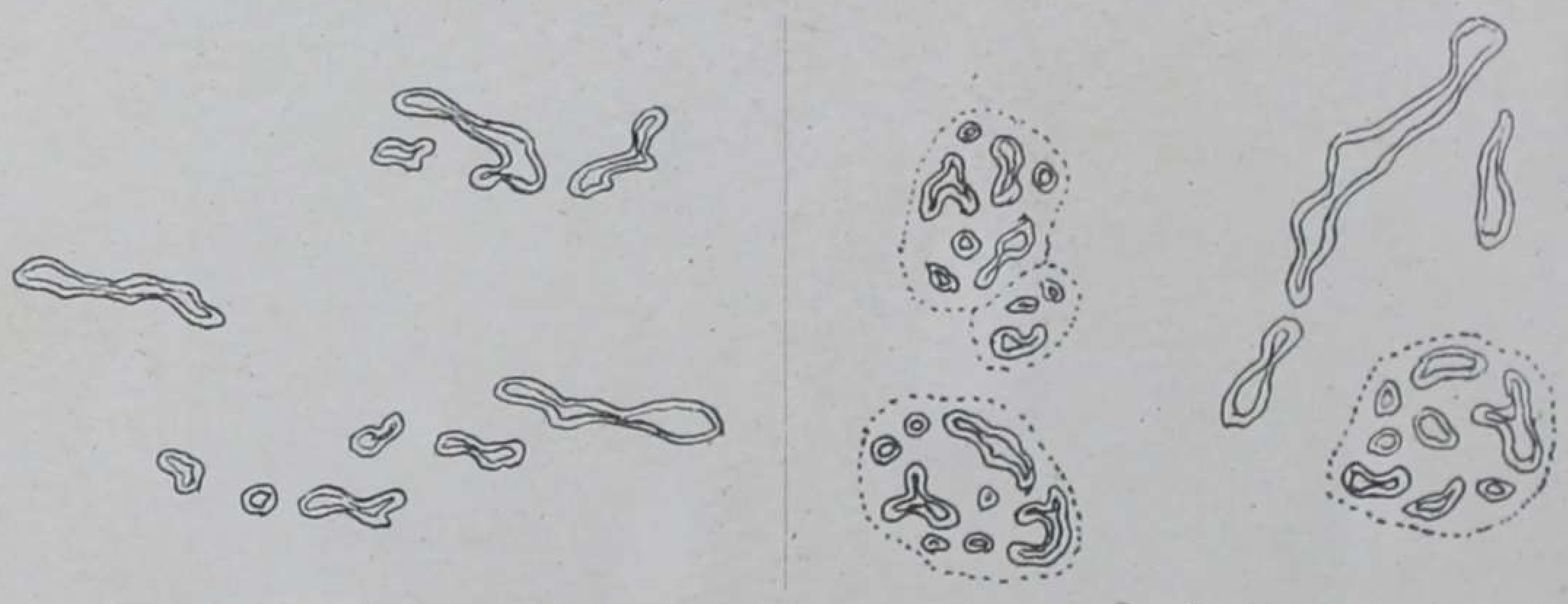

Fig 26.—Diagram to illustrate growth activity: A, In child of 8 years—pre-puberty; B, In girl of 17 years—post-puberty. (*After E. K. Dawson.*)

of which the inner is cylindrical or cubical, and the outer is cubical in larger ducts and flatter in the smaller ones (*Fig.* 27). Between the outer cells and the basement membrane can be found an occasional flattened cell, resembling a myo-epithelial cell. The terminal part of the duct, particularly as puberty approaches, may be lined by only one layer of cells, and fat droplets are sometimes present in these. The duct development is quite irregular in different parts of the breast, but is usually greater near the muscle than near the nipple (Ingleby): the appearance thus varies with the plane of the section.

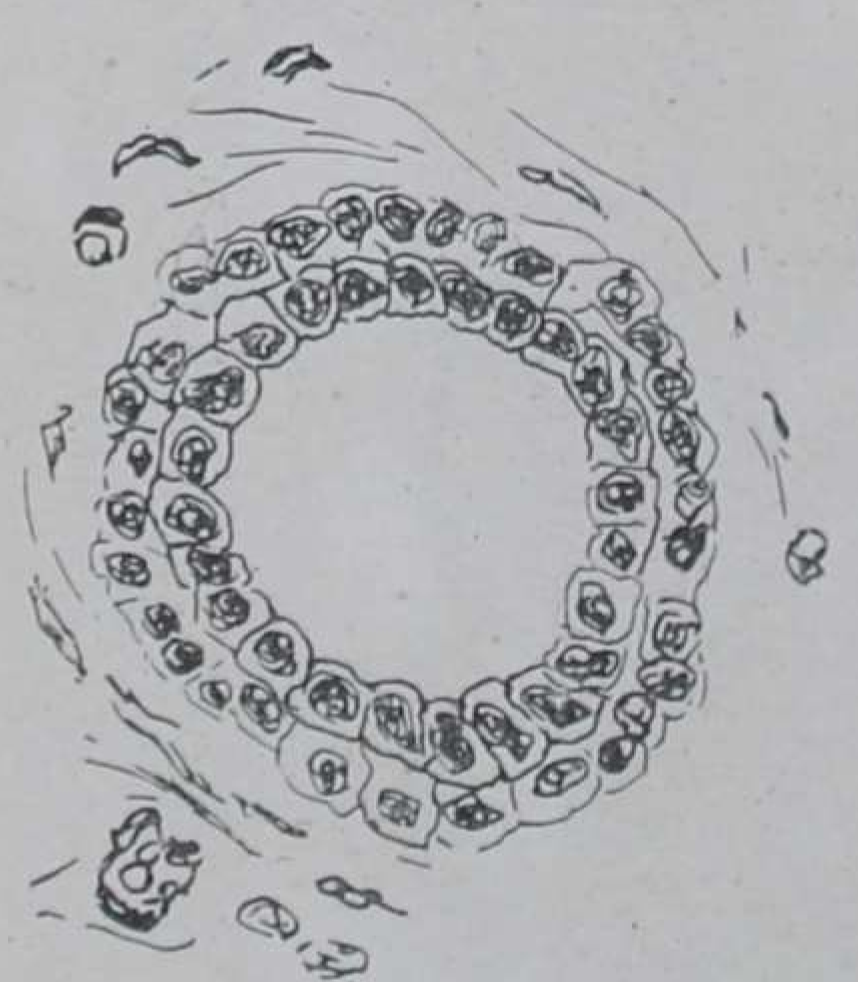

Fig. 27.—Cross-section of small duct of mammary gland. Woman aged 45 years. Note the typical two-layered epithelium. Stained with hæmatoxylin and Biebrich scarlet. (× 300.)

b. Stroma.—The interlobular connective tissue still forms the bulk of the gland, and is moderately dense with scattered cells. The periductal connective tissue is now clearly differentiated: it is very cellular, particularly near the ducts, and the collagen fibres are slender. A very few elastic fibres are present, such as there are being round the larger ducts. As development proceeds, the periductal tissue becomes looser and more spongy, with some mucoid degeneration as the parenchymatous tissue proliferates.

3. Adult, or Sexually Mature.—

i. Male.—The appearance of the glandular tissue is very similar to that seen at puberty. There is a considerable amount of fat present :

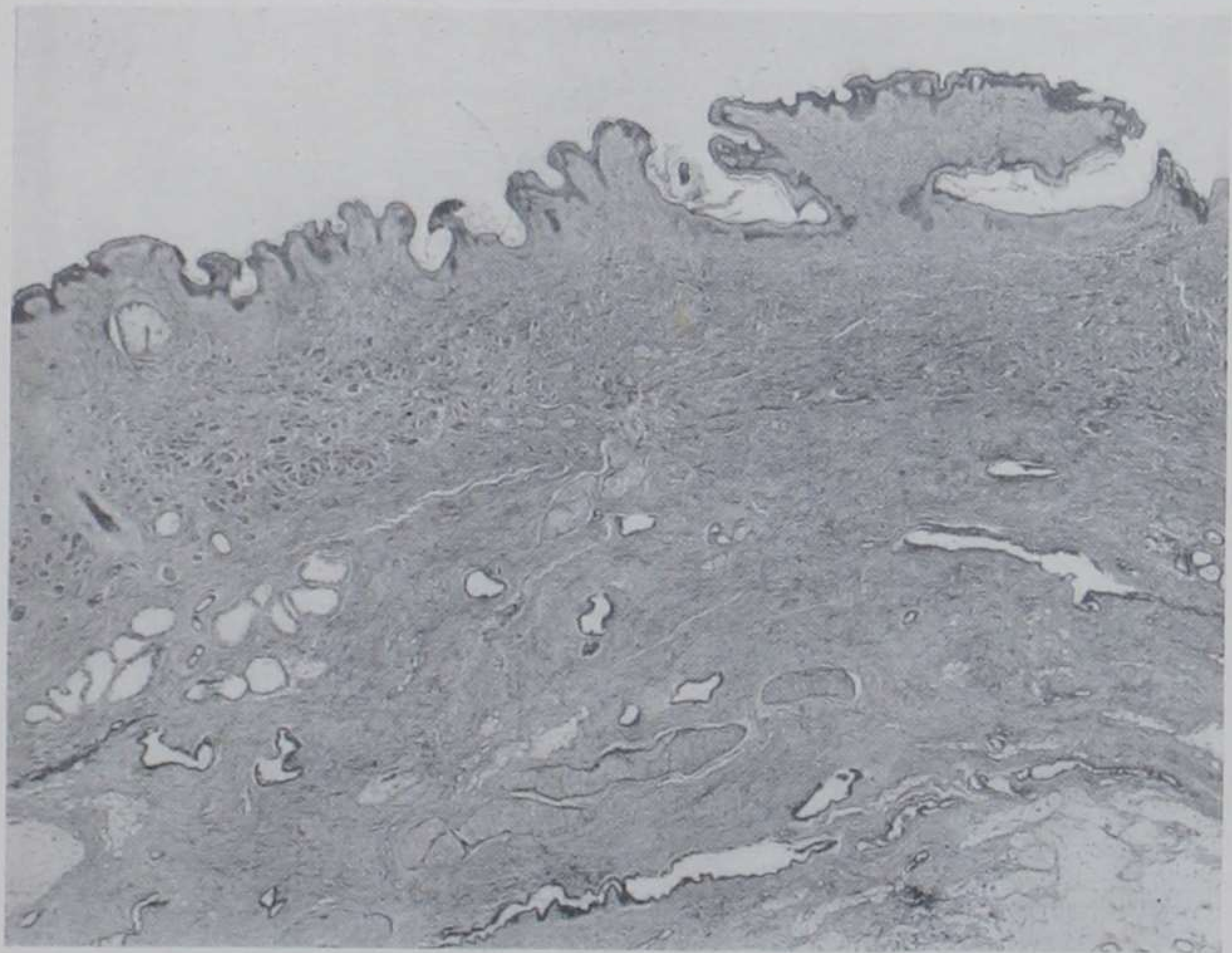

Fig. 28.—Section of breast tissue of man aged 24 years. Stained with hæmatoxylin and Biebrich scarlet. (*Photograph.*) (× 15.) (*See also Figs.* 29, 30.)

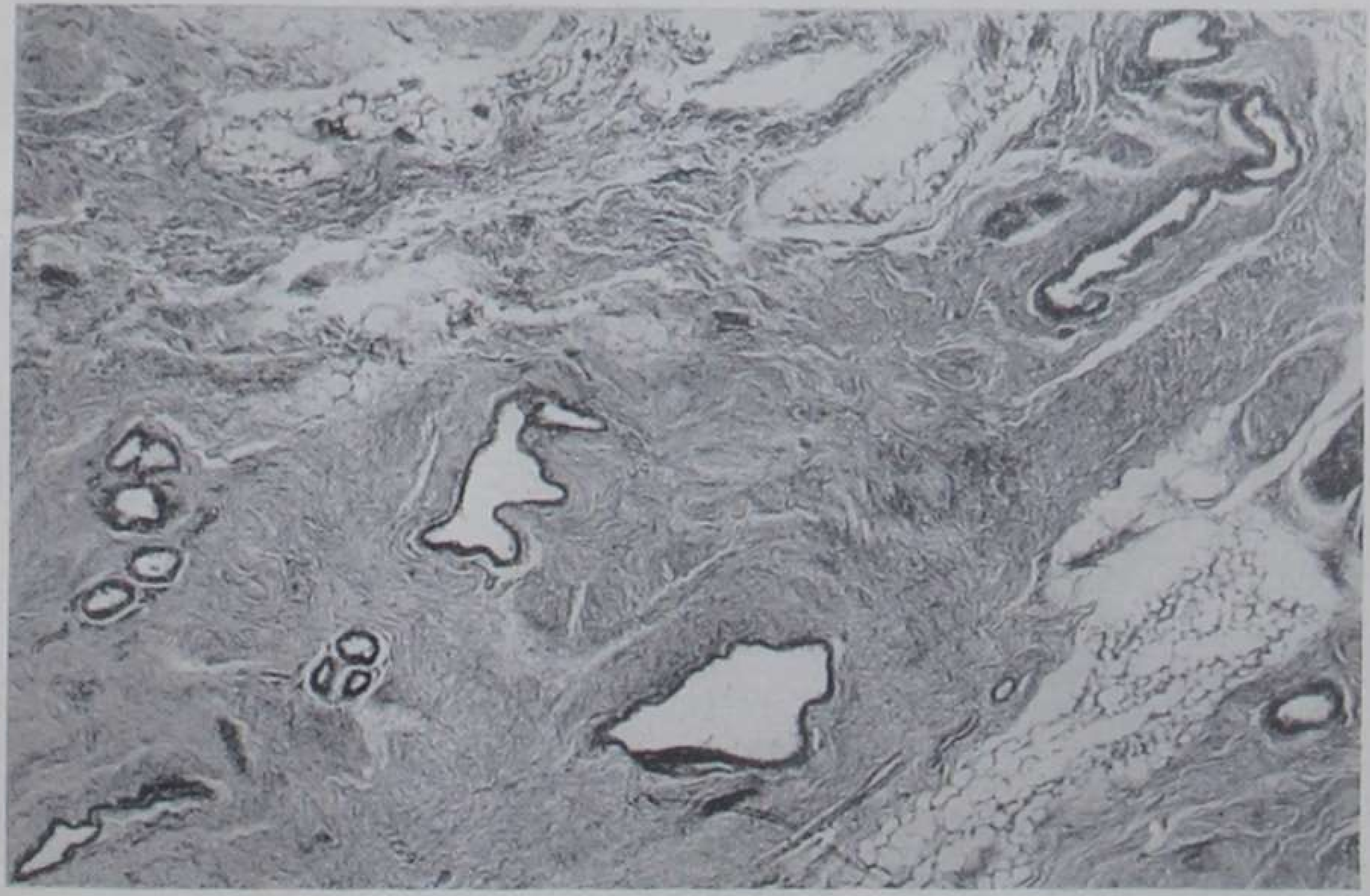

Fig. 29.—Section of breast tissue of man aged 24 years. Stained with hæmatoxylin and Biebrich scarlet. (*Photograph.*) (× 36.) (*See also Figs.* 28, 30.)

the connective tissue is on the whole very dense, and shows no differentiation into interlobular and periductal types. No true lobules are found, but branching ducts are present, some of them dilated. The ducts are lined by two layers of epithelium, which in some cases shows a breaking down of the internal layer, and sometimes the 'pale' change described below (*see* p. 47) (*Figs.* 28–30).

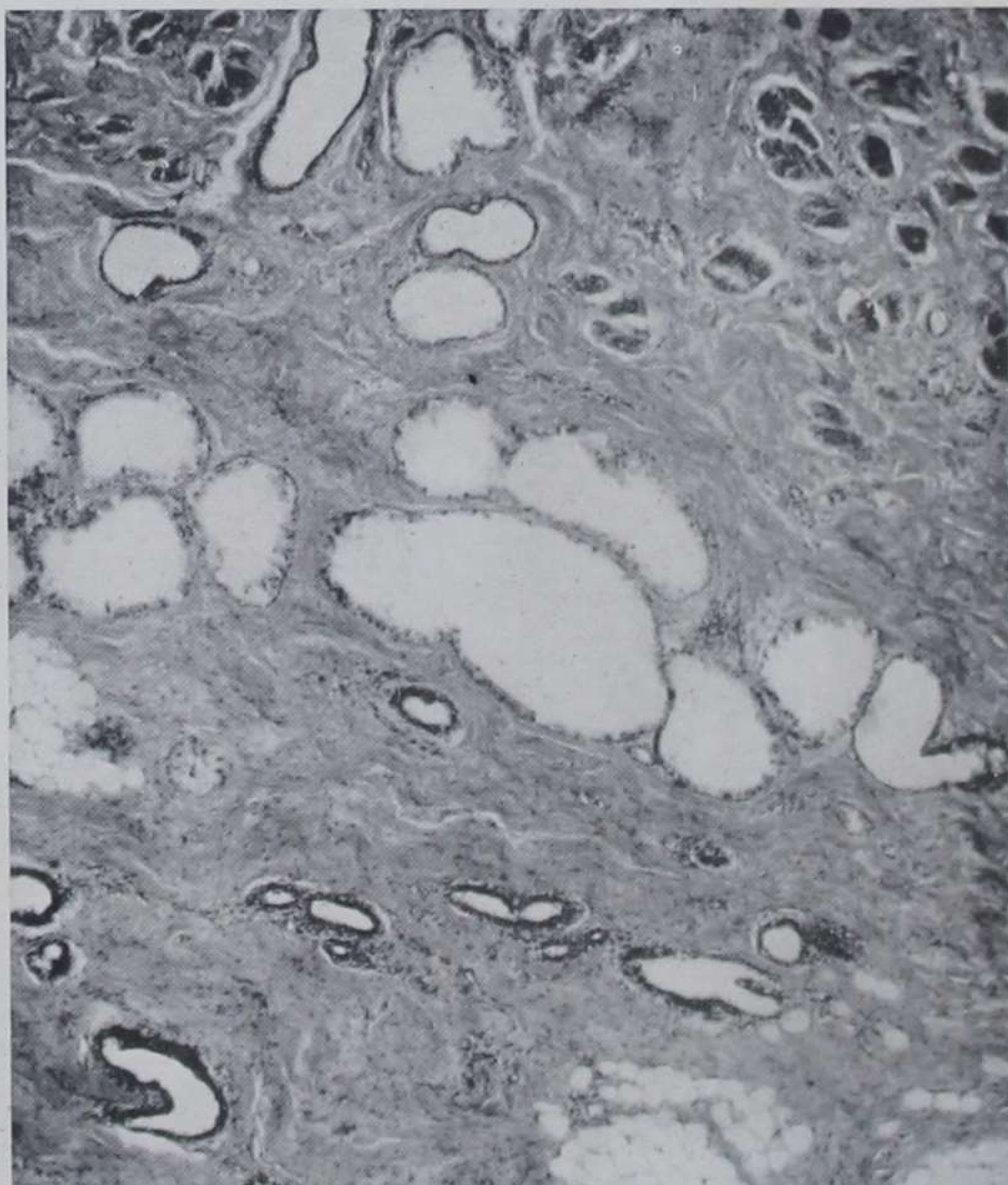

Fig. 30.—Section of mammary gland of man aged 24 years. Note some dilated ducts with 'pale' epithelium (centre), and some degenerating (top right). Stained with hæmatoxylin and Biebrich scarlet. (*Photograph.*) (×48.) (*See also Figs.* 28, 29.)

ii. Female, throughout the Menstrual Cycle, including the ordinary 'Resting' Phase.—The typical inactive mammary gland consists chiefly of interlobar and interlobular connective tissue, with scattered groups of branching ducts: the latter end in blind terminal (alveolar) ducts or solid cords of cells, and the whole group is embedded in cellular periductal connective tissue to form a lobule (*Fig.* 31).

a. Parenchyma.—The epithelial structures in the young nulliparous woman consist almost exclusively of ducts and their branches.

The ducts in general are lined by the usual two layers of cuboidal cells: the terminal (alveolar) ducts have only one layer of low columnar glandular cells very incompletely surrounded by flattened myo-epithelial* cells (said to be arranged spirally), and outside these a basement membrane. The myo-epithelial cells are said to be particularly numerous near the opening of these ductules into larger ducts. In the main ducts the lining is pseudo-stratified, and the lactiferous duct, near its opening, is lined by the invaginated skin epithelium of the nipple.

Fig. 31.—Section of mammary gland of woman of 25 years. Nulliparous. Note relatively small development of lobules. Stained with hæmatoxylin and eosin. (*Photograph.*) (× 17.)

In the older nulliparous woman there are usually some alveoli, either collapsed or distended, that have budded off from the terminal ducts, passing over without any definite boundary into them (*Fig.* 32).

b. Stroma.—The *interlobar* and *interlobular* connective tissue (i.e., away from the gland elements) is dense and fibrous. The collagen fibres are thick, and the elastic fibres fine: the latter make dense networks, particularly along the outer surface of the large ducts. Cells are few, chiefly fibroblasts and histiocytes. The *periductal* connective tissue, surrounding the secretory ducts, is, on the other hand, rich in cells—fibroblasts, histiocytes, mast cells, plasma cells, and lymphocytes: these lie in a matrix of fine, loosely-arranged

* These myo-epithelial cells are similar in form and distribution to the cells found in the sweat-glands, sebaceous glands, salivary glands, glands of Moll, axillary glands, and mucous palatine glands.

collagen and a few elastic fibres: there are no elastic fibres between alveoli. This tissue is vascular, and provides an easily distensible medium for the hypertrophy of the epithelial portions of the gland during pregnancy and lactation (*Fig.* 33).

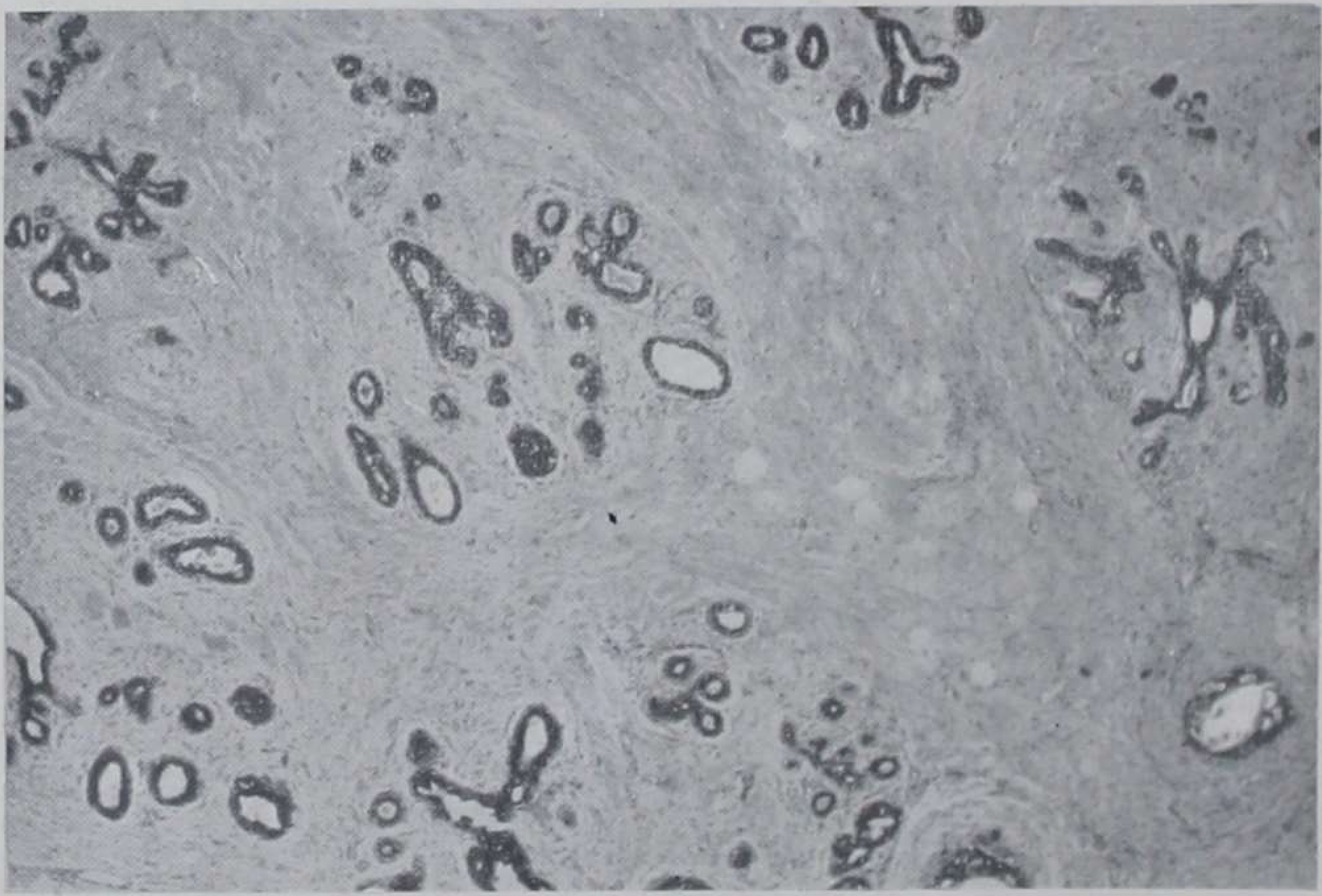

Fig. 32.—Section of mammary gland of woman aged 45 years. Nulliparous. Note inactive appearance. Some lobules are defined within their periductal connective tissue, and show some branching of small ducts but no definite alveoli. Stained with hæmatoxylin and Biebrich scarlet. (*Photograph.*) (× 14.)

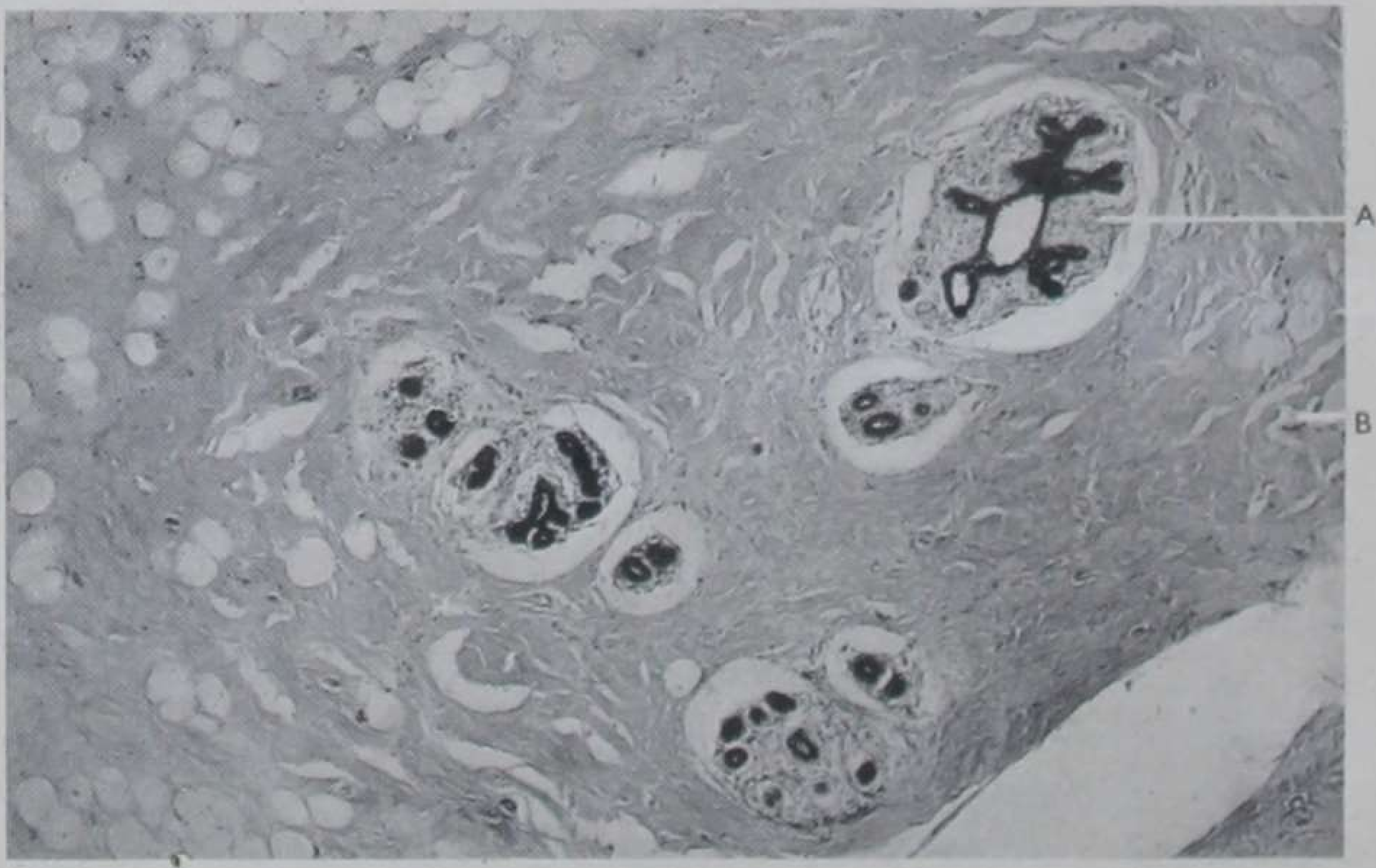

Fig. 33.—Section of mammary gland of woman aged 20 years. Premenstrual phase of ovarian cycle. The differentiation between the cellular periductal (intralobular) tissue (A) and the dense interlobular connective tissue (B) is clearly seen. Stained with hæmatoxylin and Biebrich scarlet. (*Photograph.*) (× 41.)

c. Changes during the menstrual cycle: It is difficult to obtain material in any quantity at definitely known stages of the menstrual cycle. But it is generally accepted that at each such period there is "a limited growth of the gland, which is followed by a retrogressive change that does not entirely undo the work of the preceding growth rhythm, so that the gland slowly enlarges step by step" (Loeb). The development and retrogression of lobules is not uniform, and different parts of the breast present very different pictures. Probably some parts only proliferate with each cycle, as occurs in other organs.

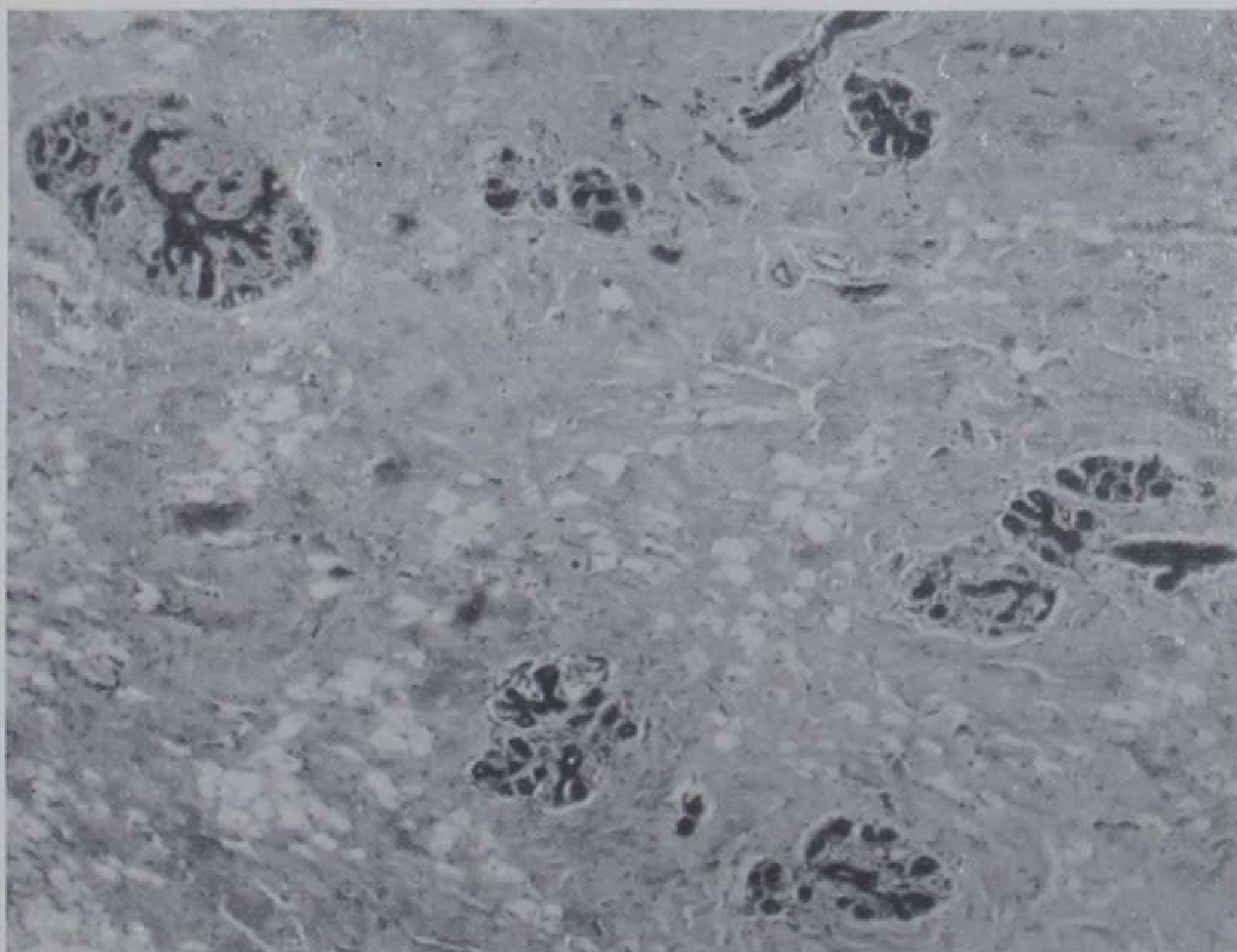

Fig. 34.—Section of mammary gland of girl aged 15 years. Three days post-menstrual. Note well-defined lobules, with cellular periductal connective tissue clearly marked off from the denser interlobular tissue: the latter contains fat. Stained with hæmatoxylin and Biebrich scarlet. (*Photograph.*) (× 44.)

In the premenstrual period (*Fig.* 33) the smaller ducts proliferate and possibly produce some alveoli; in the following intermenstrual period the gland tissue is reduced. A corresponding activity of the periductal stroma is always associated with epithelial proliferation, the cells showing mitoses: before menstruation the connective tissue is fibrillar and œdematous, after menstruation it becomes more fibrous (*Fig.* 34). When the cells are undergoing involution, or resting, they often contain fat as large vacuoles. Infiltration with lymphocytes commonly occurs. These cyclic changes may show great irregularity within physiological limits, particularly in the older adult, and the normal cycle may be interfered with so that there is undue hyperplasia or delayed involution.

No other changes occur during the adult phase until the menopause, unless pregnancy supervenes.

iii. Female, throughout Pregnancy and Lactation, including the Subsequent Retrogression.—

α. Pregnancy.—Throughout pregnancy the gland undergoes considerable development, and becomes functionally active at the birth of the child.

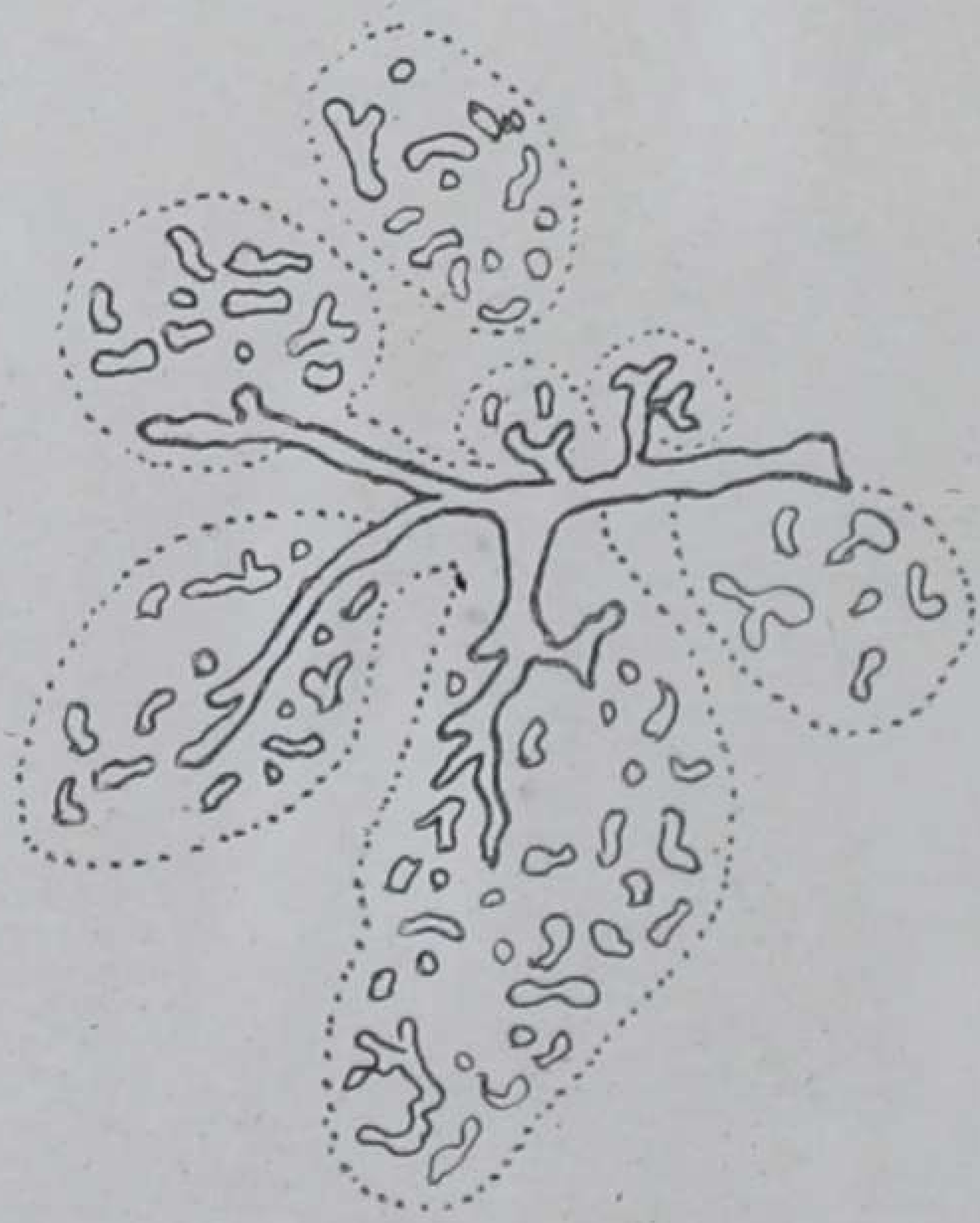

Fig. 35.—Diagram to illustrate new lobule formation, at tenth week of pregnancy. (*After E. K. Dawson.*)

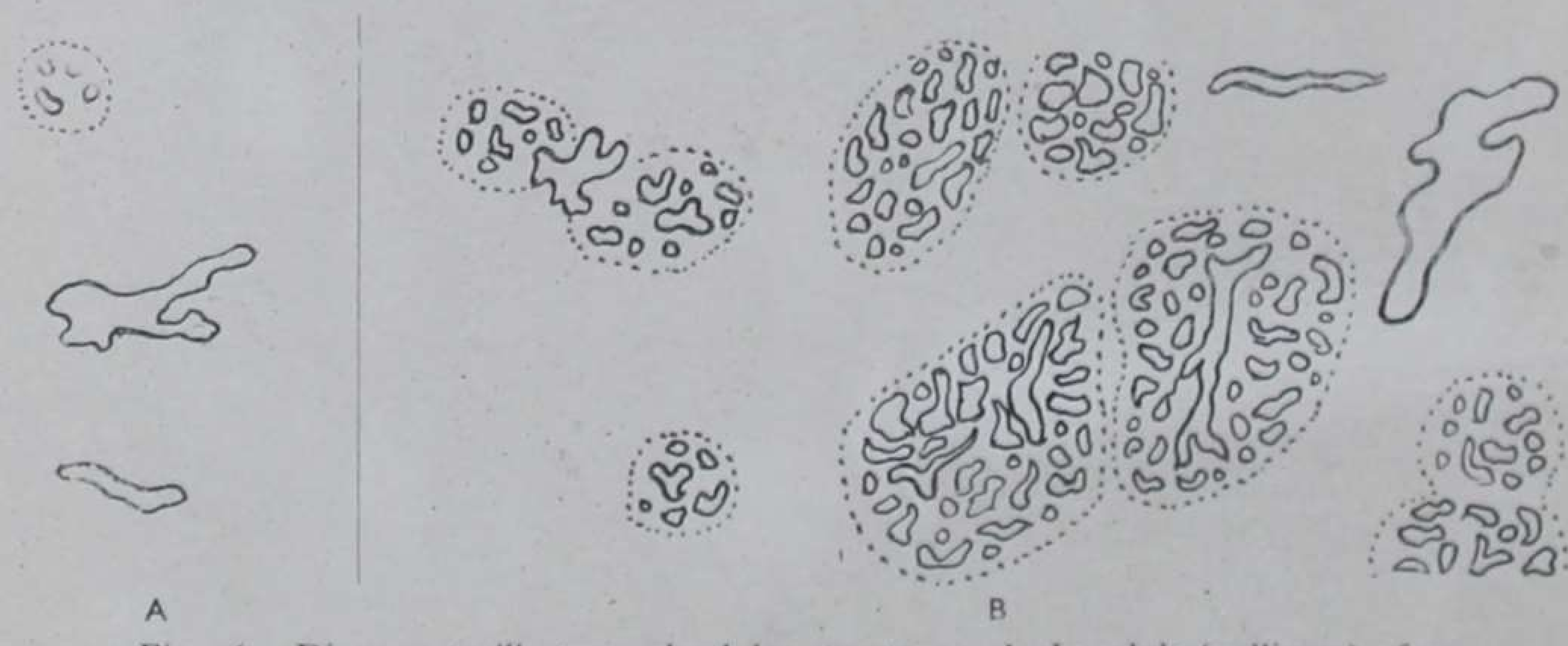

Fig. 36.—Diagram to illustrate glandular structure: A, In adult (nullipara) of 21 years; B, In pregnancy. (*After E. K. Dawson.*)

During the *early period* of pregnancy, evident within 8 weeks, there is very active growth with mitotic proliferation; the ends of the terminal ducts give rise to vast numbers of alveoli of varying size and shape, the compound tubular gland thus becoming transformed into a compound tubulo-alveolar gland (*Figs.* 35–37). The connective tissue, previously abundant, is consequently reduced: thin septa of interlobular tissue enclose the lobules and larger ducts, while the periductal tissue consists of the small amount of vascular packing tissue between the alveoli and small ducts (*Fig.* 38). During the *latter part* of pregnancy the proliferation diminishes, the actual cells

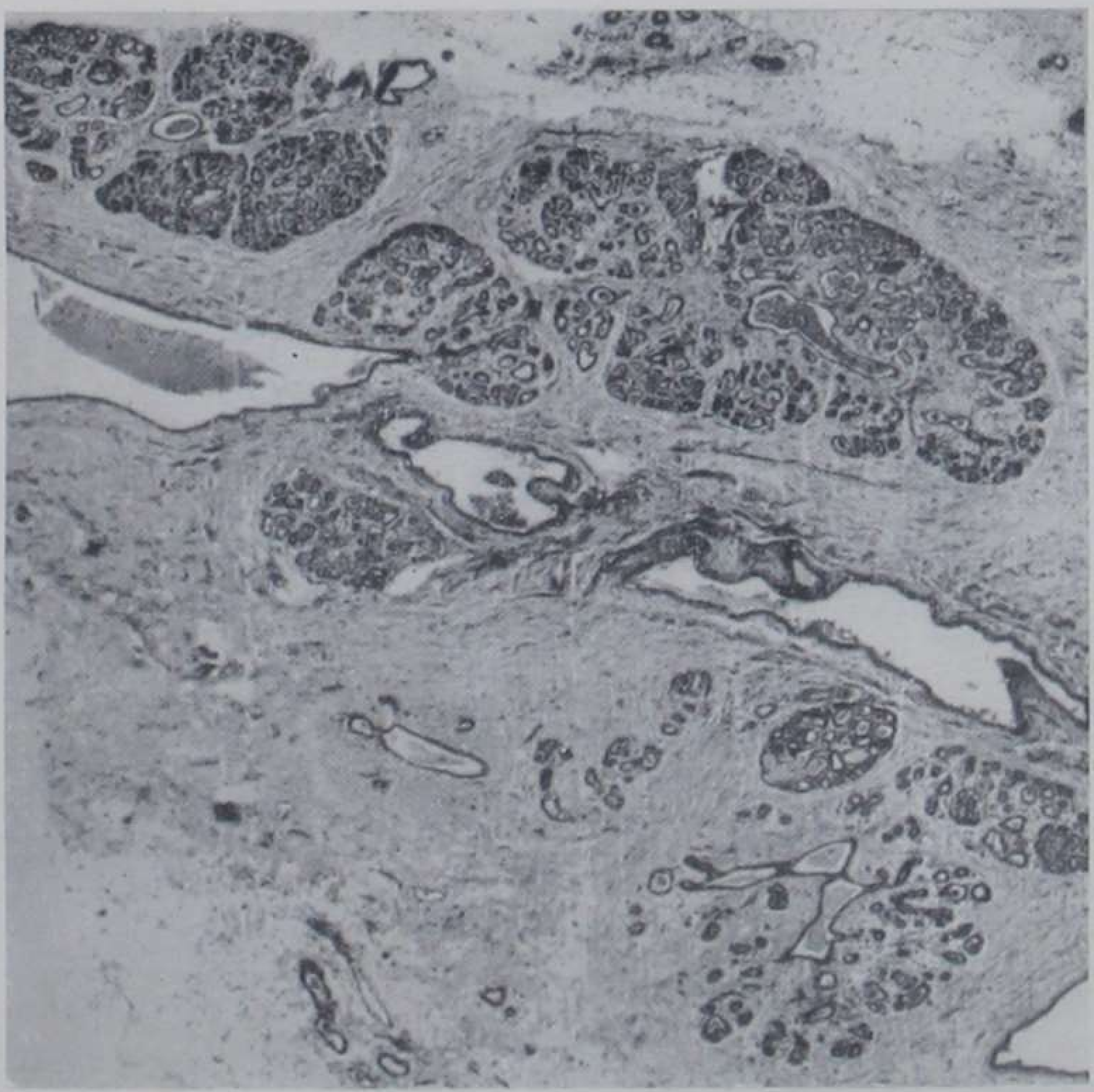

Fig. 37.—Section of mammary gland of woman aged 25 years; pregnant 16 weeks. Note increase of parenchyma with consequent diminution of stroma. The lobular development is well shown. At lower right, the branching of ducts with early lobular formation can be seen. Stained with hæmatoxylin and eosin. (*Photograph.*) (× 21.)

of the alveoli enlarge and often contain secretion. The discharge of this secretion into the lumina of the alveoli causes enlargement of the gland as parturition approaches.

Considered in further detail, the gland presents the following structure during pregnancy:—

a. Parenchyma.—The appearance is that of unbounded epithelial activity. The *alveoli* are lined by one layer of cells, cuboidal or low columnar: the nucleus is large and spherical with chromatin throughout. There are many fern-like epithelial projections into the lumen, thus increasing greatly the secretory elements. Outside these cells are found in some places elongated, flattened myo-epithelial cells with fusiform nuclei, and outside these again is a basement membrane.

The cells contain granular cytoplasm and basal mitochondria: as pregnancy advances they also contain fat droplets. The actual terminal *ducts* from which the alveoli have budded off are lined by 2 layers of cells, but the transition between duct and alveolus is not at all abrupt, so that some of the smallest ducts have only one layer of cells. The cells of these small ducts, when one row deep, often contain

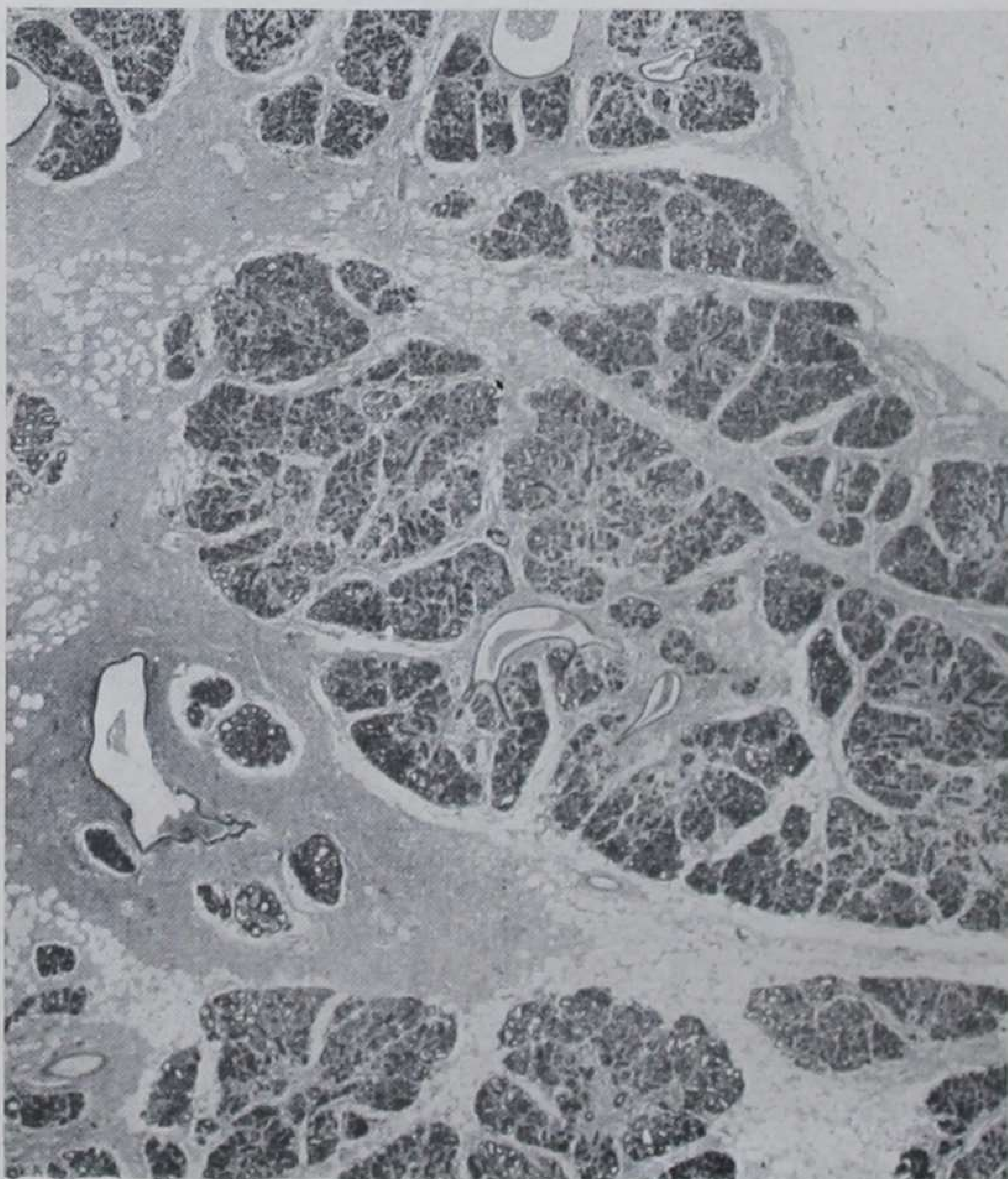

Fig. 38.—Section of mammary gland of woman aged 26 years: pregnant 36 weeks. Note that lobular development is further advanced than in *Fig.* 37. The distinction between periductal and interlobular connective tissue can be seen. Stained with hæmatoxylin and eosin. (*Photograph.*) (× 17.)

globules of fat in the early part of pregnancy, and the ducts may contain an eosinophil secretion: such secretory activity is manifested before the actual alveoli are formed. The newly-formed smallest ducts appear to throw off the superficial of the two lining layers of cells, leaving the basal deep layer as the lining of the alveolus. Lysis of this epithelial debris helps to form the secretion mentioned above. There is no evidence (Dawson) that a true alveolus can bud off other alveoli, nor that alveolar cells divide at this stage. Concurrently with this progressive differentiation of the alveoli there is evidence of continued

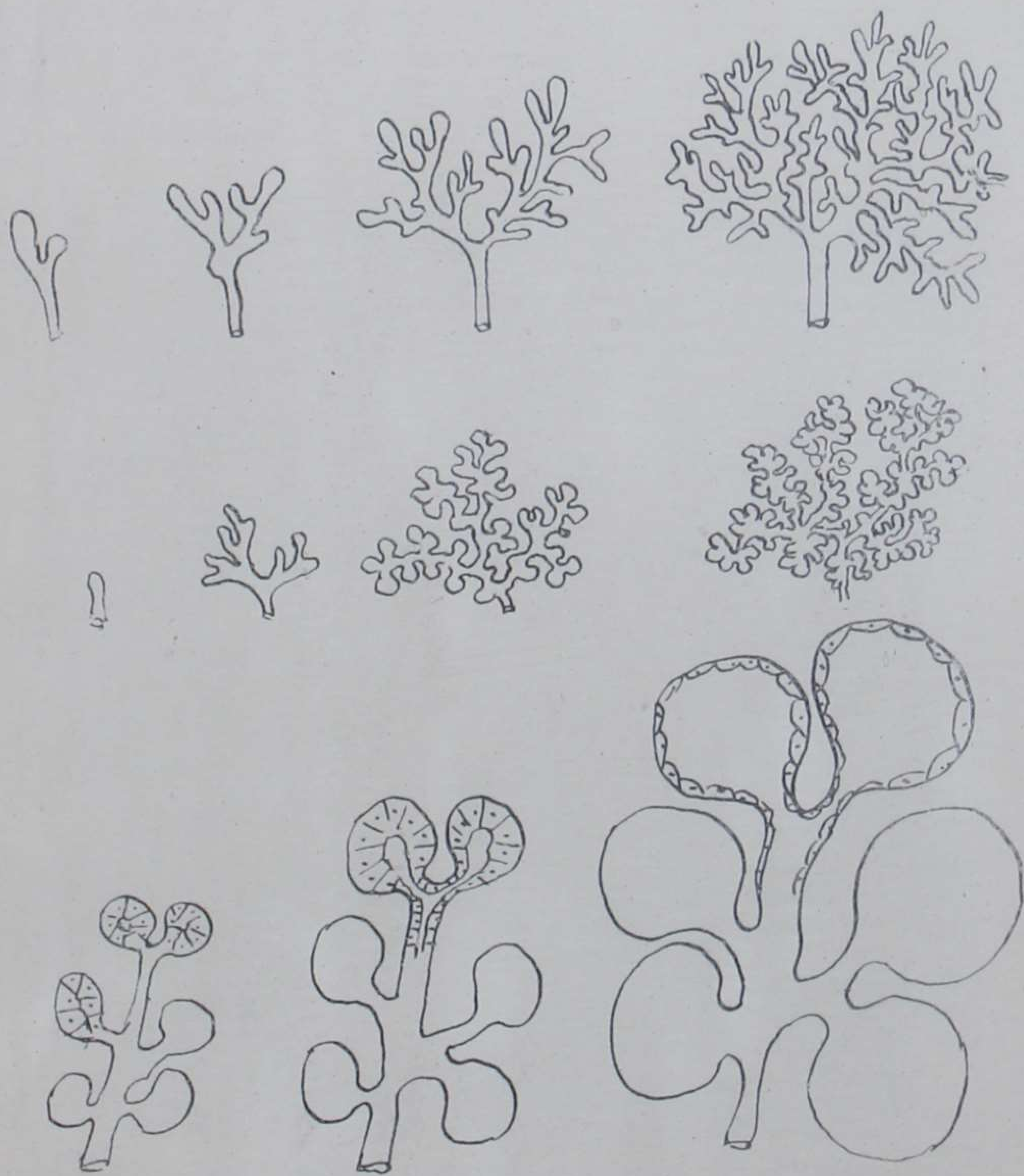

Fig. 39.—Diagram illustrating development of mammary gland during pregnancy. The compound tubular gland shows proliferation of the ends of the ducts and the development of vast numbers of alveoli : it is thus transformed into a typical compound tubulo-alveolar gland. The alveolar cells then enlarge and discharge their secretion into the lumina, with consequent enlargement of the whole gland. (*Redrawn from C. W. Turner, in Sex and Internal Secretions, Allen*, 1939.)

growth and division of the small ducts, and a continued formation of undifferentiated lobules (*Fig.* 39).

b. Stroma.—The *interlobar and interlobular* connective tissue does not vary much in structure although greatly reduced in amount. It is dense, consisting of coarse collagen fibres with a few fine elastic fibres particularly near the large ducts: cells are few and scattered and the amount of fat is usually small. The *periductal* tissue round the small ducts and alveoli consists of very fine collagen fibres and comparatively numerous cells: the latter include fibroblasts, histiocytes, plasma cells, and many lymphocytes. There are many capillaries, particularly round the alveoli, but the total amount of the

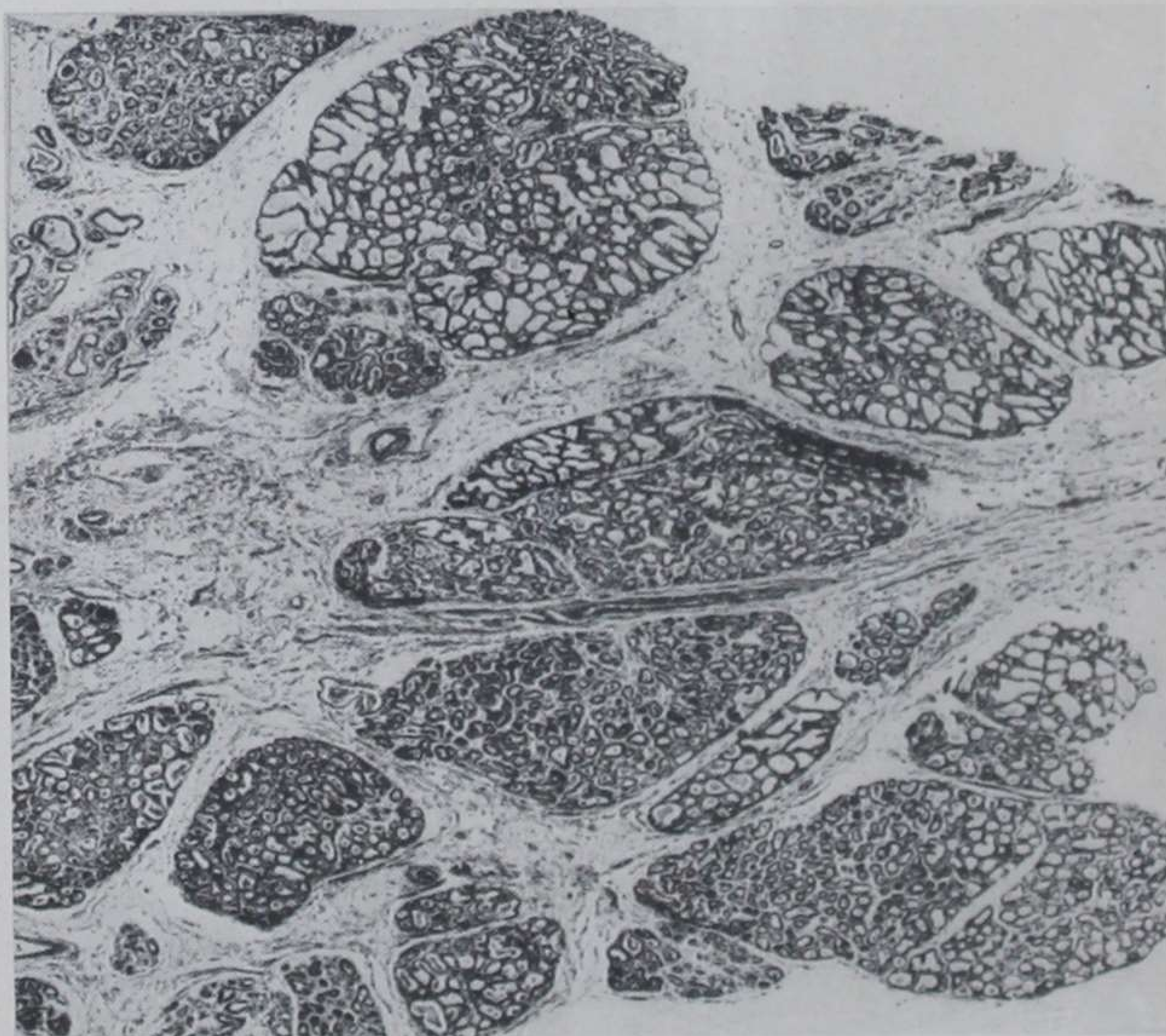

Fig. 40.—Section of mammary gland of woman aged 37 years: 5 days after birth of child. Mother did not suckle the baby. Note great variety in degree of distension and of contents of alveoli. Stained with hæmatoxylin and Biebrich scarlet. (*Photograph.*) (× 28.)

periductal tissue is small and chiefly round the small ducts and as narrow strands between adjacent alveoli.

β. Lactation (*Figs.* 40–46).—Towards the end of pregnancy mitosis ceases as secretory activity begins in the alveolar cells: the actual external secretion occurs a few days after parturition. Secretion occurs as follows. The nuclear chromatin is clumped round the nuclear membrane and minute droplets of fat appear in the cytoplasm chiefly round the basal nucleus: these then coalesce into large globules in the free end of the cell which looks elongated. The peripheral layer of the cell then constricts off and the fat is set free into the alveolar lumen, while the nucleated basal part of the cell remains behind. The cell soon regenerates what it has lost, and the secretory process is repeated. Not all the alveoli are actively secreting at one time, so that any lobule contains both active and resting alveoli. In some parts of the gland the secretory portions are full of milk, the

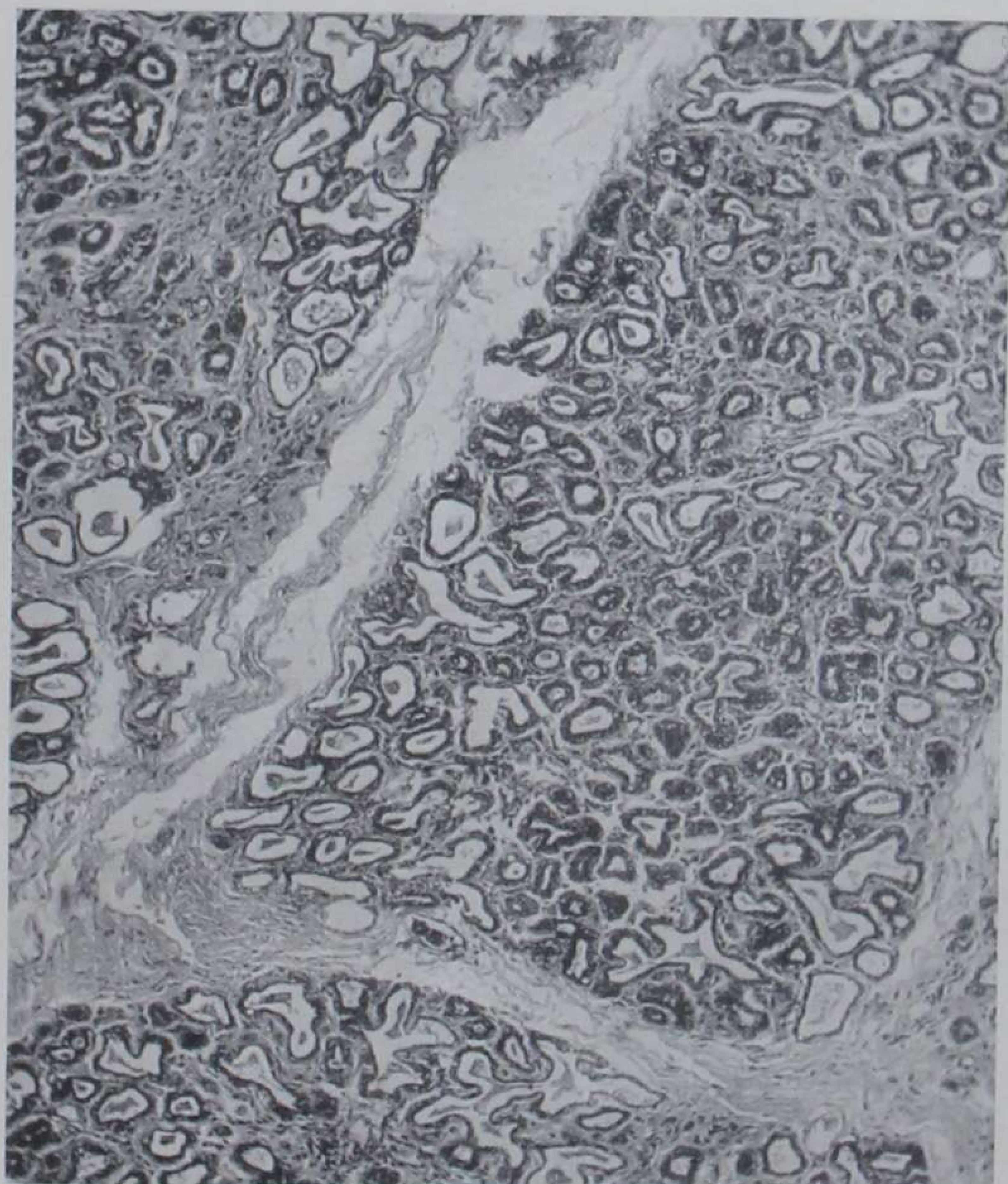

Fig. 41.—Section of mammary gland of woman aged 37 years. In full lactation: 7 days after birth of baby. Stained with hæmatoxylin and eosin. (*Photograph.*) (× 74.)

alveolar lumen being wide and the wall stretched and thin; in other parts the lumen is narrow and the epithelium thick; again, in parts the alveoli are distended with secretion and in others free from it. Peripheral alveoli usually secrete less actively than the more central ones. Unless the distended alveoli are emptied, the secretion flattens the lining epithelial cells, inhibiting their activity, and ultimately causing their degeneration.

The *secretion* is found in the alveoli and in all the ducts : it consists of fat droplets enclosed in a thin albuminous membrane, and of cellular

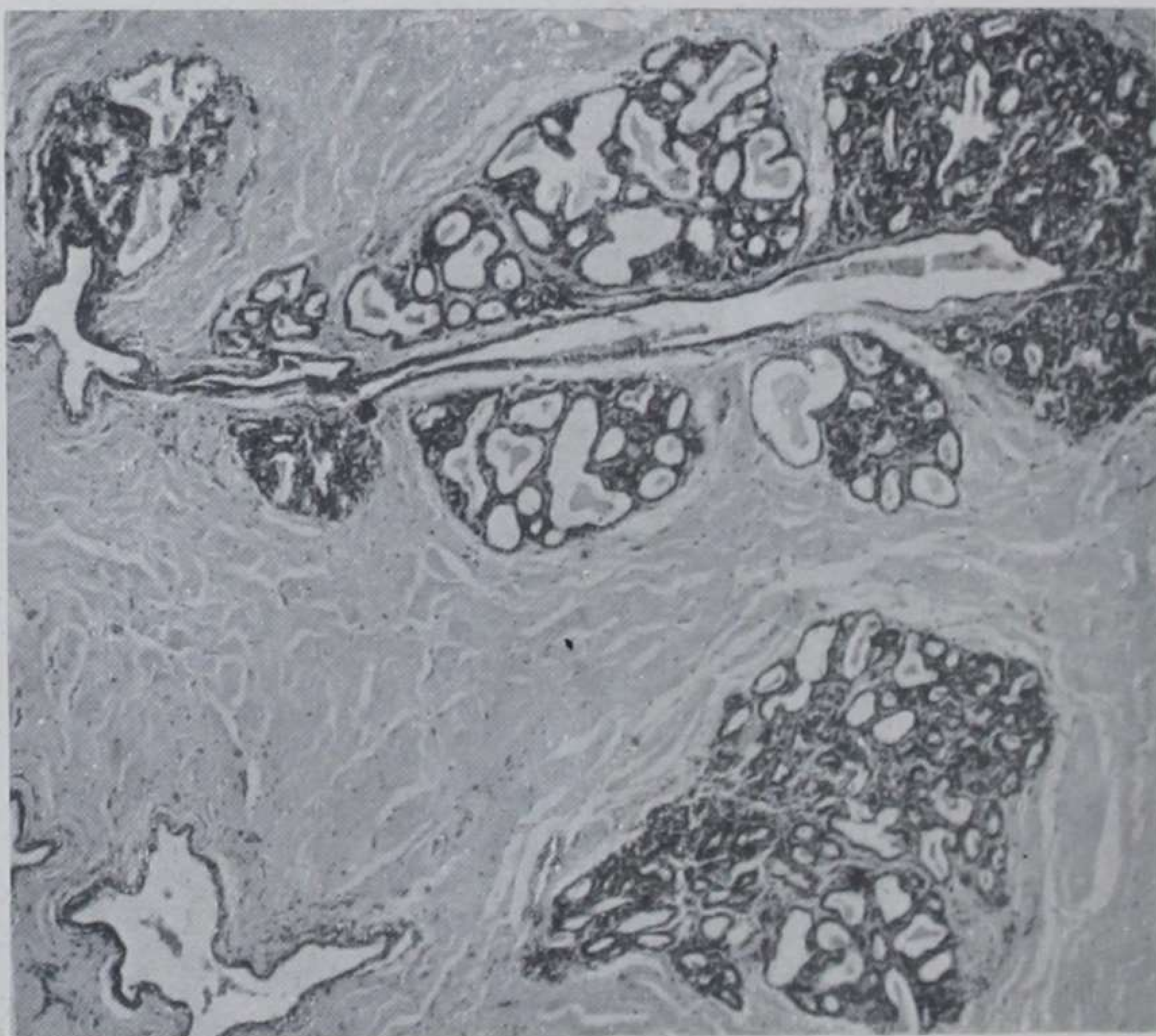

Fig. 42.—Section of mammary gland of woman aged 32 years. In full lactation, feeding the baby for one month. Note variation in appearance of alveoli, and the distinction between the cellular periductal connective tissue, and the surrounding fibrous type of tissue. (*Photograph.*) (× 42.)

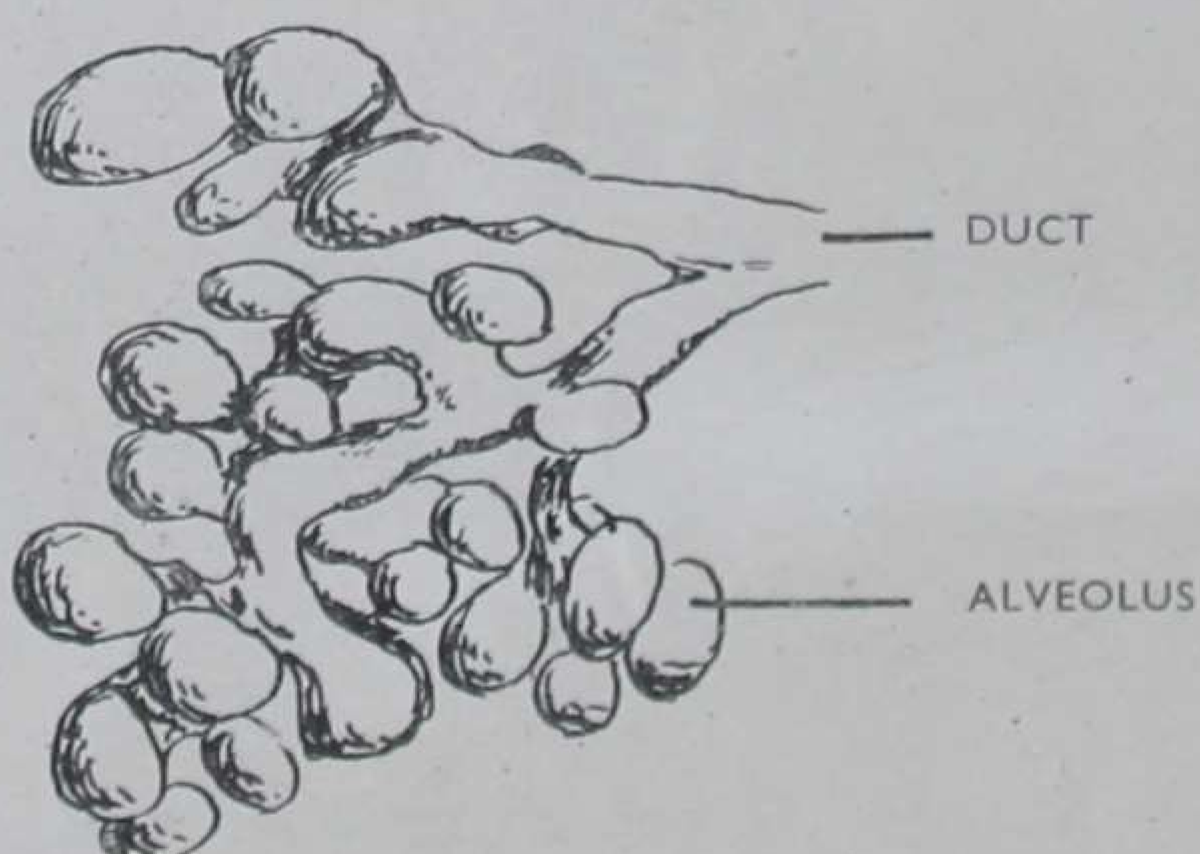

Fig. 43.—Model of portion of active mammary gland. (*After Maziarsky, redrawn from Bailey's ' Textbook of Histology '.*)

debris, all suspended in a fluid containing caseinogen, albumin, globulin, lactose, and salts. (The protein constituents of the fluid are precipitated and the fat dissolved out by the usual histological processes, so that in

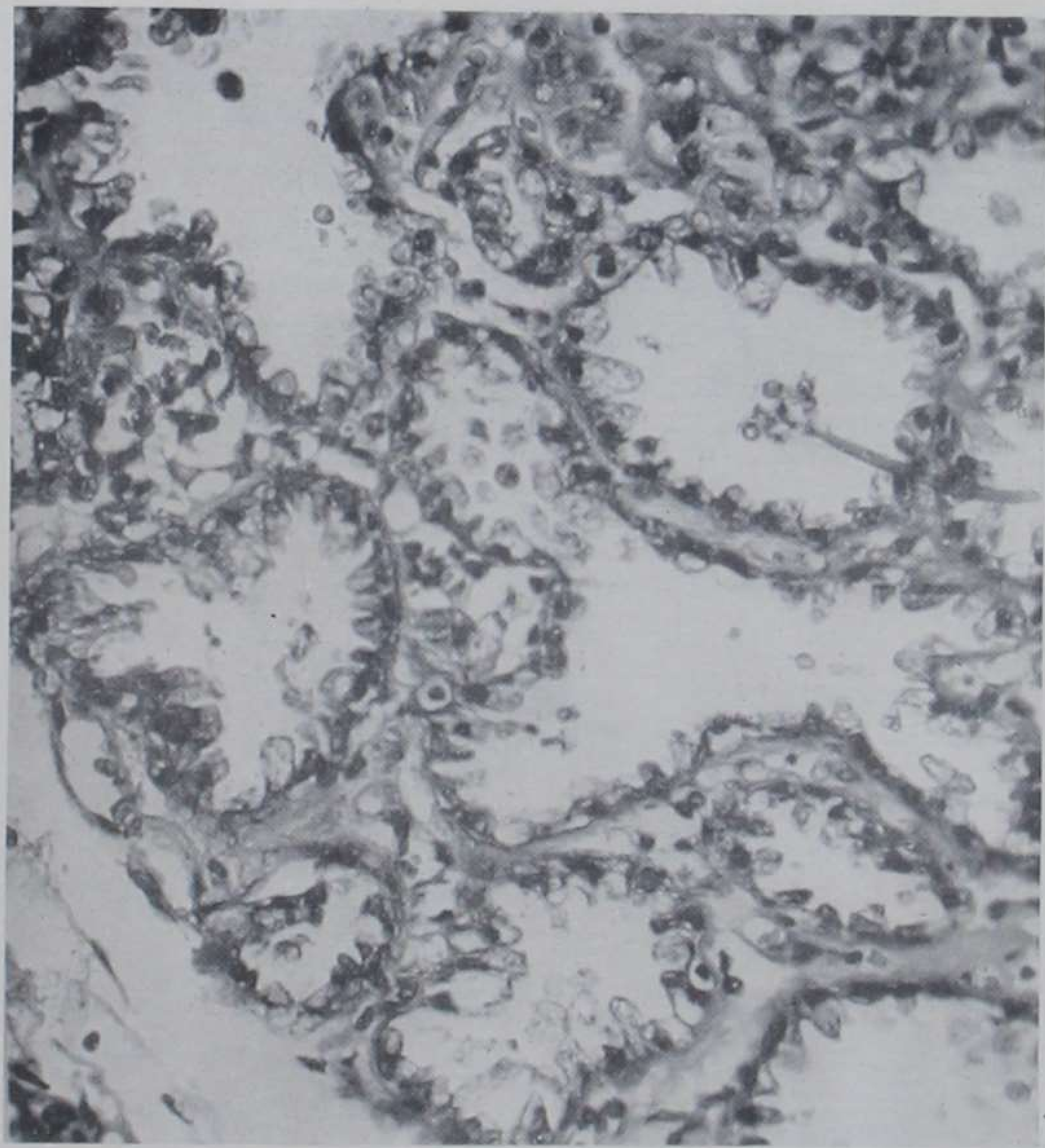

Fig. 44.—Section of mammary gland of adult woman. Full lactation. Note fat vacuoles in alveolar epithelium, the elongation of these cells, and the uneven appearance due to breaking off of the fat-containing portion into the alveolar lumen. Stained with hæmatoxylin and eosin. (*Photograph.*) (× 268.)

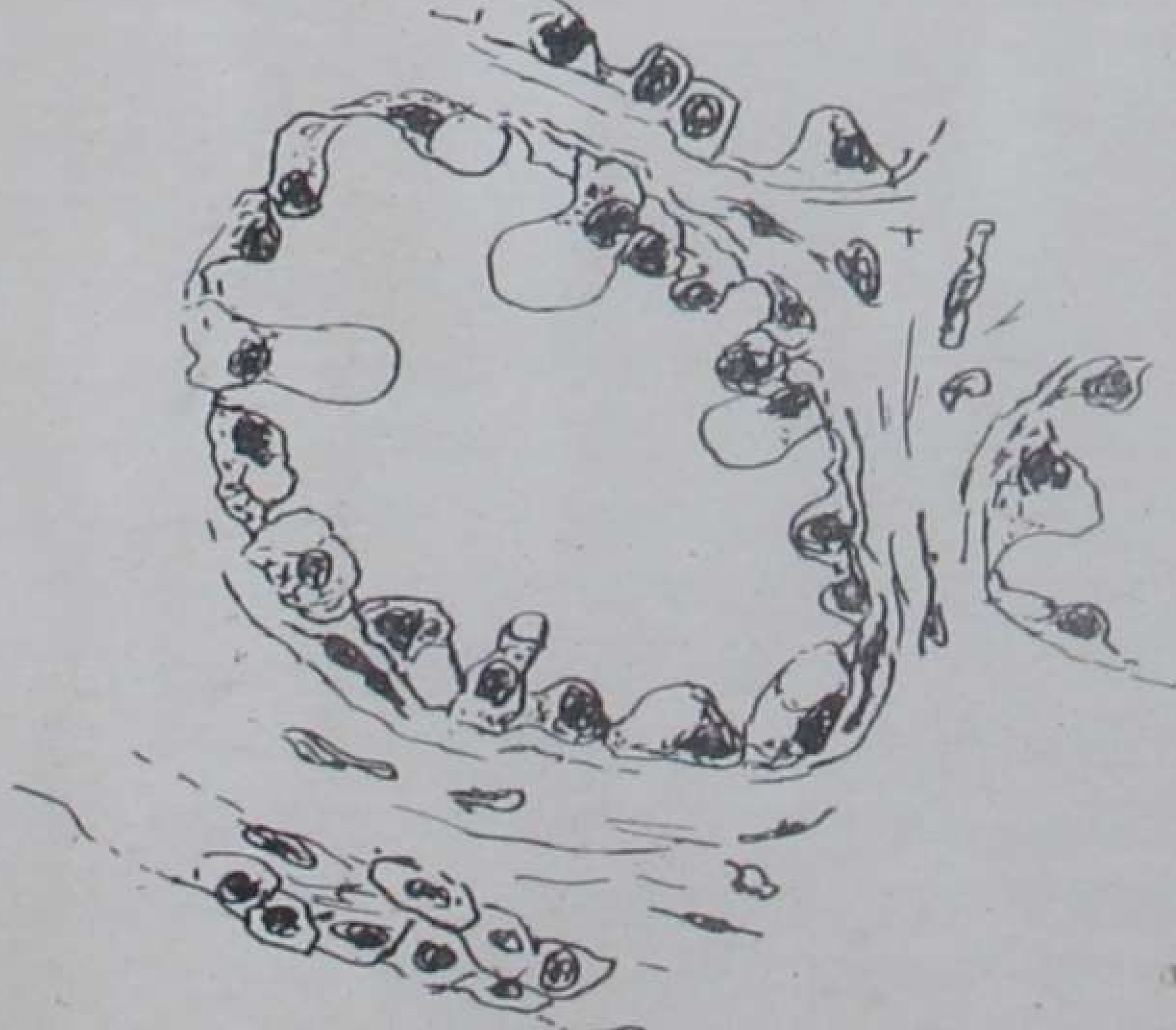

Fig. 45.—Section of mammary gland, in full lactation. Human. Note the fat formation in the alveolar cells. Stained with hæmatoxylin and eosin. (× 300.)

a section the secretion looks like a granular, eosinophil mass containing vacuoles.)

The secretion of the first few days after parturition is somewhat different from ordinary milk, being poorer in fat and richer in cells: it is known as *colostrum*. Cells from the periductal stroma and the blood-stream reach the alveolar lumen by passing through the basement membrane: these entering cells are chiefly lymphoid, but there are also numerous eosinophil cells, plasma cells, monocytes, and polymorphonuclear leucocytes. Many of the cells contain engulfed fatty debris.

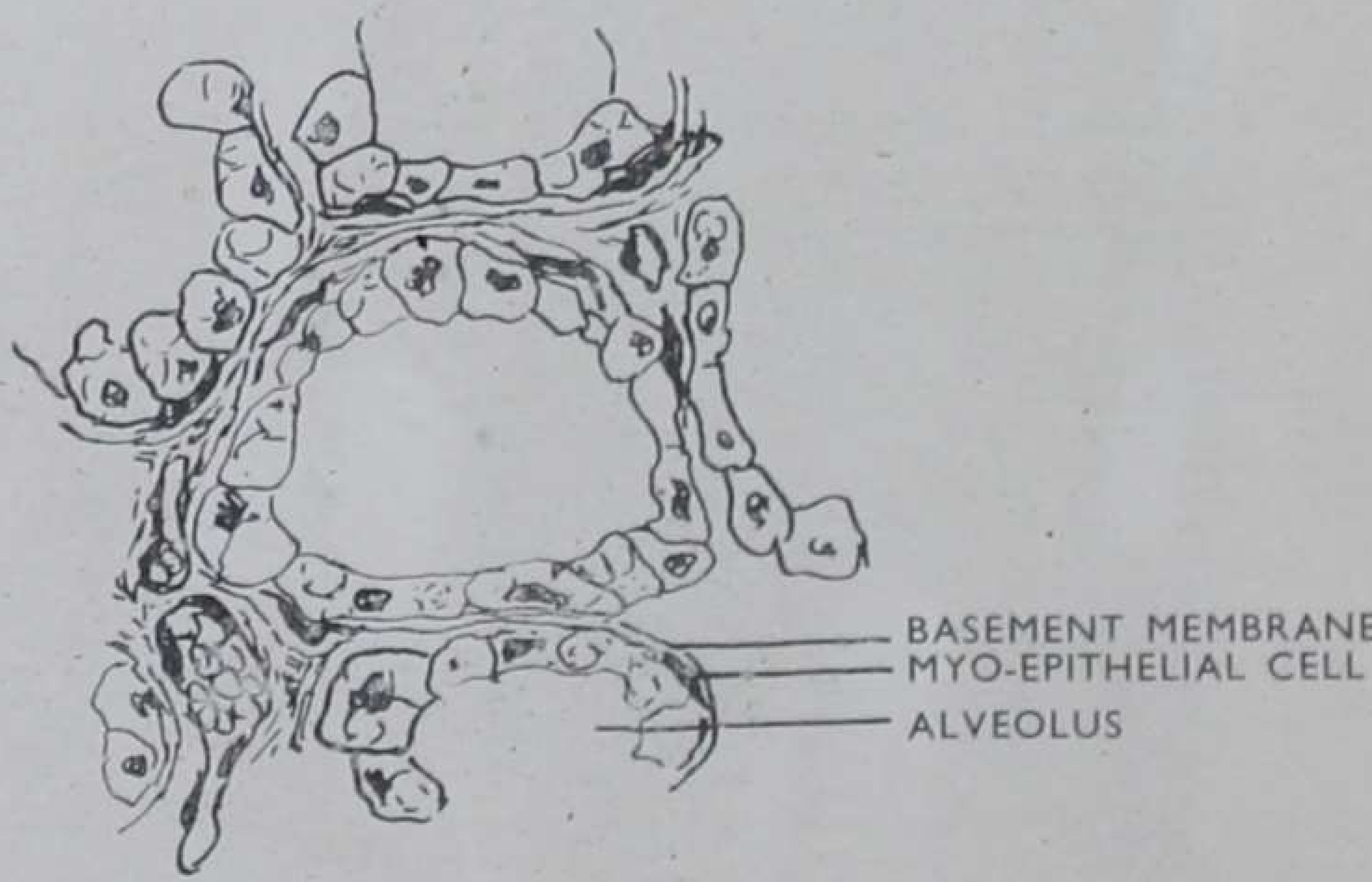

Fig. 46.—Section of mammary gland: 10th day of lactation. Woman aged 29 years. Note relation between alveolar epithelium, myo-epithelium, and basement membrane. Stained with hæmatoxylin and eosin. (× 300.)

γ. Retrogression (Involution).—With the cessation of milk production, involution of the organ occurs, but this is incomplete, and although the bulk of the glandular overgrowth disappears, some epithelial and fibrous hypertrophy still remains: the appearance consequently varies in different parts.

The secretion stagnates in the lumen of the alveoli and ducts, and the distending alveoli press on one another producing circulatory decrease: if the circulatory interference is pronounced, actual disintegration occurs; if it is of a lesser degree atrophy follows. Most of the alveoli that have produced milk degenerate and lose their lumina; any that survive do not change back into ducts, but the lining columnar cells become flattened and the alveoli return to their former size. The terminal parts of the ducts retrogress with reduction of ramification and sometimes loss of lumen. There is a considerable increase of the stroma, and any remaining secretion is absorbed.

The general result is an enormous decrease in the size of the whole organ: although the general picture is similar to that of the resting gland of a nulliparous adult, some traces of the cycle of secretory activity remain. Dilatation of alveoli or of ducts is common, giving rise to small cysts; in addition, round-cell infiltration round the blood-vessels and ducts is frequent, and it is not unusual to find signs of hyperplasia such as multiplication of the layers of cells lining alveoli and ducts with obliteration of the lumen.

'Pale' Eosinophilic Epithelium.—Structures lined by 'pale' eosinophilic epithelium are frequently found in the breast, at all ages. These have been studied exhaustively by Dawson: she states that they are not of sweat-gland origin, as has been said, but are derived from normal mammary tissue. Such structures are cystic, and are not found in normal breast tissue. The 'pale' change is post-proliferative, and indicates a degeneration which supervenes on an epithelial activity of normal cells and checks it. The absence of cell infiltrations in the stroma surrounding such 'pale' structures contrasts with the cell accumulations near glandular tissue which shows fatty change, as in colostrum formation.

4. At the Menopause (or shortly after cessation of reproductive activity).—Menopausal involution, in contrast with post-lactational involution, seems in its first stages hyperplastic (Dawson), but the initial cellular increase in ducts and alveoli should be followed by "atrophy of glandular structure and permanent quiescence"; usually this occurs, but loss of control of the proliferating cells may give rise to a pathological condition.

In general, a very gradual involution occurs with retrogression of the parenchyma. The process is not continuous (cf. irregular cessation of ovulation) and is often interrupted by irregular proliferation. Dawson states that "the usual form of involution with the menopause is adenosis followed by fibrosis and quiescence", defining adenosis in this case as "glandular hyperplasia which produces more and larger lobules of normal or exaggerated physiological pattern" characteristic of pregnancy and to a lesser degree of adolescence and the climacteric. Cyst formation is common.

Gradually the alveoli begin to disappear and the ducts diminish in number. The epithelium of the secretory parts atrophies, and the connective tissue obliterates the lumen of the ducts, leaving strands of elastic tissue to mark the position of larger ducts. The connective tissue becomes less cellular, and vascularization diminishes. The process continues until the structure is that seen in senility.

5. In Senility.—The bulk of the organ consists of connective tissue which appears as a fairly homogeneous, faintly eosinophilic mass. There is an increase of elastic fibres, particularly round the remains of the ducts, and a decrease in the number of cells. The distinction between interlobular and periductal connective tissue is

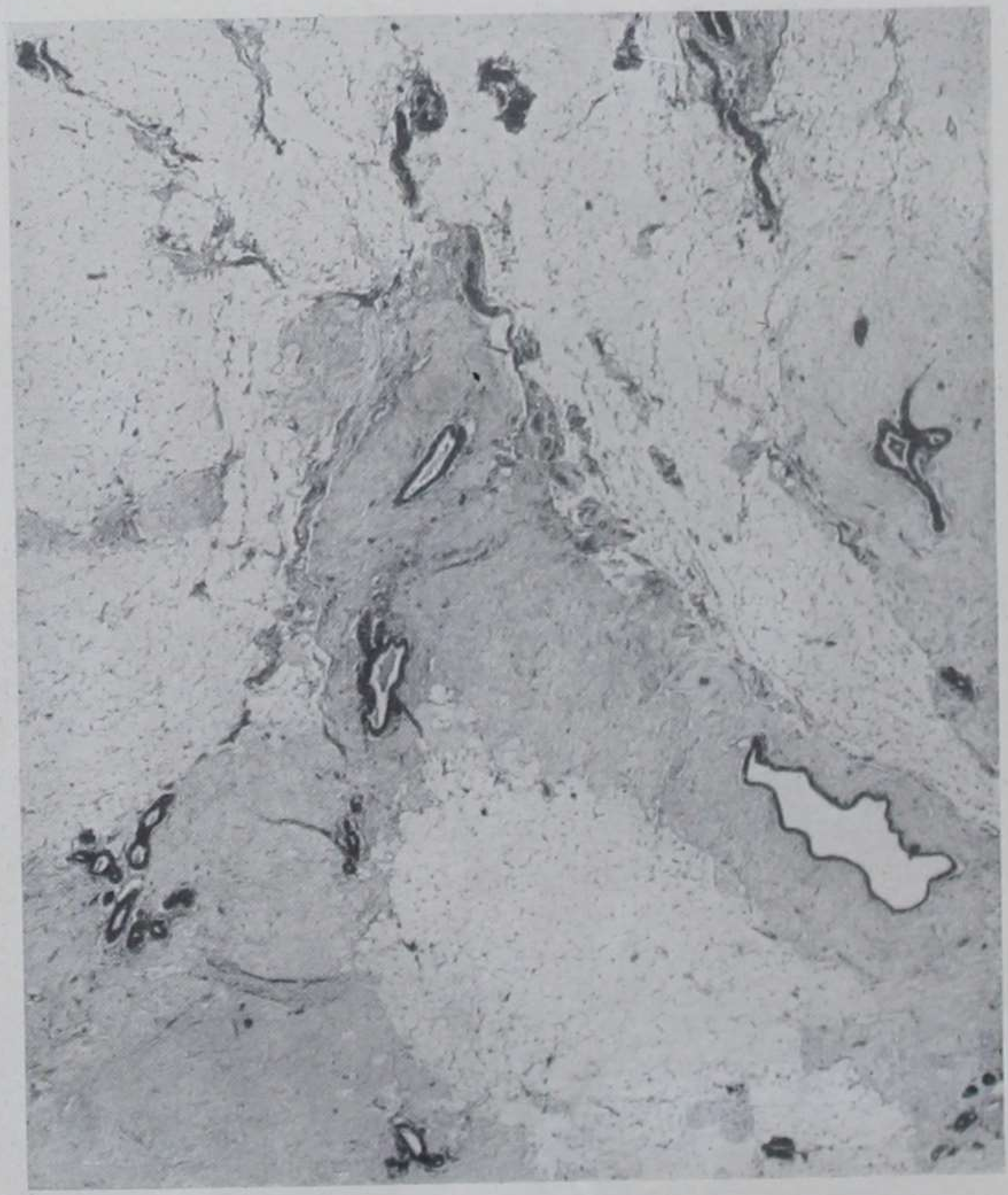

Fig. 47.—Section of breast tissue of woman aged 70 years. Note remains of ducts, dense stroma, and presence of fat. Stained with hæmatoxylin and Biebrich scarlet. (*Photograph.*) (× 18.)

lost. No alveoli are present, and the remains of the ducts are either lined by the usual two layers of cells or obliterated by a proliferated epithelium. Between the ducts there may be some replacement of the stroma by fat (*Fig.* 47). Lymphocytic infiltration round the blood-vessels and remains of ducts is usual.

In the male the appearance is similar to that seen in the female, except that in the former the gland looks as if it had never been actively functional (*Fig.* 48), whereas in the latter traces of previous activity can nearly always be found.

Fig. 48.—Section of breast tissue of man aged 64 years. Stained with hæmatoxylin and Biebrich scarlet. (*Photograph.*) (× 30.)

LACTIFEROUS DUCTS AND NIPPLE

1. Ducts.—The large, excretory ducts are lined by a columnar, stratified epithelium ; the sinus lactiferus (ampulla) has a two- or three-layered epithelium, and the lactiferous ducts a stratified epithelium that tends to become flattened near the external opening on to the surface of the nipple. Beneath the epithelium is loose connective tissue containing many elastic fibres, and outside this again some unstriped muscle. The lining is often thrown up into folds, and all the ducts allow of considerable distension (*Fig.* 49).

Fig. 49.—Section of nipple region in woman aged 46 years. Note ducts converging on to nipple. Stained with hæmatoxylin and Biebrich scarlet. (*Photograph.*) (× 3.)

2. Nipple and Areola.—Surrounding the nipple, in both sexes, is a circular pigmented area, the *areola* : in the female the pigment (melanin) which is in the basal epithelium of the skin, increases after the first pregnancy.

In both the nipple and the areola the dermis is pushed up into high papillæ (*Fig.* 50). In the areolar area the overlying epidermis is

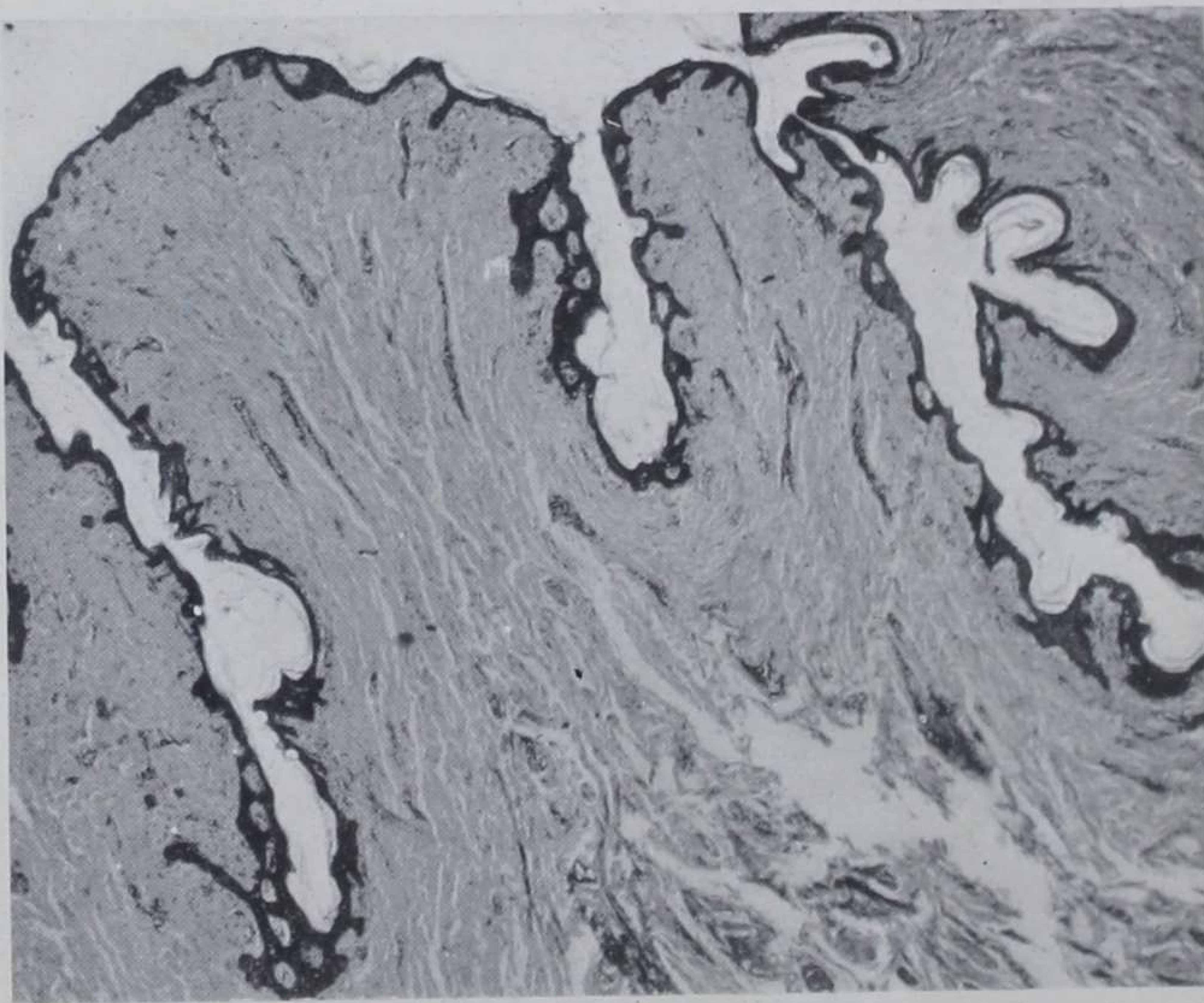

Fig. 50.—Section through nipple of woman aged 55 years. Note openings of lactiferous ducts, and absence of hairs and sweat-glands. Stained with hæmatoxylin and Biebrich scarlet. (*Photograph.*) (× 36.)

Fig. 51.—From section of subareolar tissue of breast of woman aged 46 years. Nulliparous. Stained with Weigert's resorcin fuchsin to show elastic fibres. (*Photograph.*) (× 213.)

very thin. In the areolar region there are large sebaceous glands, some without hairs, and also large sweat-glands: these glands sometimes have a common opening on the surface. Some sebaceous glands open on the surface of the nipple between the lactiferous ducts. In the underlying connective tissue there is a considerable amount of unstriped muscle: some of these fibres encircle the lactiferous ducts, some lie vertically to the surface, and many are arranged like a meshwork

Fig. 52.—Section showing Pacinian corpuscle (encapsulated nerve-ending) in the mammary gland. Woman aged 45 years. Note cross-section of nerve on right of corpuscle, and a lobule at top of section. Stained with hæmatoxylin and Biebrich scarlet. (*Photograph.*) (× 56.)

between the ducts. In this tissue there is also found a dense network of elastic fibres, particularly in the neighbourhood of the large ducts (*Fig.* 51).

In this region also are sometimes found some small collections of large sebaceous glands, the areolar glands (Montgomery).

In the dermal papillæ there are many nerve-endings, some free but mostly of the encapsulated type. Pacinian corpuscles are found in the connective tissue between large ducts (*Fig.* 52).

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CHAPTER II

THE FUNCTION OF THE BREAST

By Patricia P. Scott, Raymond Greene, C. S. Lane-Roberts, and Valentine Swain

I. PHYSIOLOGY OF GROWTH AND SECRETION

Mammary glands are apocrine organs, peculiar to the mammalia, which produce and temporarily store a complex secretion, milk. This secretion nourishes the young in the post-partum period until the alimentary tract is sufficiently differentiated for the digestion of ordinary food.

The primordia of the breast make an early appearance in the human embryo, and differentiation into nipple and ducts is clearly marked in both sexes at birth. After birth male breasts undergo relatively little further development, and normally never become functional. Female breasts develop mainly by two further stages, at adolescence and during pregnancy, and are thus prepared for lactation, which occurs only after parturition.

The control of growth of the breasts, which is not 'in step' with general bodily growth, and their secretory activities, appear to depend on the following: (1) Secretions of the gonads; (2) Secretions of the adrenal cortex; (3) Secretions of the anterior pituitary gland; (4) Secretions of the thyroid and other glands affecting metabolism; (5) General nutrition; (6) Nervous mechanisms.

When evaluating the relative importance of these factors in the growth and secretory activity of the breasts it must be remembered that most experimental observations have been made on animals whose reproductive cycles differ from those of primates. In addition, satisfactorily controlled experiments are not easily carried out on human subjects, even where results of a large number of cases can be subjected to statistical analysis.

A. ENDOCRINE CONTROL

1. Secretions of the Gonads.—

Three groups of sterols secreted by the gonads (and possibly by other tissues such as the adrenal cortex and the placenta) are of first importance in the development of the mammary glands: (*a*) Œstrogens; (*b*) Progesterone; (*c*) Androgens.

a. Œstrogens.—This group includes œstradiol, a sterol which may be extracted from the ovaries, and a number of closely related sterols and their derivatives extracted from other tissues and from urine. In addition, certain synthetic products, not necessarily sterols, have a similar pharmacological activity, e.g., diethyl stilbœstrol. Œstradiol brings about changes in the uterine endometrium associated with the œstrous cycle in lower mammals and with the first half of the menstrual cycle in primates.

Innumerable experiments, reviewed by Nelson (1936), Turner (1939), Folley (1940), and Petersen (1944, 1948), have shown that injections of œstradiol (or other œstrogen) into immature or castrated animals of either sex bring about rapid growth of the mammary glands. In most species this development is limited to a very marked extension of the duct system alone, but in ruminants a more complete development of the udder, followed by secretion of upwards of two gallons of milk daily, can be achieved by injections of œstradiol or by implantation of stilbœstrol tablets into virgin animals. However, Petersen (1948) states that the response obtained is extremely variable and absence of growth is common particularly in parous bovine animals. This is interesting, as a breast which has lactated once might be expected to be more susceptible to stimulation by œstrogens than that of a nullipara.

Gardner and van Wagenen (1938), working on male and immature oöphorectomized female monkeys (*Macaca mulatta*=*rhesus*), found, since the development of the breast is spread over a longer period in primates than in other mammals, that injections of œstrogens must be continued for at least thirty weeks to bring about development under experimental conditions. "The initial changes occurring in animals receiving œstrogens . . . were largely confined to a proliferation of the branching ducts, and an enlargement of the breast area by peripheral growth . . . Later, the peripheral growth of the ducts and the formation of lobules of alveoli occur simultaneously, the latter progressing from the region of the nipple to the periphery." *Figs.* 53 to 56 represent gross preparations of breasts of two of these young monkeys. *Fig.* 53 is the control left breast of a male monkey removed at operation. It consisted of thin ducts with a few short branches which were confined to a small area. *Fig.* 54 is the right breast removed at autopsy from the same monkey, after 36,000 I.U. of hydroxyœstrin benzoate had been injected during nine weeks. This

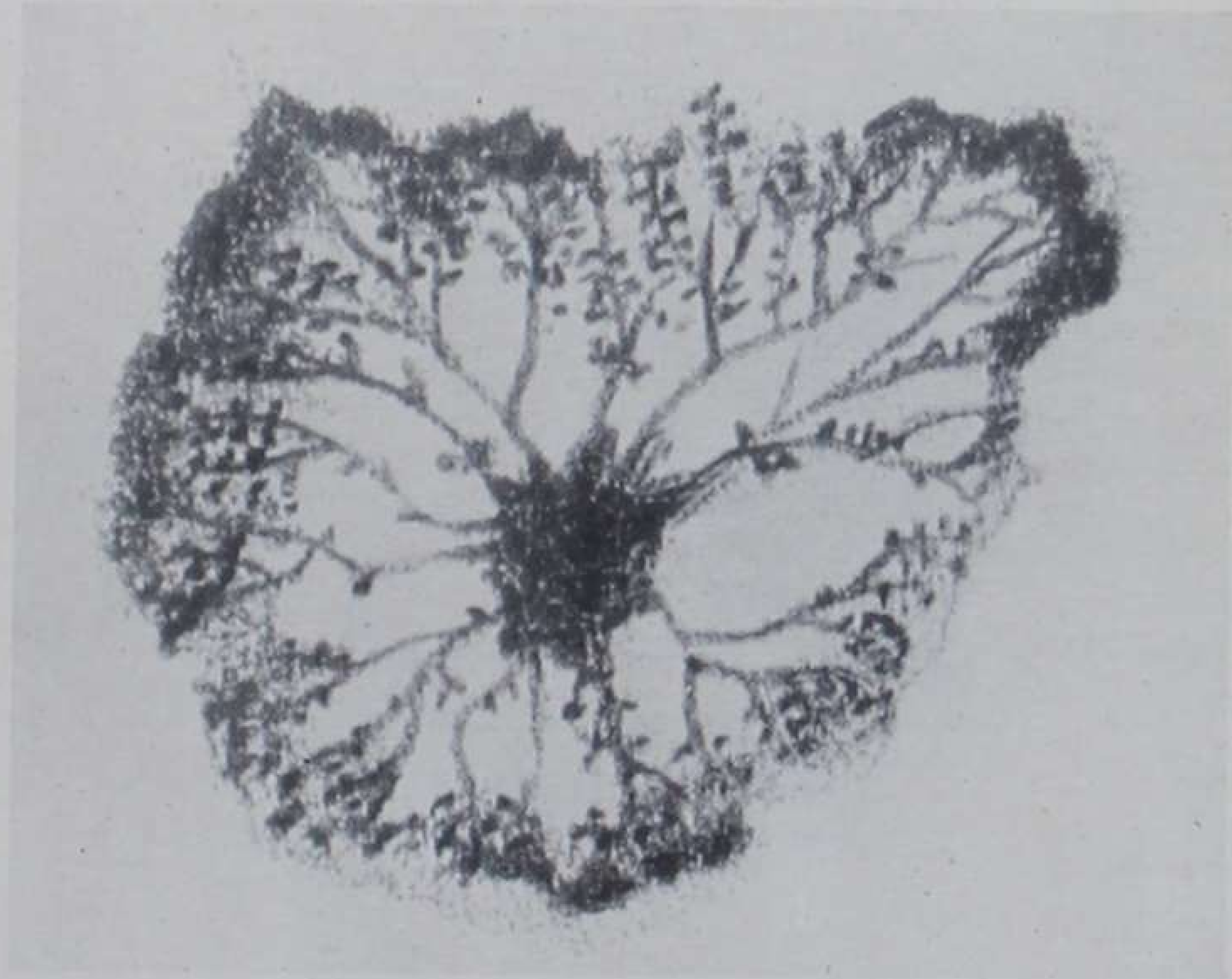

Fig. 53.—Normal left breast (control preparation) of a young male monkey. (*Figs.* 53–57 *by kind permission of Dr. W. U. Gardner and 'Endocrinology'*.

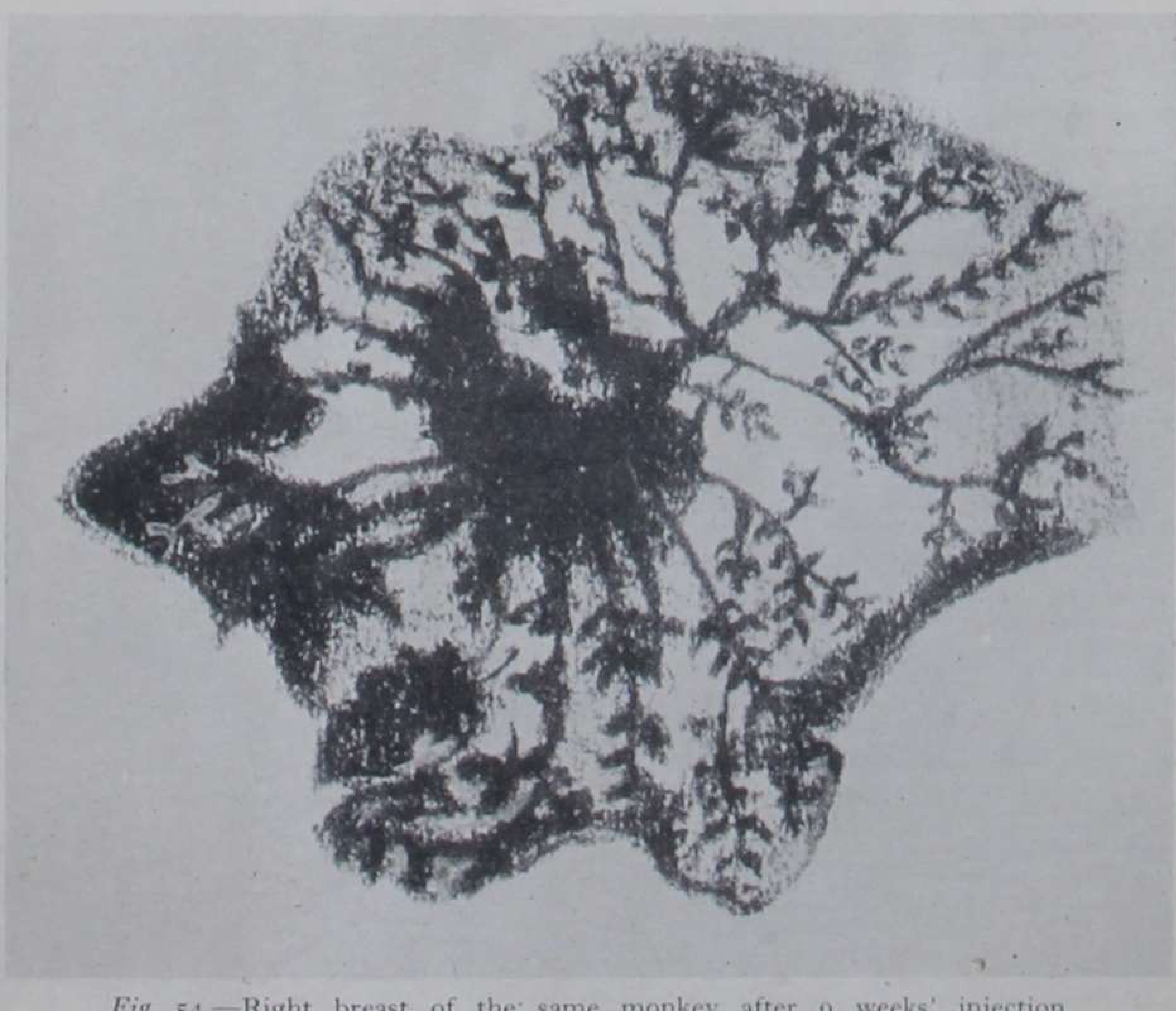

Fig. 54.—Right breast of the same monkey after 9 weeks' injection of 36,000 I.U. hydroxyœstrin benzoate.

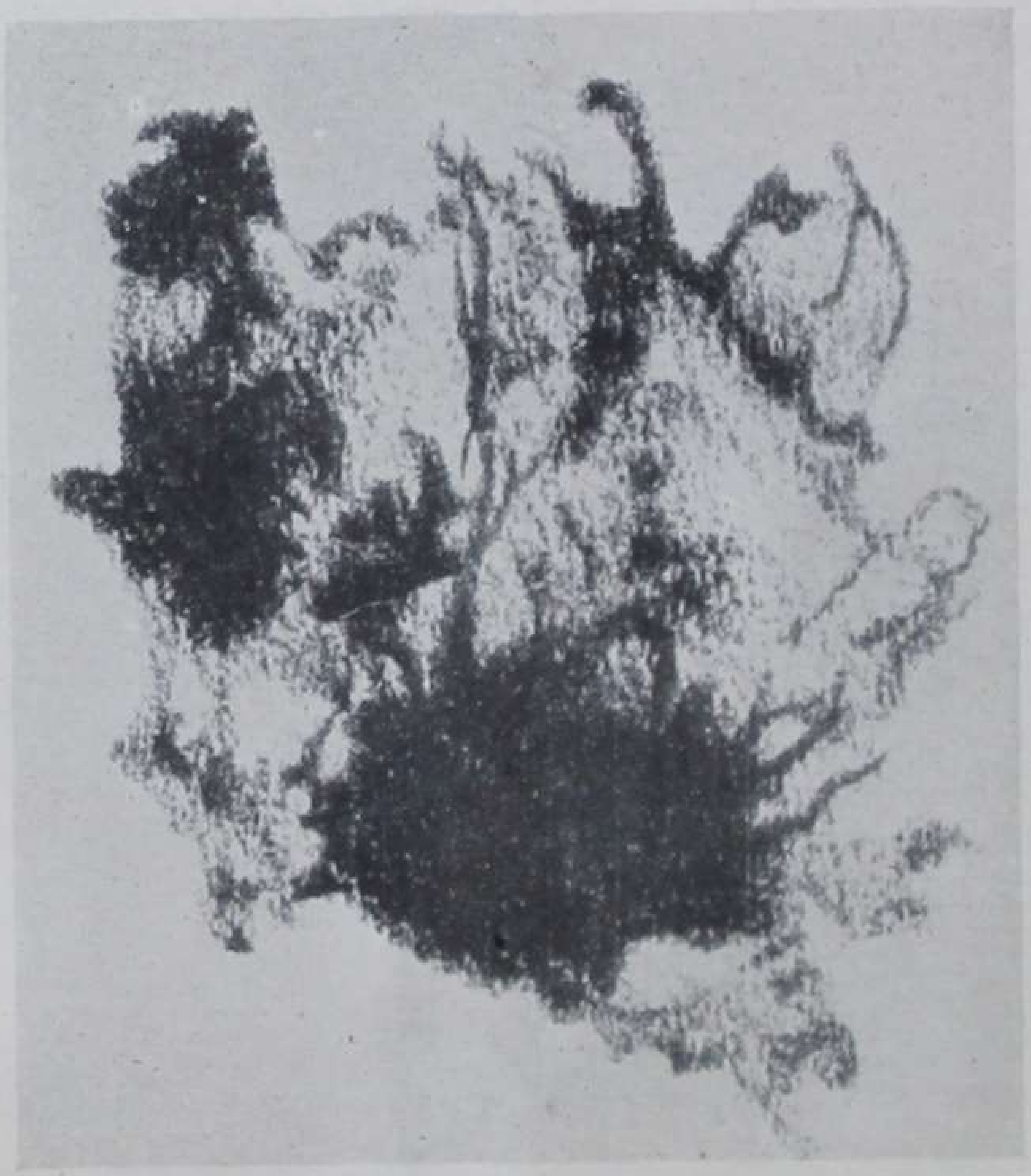

Fig. 55.—Normal left breast (control preparation) of a young female monkey.

Fig. 56.—Right breast of the same monkey after 21·5 weeks' injection of 136,000 I.U. hydroxyœstrin.

gland was approximately three times the size of the control breast, but still consisted only of a system of branching ducts. That the peripheral growth of the gland was continuing was indicated by the slightly distended end buds, and the increased number of connective tissue cells found in the region. *Fig.* 55 is the normal left breast of an immature female monkey removed at operation at the same time as

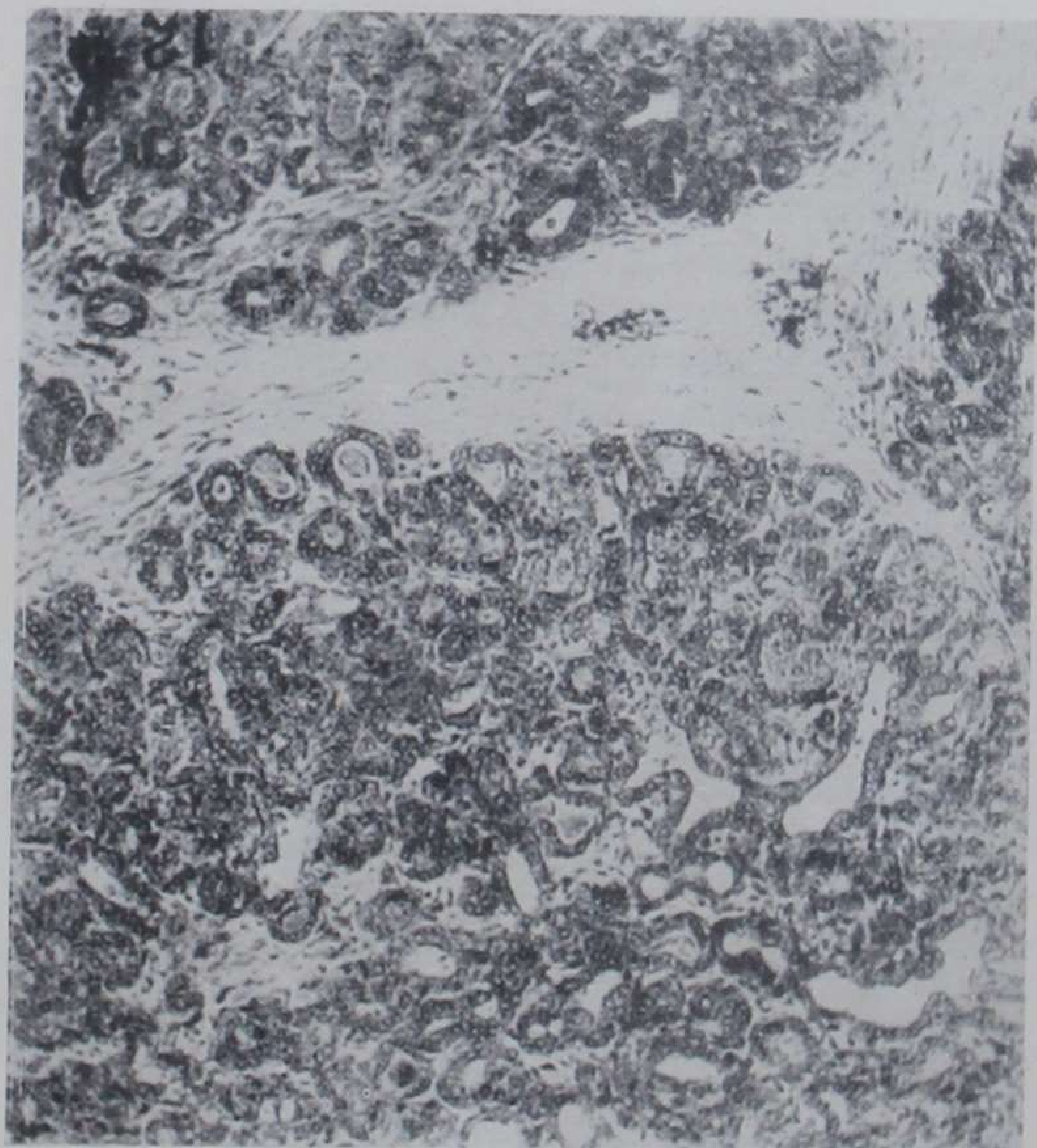

Fig. 57.—Microscopical preparation of the breast seen in *Fig.* 56, showing well-developed lobules. (×80.)

oöphorectomy was performed. It consisted of a system of branching ducts and at the time of removal showed no evidence of proliferation. *Fig.* 56 is the right breast of the same monkey after receiving 136,000 I.U. of hydroxyœstrin benzoate during 21·5 weeks. Although this breast was somewhat smaller than that of an adult female monkey, well-developed lobules were present throughout (*see Fig.* 57). Rapid peripheral growth was not apparent. The ducts and alveoli were slightly distended with secretion. Cystic terminal distension of the ducts occurred at one point along the periphery. *Fig.* 57 is a histological preparation of the same breast showing the lobules, and secretion in the alveoli, though the amount of the latter was not comparable to that seen in a section from a lactating animal.

Evidence of the action of œstrogens on the human breast is mostly of an indirect kind. Whether or not the breast of the fœtus is influenced by maternal hormones in utero is uncertain, but new-born infants of both sexes may show breast enlargement (erroneously referred to as infantile mastitis), and œstrogens administered after subsidence of this swelling will produce renewed activity, even leading to secretion by such tissue as is present at this stage. In childhood breast enlargement has been noted in cases of gonococcal vaginitis treated with œstrogens. Similarly the small flat, or even apparently absent, breasts of girls suffering from hypogonadism develop noticeably during treatment with the same substances. Since sex is genetically determined, the behaviour of each body cell is conditioned by the sex of the individual, and therefore a greater growth response to œstrogens occurs in young women, though a degree of enlargement of the male breast may be obtained under experimental conditions. This enlargement is a usual occurrence during treatment of carcinoma of the prostate with stilbœstrol, and is observed in male workers employed in the manufacture of synthetic œstrogens.

The mode of action of œstradiol on breast tissue is much disputed. Some workers believe that the effects are produced indirectly through the pituitary gland. MacBryde (1939), however, demonstrated a direct local action by rubbing one breast of each of three women with an ointment containing a high concentration of œstradiol (25,000 I.U. per day), while the other breast acted as a control and was rubbed with the ointment base alone. On the side treated good development was obtained, while the control showed much less enlargement. Similar results have been obtained in animals. It is thought that œstradiol produces hyperæmia and vasodilatation of the developing breast (as it does of the uterus), and thus by increasing the blood-supply enables metabolites and other hormones to reach the breast tissues more readily.

In large quantities œstrogens have a depressant effect on the secretory activity of the lactating breast of women and of animals when administered early in the lactation period. Administration to lactating rats brings about such a drastic fall in milk-supply that they are unable to rear their litters, and stilbœstrol has been successfully used clinically for the suppression of an excessive or unwanted lactation. It has been suggested that œstrogens are the agents which normally suppress lactation during pregnancy.

b. Progesterone.—This substance, secreted by the corpus luteum of the ovary, controls the changes which occur in the endometrium during the second half of the menstrual cycle of primates and during pregnancy. An identical substance is secreted by the adrenal cortex and probably by the placenta.

Most experimental animals require injections of progesterone following the administration of œstrogens to complete the development of the lobule-alveolar system of the breast until it is comparable with that seen towards the end of pregnancy. Even in ruminants it is claimed that a less cystic type of development results from the use of progesterone than that which is produced by giving œstrogens alone.

The function ascribed to progesterone in women is somewhat speculative. Progesterone, unless from the adrenal cortex, is probably not present in the female body until luteal tissue is formed after ovulation. Ovulation does not occur in childhood, and it seems likely that the early menstrual cycles of the adolescent are anovular. Thus progesterone begins to exert its effect on the growth of the mammary system in late adolescence, but even then only to a very limited extent. Speert (1940) has shown in monkeys that lobular growth in the premenstruum can be prevented by removal of the corpus luteum, while Geschickter reported on a case of secondary amenorrhœa in a woman whose breast was submitted to biopsy before and after treatment with progesterone. Biopsy showed extensive lobule formation after treatment and also proliferation of the intralobular connective tissue. In many women the breasts enlarge, becoming firmer, nodular, and not infrequently painful, a few days before menstruation. This is probably due to some cyclic extension of the lobule-alveolar system, but is in part also due to hyperæmia and alterations in the water relations of the mammary tissues (œdema).

These changes are all an expression of alterations in the œstrogen–progesterone balance during the menstrual cycle. A more extensive development accompanied by similar symptoms of discomfort occurs in the early stages of pregnancy, when the breast is continually under the influence of progesterone produced by the persistent corpus luteum of pregnancy, and also by the placenta.

c. Androgens.—Testosterone, the principal sterol of this group, is secreted by the interstitial cells of the testis, while other androgens are formed by various tissues of male and female organisms. They bring about the development of the male organs at puberty. If administered in sufficient quantities androgens cause changes in the mammary glands of young castrated experimental animals similar to those produced by œstrogens, bringing about as a rule a development of the duct system only. In the rat and the monkey, however, the effect of injections of testosterone propionate resembles that produced by progesterone, a fact which accords with the other progesterone-like effects of androgens observed in animals. Androgens can cause transient enlargement of the breasts in man as is shown by its occasional occurrence during administration of methyl testosterone. The pubertal enlargement of the breasts seen in otherwise normal boys may be due to the activity of the gonads at this stage. Androgens in large doses have a depressant effect on lactation similar to œstrogens and have been used clinically for this purpose.

2. Secretions of the Adrenal Cortex.—

The adrenal glands are probably necessary for the normal development and secretory activity of the mammary glands, owing to the control of metabolism exerted by secretions of the cortex. Removal of both adrenal glands in animals results in a derangement of the metabolism of water, sodium chloride, carbohydrates, and fats, and is invariably fatal.

Secretions of the cortex also have a specific effect. Speert (1940) and Mixner and Turner (1942), showed that desoxycorticosterone has a definite progesterone-like action on the mammary glands when tested on œstrogen-sensitized animals. This suggests an explanation for the full development of these glands that is obtained with œstrogens alone in castrated female ruminants and in oöphorectomized monkeys in which the adrenal cortex apparently acts as a source of a progesterone-like substance.

Enlargement of the breasts has been noted in male patients with adrenal tumours, and in those under treatment with cortical extracts. Precocious mammary development is sometimes associated with adrenal tumours in girls, but it seems probable that, normally, the progesterone-like substance acting on the breasts of adolescent girls and pregnant women is derived from the corpus luteum rather than from the adrenal cortex.

3. Secretions of the Anterior Pituitary Gland.—

Secretions of the anterior pituitary gland which affect the development and secretory activity of the breast are: (*a*) Gonadotrophic hormones; (*b*) Mammogenic substances; (*c*) Thyrotrophic hormone; (*d*) Adrenotrophic hormone; (*e*) Prolactin.

a. Gonadotrophic Hormones.—The gonadotrophic hormones affect the breast only indirectly; their function is to control activity of the ovary and the testis. In the absence of these hormones œstradiol and progesterone are not secreted by the ovary and development of the breast therefore cannot occur.

b. Mammogenic Substances.—Since 1935 much controversy has centred on the way in which œstrogens and progesterone exert their gynergic action on the breasts. Selye and Collip (1936) and many other workers found that it was extremely difficult, and with low dosage impossible, to produce mammary growth in hypophysectomized animals (castrate or entire), by injections of œstrogens, androgens, or progesterone. Turner and co-workers (1943), of the Missouri school are of the opinion that œstrogens and androgens act on the anterior pituitary gland causing it to secrete mammogen I, and that mammogen II is produced by the pituitary in response to progesterone. They claim to have isolated the mammogens from pituitaries of animals stimulated by œstrogen injections, and to have identified them as proteins. Also, they suggest that the placenta may be an additional source of these substances. On injection into an immature ovariectomized animal mammogen I is said to produce duct growth only, while mammogen II will bring about lobule-alveolar development.

c. and *d. Thyrotrophic and Adrenotrophic Hormones.*—Other workers, who deny the existence of the mammogens, point out that hypophysectomy not only removes a possible source of these substances, but entirely alters the metabolism of the animal by the absence of thyrotrophic, adrenotrophic, and other hormones. Hypophysectomized animals show severe anorexia, and nutrition rapidly falls below the level at which development of the mammary glands can be initiated or continued. The thyrotrophic and adrenotrophic hormones, like the gonadotrophic, do not directly affect the breast tissue, but control the secretory activities of the thyroid and adrenal cortex respectively. Both these glands produce secretions essential to its normal development. Folley and Young (1938) found that injections of thyrotrophic hormone had a similar stimulating effect to thyroxine on milk production, although no change was noted in milk fat percentage.

e. Prolactin.—During the later stages of pregnancy hypophysectomy of animals does not interfere with adequate mammary development or with normal parturition, but lactation fails completely. The same procedure abruptly terminates milk secretion if carried out at any time during the lactation period. On the other hand, provided that the mammæ of immature oöphorectomized animals have been developed by suitable doses of œstrogen and progesterone, lactation can readily be induced by injections of a hormone extracted from the hypophysis, the blood, or the urine of a lactating animal, even of a different species. This lactogenic hormone has been identified by most workers with prolactin (mammotropin), a protein secreted perhaps by the eosinophil cells of the anterior pituitary gland which stimulates crop-gland growth in young pigeons. Pigeons are therefore used in the assay of the hormone, although the use of a mammal would be more satisfactory. Meites and Turner (1942) compared the prolactin contents of the pituitary and of the blood of pregnant and non-pregnant animals, finding little difference between them, but in animals 2–5 days post partum a remarkable increase in prolactin was shown, coinciding with the onset of lactation. This rise has been ascribed to the removal of some suppressing influence associated with pregnancy, such as progesterone, œstrogen, the presence of the placenta, etc., which is removed at parturition.

Large amounts of prolactin have been found by Lyons (1937) in the urine of lactating women and of newborn babies. It has been estimated that breast enlargement is shown by two-thirds of babies of both sex shortly after birth, and that approximately a further two-thirds of these enlarged breasts actually 'secrete' colostrum or milk. Lyons suggests that the breasts of the newborn are stimulated, firstly by œstrogen from the placenta, and secondly by prolactin from the maternal or even from the child's own pituitary gland. Abraham (1930) found that if the enlargement was allowed to subside naturally administration of an œstrogen to the infant caused the breasts to swell again and 'secrete' actively—possibly by stimulating the child's pituitary to a further outpouring of prolactin.

Variable results have been obtained by superimposing prolactin injection on a normally established lactation. Repeated high doses of pituitary extract increase milk production in the declining phase of lactation in cows, but it is doubtful if this is entirely due to prolactin, as the thyrotrophic hormone present in relatively crude pituitary extracts can have a stimulating action, as mentioned above. It is not surprising that prolactin administration to women in whom lactation is deficient has produced unsatisfactory results, as in the cases examined it was not established that prolactin was deficient. The existence of such a deficiency could be established by assaying the urine for its prolactin content. Tedious and expensive biological assay will probably be replaced for clinical purposes by spectrophotometric and paper chromatographic methods which will enable relatively rapid estimation of small amounts of hormones in serum or urine. (*See* FAILURE OF LACTATION, p. 74.)

4. Secretions of the Thyroid and other Glands affecting Metabolism.—

The secretions of the thyroid gland are thought to have a specific effect on the metabolism of breast tissue, in addition to a general metabolic effect shared by the breasts with other regions of the body.

It has been shown, and more recently confirmed by Mixner and Turner (1942), that thyroxine administered to female rats stimulates the development of the mammary glands. Gardner (1942) found that this effect extends to intact male rats, but not to castrated controls, suggesting that the effect of thyroxine may be exerted through the gonads. But stilbœstrol alone cannot bring about mammary development in a thyroidectomized myxœdematous heifer, growth occurring only when thyroid is given at the same time (Petersen, Knodt, et al., 1944). Spielman et al. (1941) also observed that mammary development was delayed in pregnant thyroidectomized heifers until mid-term, at which time myxœdema also disappeared owing to the production of thyroxine by the fœtal thyroid. Development of the breasts is delayed in hypothyroid girls, but in such cases a resumption of normal mammary growth follows the administration of therapeutic doses of thyroxine.

Folley and White (1936) and other workers found that thyroxine injections increased the milk yield of cows over that of the preceding lactation. They observed a raised pulse-rate in animals receiving these injections, and found—as Fuller (1938) had done previously—a direct relationship between pulse-rate and milk yield under conditions amounting to hyperthyroidism, suggesting that secretory activity is promoted by increasing the blood-supply to the gland. Kustner (1934) administered di-iodotyrosine to women with histories of inadequate lactation and obtained an increase in milk output. More recently, extensive experiments have demonstrated the possibility of raising the milk yield of cows some 20 to 30 per cent by feeding iodoproteins such as iodocasein. Since an increase of 20 per cent can be achieved with very little loss of weight (that is, without unduly raising the metabolic rate) Folley (1947) has recommended the clinical use of these substances as galactogogues. (*See* FAILURE OF LACTATION, p. 74.)

Administration of thyroxine also affects the composition of milk, increasing the percentage of the fatty solids markedly and the non-fatty solids to a smaller extent. This appears to be the result of a rise in the level of precursor substances of these constituents of milk in the mammary blood-supply. Dinitrophenol, a drug which, like thyroxine, raises the metabolic rate and alters the percentage composition of milk, does not, however, affect the total output, and in large doses actually depresses lactation. It seems, therefore, that thyroxine has a specific stimulating effect on the gland cells of the breast.

According to Folley and his co-workers (1942, 1945), parathormone, the secretion of the parathyroid glands, which plays a part in calcium metabolism, is essential for normal maximal milk production.

Chaikoff and Lyons (1933) have shown that depancreatization impairs lactation in the bitch although it is not completely suppressed. This is probably due to disturbance of carbohydrate metabolism, rather than to any specific influence of insulin on the mammary gland. Alloxan diabetes has a similar depressant effect on lactation.

B. GENERAL NUTRITION

The growth of the breasts during pregnancy and their ability to secrete milk are affected by diet. Hypofunction may be expected whenever the diet is deficient by ordinary standards.

During lactation the additional calorie requirement might be computed from the calorie value of the milk secreted, but the high metabolic rates found in this condition by Allen (1940) suggest that a further allowance should be made for the activity of the breast tissue.

Body-building protein requirements are raised during pregnancy, part of this increase being necessary for breast development. During lactation the daily output of protein, and also of calcium and phosphorus, must be balanced by an equivalent dietary intake to avoid a breakdown of maternal muscle, bone, and other tissues. Thus maternal weight-loss may occur on a diet adequate in calories where these are largely supplied by carbohydrate, without any diminution of milk secretion. Frank osteomalacia may be precipitated during lactation owing to the removal of calcium from the skeleton on a diet lacking in calcium and vitamin D.

Breast growth and secretory activity can occur on a low-fat diet, but in normal individuals a high-calorie intake is more easily achieved by the inclusion of fat in the diet, since, weight for weight, fat has at least twice the calorie value of carbohydrate. Moreover, this fat contains phospholipids as well as triglycerides of fatty acids, and acts as a vehicle for the fat-soluble vitamins. These must be given in synthetic form to patients receiving a fat-free diet.

In general, vitamin deficiencies affect the quality rather than the quantity of milk secreted. The riboflavin content of milk, for example, closely follows the dietary intake of this B vitamin. Williams and Spies (1938) have shown that polyneuritis, curable by administration of aneurin (thiamine B_1), is more severe and more frequent in occurrence in pregnant and lactating women than in the general American population. Perla (1937), on the other hand, has shown the danger attending excessive administration of aneurin, which he found to depress lactation in rats. Hertz (1948) suggested that folic acid deficiency may prevent the optimum utilization of œstrogen by the breast tissue during pregnancy. His experiments on monkeys support this view, while Cerecedo and Vinson (1944) found that folic acid is required for normal lactation in the rat. Baumann and Rappolt (1937), and other workers, have calculated that a lactating woman secreting 800 ml. of milk daily requires at least 50 mg. of ascorbic acid above the normal daily requirement of roughly 1 mg. per kilo of body-weight. Finally, limitation of water intake will rapidly diminish the volume of milk secreted.

Thus, minor variations in the diet of populations with a relatively high standard of nutrition, such as in Britain, appear to have little influence on breast development or secretion ; but observations on populations on grossly deficient or semi-starvation diets show that under-development and a secretion deficient in quality and quantity may be the result of malnutrition.

C. NERVOUS MECHANISMS

The actual stimulus of suckling is an important factor in the initiation and maintenance of lactation. Milk output falls if the suckling (or milking) stimulus is irregular, while complete cessation of this brings about noticeable changes in the secretory epithelium of lactating animals in a few hours.

Petersen et al. (1929, 1932) have shown, contrary to earlier views, that milk is secreted by the gland in the intervals between suckling, and that failure to remove the milk may lead to the building-up of a back pressure in the alveoli and smaller ducts which slows the rate of secretion. This mechanism is probably responsible for adjusting the daily output to the requirements of the infant. At the actual time of nursing or milking a release or 'let-down' of milk, accumulated since the previous time of nursing, occurs. No secreto-motor nerve-supply to the gland has been found to explain this phenomenon ; in fact, one of the earliest experiments by Ribbert

(1898) consisted of transplanting the mammary glands in a rabbit and showing that—although completely denervated—they were still capable of lactation. Similarly section of the nerve-supply to the mammary glands does not usually have any effect on milk yield. Any diminution is more attributable to deficient blood-supply (the result of section of the autonomic nerves) than to changes in the secretory tissues. Selye et al. (1934) observed that even if the milk-sinuses in lactating rats were cut (to prevent loss of milk and maintain distension) a continual provision of actively suckling litters was able to extend lactation in the mothers beyond their normal weaning time. Similarly, by removal of some nipples and active suckling of others, milk secretion was maintained in all the glands, whether drained of milk or not. Evidence that an afferent stimulus of some kind is necessary to promote successful lactation was further strengthened by Ingelbrecht's observations on rats with the spinal cords transected so that only the anterior breasts remained innervated. Young rats suckled on the posterior denervated breasts only, and shielded from the mother's sight, were unable to obtain milk and died of starvation. But when sucklings were placed at the same time on the anterior innervated breasts then both groups of young received an adequate supply of milk. This nervous mechanism does not appear to be responsible for the secretion of milk into the alveoli, but for its expression from the alveoli and finer ducts into the sinuses. Some indication of the pathway taken by these afferent stimuli was given by Herold's (1939) observation that the litters of rats in which the pituitary stalk of the mother had been transected died of starvation. Further, Petersen et al. (1942, 1944) found that blood from cows stimulated to let-down their milk will cause let-down to occur in a perfused isolated udder. Blood from cows not thus prepared produced no effect in the isolated gland: but oxytocin, extracted from the posterior pituitary gland, had a similar effect to that of blood from stimulated cows. Where milk production has been depressed by incomplete evacuation of milk, it can be restored to normal by injections of oxytocin.

Let-down of milk thus involves a reflex, the afferent pathway being usually by the sensory nerves from the nipple area, although conditioning, for example to the sight of the infant, or the sound of its cries, readily occurs. By this pathway stimuli reach the posterior pituitary gland via the hypothalamus, causing oxytocin to be liberated into the blood-stream and carried to the breast, where it brings about contraction of unstriped muscle. It is not surprising, therefore, that emotional states, such as fear or excitement, are inhibitory to the let-down of milk, since they interfere with the passage of impulses from the hypothalamic region. This may account for the difficulty experienced by temperamental and neurotic women in maintaining sufficient lactation.

D. SUMMARY

An attempt to summarize current speculation on endocrine control of the development and functional activity of the breast is hardly justifiable, but the following is an extract of some of the main points discussed above.

1. Development is initiated by œstradiol.
2. Female development is continued :—
   a. At puberty by œstradiol and in later adolescence by progesterone from the corpus luteum of menstruation.
   b. In early pregnancy by a rapid rise in the concentrations of œstrogen and progesterone from the persisting corpus luteum.
   c. In later pregnancy by these hormones produced chiefly from the placenta.
3. Lactation is initiated by :—
   a. Prolactin produced by the anterior pituitary gland after parturition as a result, possibly, of a sudden fall in the concentration of œstrogen and progesterone.
   b. Oxytocin released by the posterior pituitary gland in response to the sucking stimulus.
4. Lactation is maintained by :—
   a. Continued secretion of prolactin and oxytocin.
   b. Regular emptying of the breasts.
   c. Adequate nutrition.

II. THE COMPOSITION OF MILK AND THE MECHANISM OF ITS FORMATION

The composition of milk varies in different mammals, and individually according to the stage of lactation. Such variations have been correlated with the growth-rate of the young of the species considered. ‘Mature’ milk is the most constant in composition, and in human beings is produced from the fifth week of lactation onwards.

Although milk has a total osmotic pressure similar to that of blood, the principal constituents of milk are not in equilibrium with blood, as the following ratios, expressed on a molar basis, show (for cow's milk) :—

Constituent	*Blood*	*Milk*
Sugar	1	40
Fat	1	20
Potassium	1	7
Calcium	1	14
Magnesium	1	4
PO_4	1	7
Protein	2	1
Chloride	4	1
Sodium	8	1

On the basis of such figures it is impossible to regard milk as a filtrate of blood, although certain constituents—unimportant from a nutritional point of view—such as urea, uric acid, creatinine, and creatine are present in the same concentration in both.

Three methods have been employed in studying the synthesis of milk. Firstly, comparisons have been made between the levels of precursor substances in the arterial and venous blood of the lactating cow and goat, but the various techniques employed have been subject to considerable error. The best are probably those devised by Graham and his co-workers (1936). Secondly, thin, surviving slices from animal lactating glands have been incubated with suspected precursor substances; by this method it was shown that glucose was the only substrate giving rise to lactose. Thirdly, by the use of radio-active isotopes, a very rapid breakdown and resynthesis of phosphoric esters has been demonstrated in the mammary gland. Further discussion of these methods and the results (often somewhat contradictory) obtained from them may be found in the reviews by Folley (1940), Petersen (1944), and Espe (1941). The main conclusions are briefly summarized below.

Lactose, the sole *carbohydrate* of milk, is a disaccharide formed by the condensation of glucose with galactose, and the mammary gland is the only site of its formation in the body. It may, however, be reabsorbed from the mammary gland into the blood and excreted by the kidney. Studies of the uptake of blood glucose by the mammary gland suggest that a further source of carbohydrate is needed to supply all the requirements for milk formation, such as glucose derived within the gland from protein catabolism or from lactic acid of the circulating blood. The incubation method described above suggests, however, that lactic acid is not a source of lactose.

The *proteins* consist of caseinogen, lactalbumin, and lactoglobulin. Caseinogen is a complex phosphoprotein peculiar to milk, which is probably built up in the mammary gland from circulating amino-acids. In spite of its complexity, samples of casein from milks of different species appear identical. Lactalbumin is also synthesized by the gland, differing slightly in amino-acid composition from serum albumin. Lactoglobulin is only present in very small quantities in mature milk, but forms a higher percentage of the protein of colostrum. It is identical with serum globulin, and has great importance in carrying with it antibodies from the maternal blood.

Milk *fats* are derived ultimately from the diet, whether taken in as fat, carbohydrate, or even protein. Some fat in the diet is essential for milk formation, although a proportion can be derived from the glucose of the blood. A change in the dietary fat will alter the composition of milk fat in twenty-four hours. It is possible, however, especially in the earlier phases of lactation, that much of the fat is derived from that laid down in the breast tissues during pregnancy, since the latter is much more similar to milk fat than to the general body fat. Compared with body fat, milk fat contains higher proportions of triglycerides of short-chain fatty acids, especially butyric and unsaturated acids such as oleic. Cholesterol and phospholipids (especially lecithin) are probably derived from the blood-plasma; these, and the triglycerides, show an increase in the plasma at the onset of lactation.

The *inorganic constituents* of milk are derived from plasma, although the method of selection, which retains high proportions of bone-forming salts and rejects sodium chloride, is obscure. The bone salts, including calcium, are probably linked with caseinogen in some way.

Vitamins in milk are all derived from the circulating blood. Fat-soluble vitamins A and D, and carotenoids, are related to the fat content of the milk and vary with it. Fat estimation is subject to considerable sampling errors; the percentage of fat, and therefore of these vitamins, increases in samples of milk taken towards the end of each suckling compared with samples taken at the beginning. The carotenoids of human milk are mostly xanthophylls and therefore valueless as vitamin precursors.

Values for the principal constituents of mature human milk are given in *Table I* (Kon and Mawson, 1947).

Table I.—SOME CONSTITUENTS OF MATURE HUMAN MILK

CONSTITUENT	NO. SAMPLES	MEAN VALUE	STANDARD DEVIATION
Fat (4–6 hr. after last feed)	612	4·78 g./100 ml.	1·47
Solids—not fat	1348	8·968 g./100 ml.	0·43
Lactose	516	6·94 g./100 ml.	0·34
Total Nitrogen At 5–8 weeks At 21–24 weeks	522	 0·213 g./100 ml. 0·186 g./100 ml.	 — —
Calcium	76	29·9 mg./100 ml.	4·2
Phosphorus	76	13·0 mg./100 ml.	1·9
Vitamin A (17th week)	1390	32·1 I.U./g. fat	10·5
Vitamin D	Pooled for biological estimation	0·2–0·4 I.U./g. fat	—
Vitamin B (1944–5 Nat. bread)	295	18·3 mg./100 ml.	3·3
Riboflavin	616	24·5 mg./100 ml.	7·0
Vitamin C	1499	3·54 mg./100 ml.	1·40

Variations in the composition of milk during the lactation period are shown in *Table II* (Bell, 1928).

Table II.—AVERAGE PERCENTAGE COMPOSITION OF HUMAN MILK

TIME	PROTEIN	LACTOSE	FAT
5 days p. p.	2·00	6·42	3·2
9 days p. p.	1·73	6·73	3·7
3–4 weeks p. p.	1·37	7·11	3·6
5–6 weeks p. p.	1·30	7·11	4·0
7–8 weeks p. p.	1·21	8·11	4·0

A comparison of the main constituents of milks used for human consumption is given in *Table III*.

Table III.—COMPARISON OF CONSTITUENTS OF DIFFERENT MILKS

	Water	Proteins		Fat	Lactose	Ash
		Casein	Lactalbumin			
Human milk	88·5	0·3	0·7	3·7	6·7	0·2
Cow's milk	87·1	2·3	0·7	4·0	4·8	0·7
Goat's milk	87	4·3		4·8	4·7	0·8

III. LACTATION

MANAGEMENT OF THE BREAST AND NIPPLE

During pregnancy auxilliary breast tissue, along the axillary border (axillary tail) and other extensions, sometimes causes much discomfort. Clothing accordingly should be loose and warm without constriction anywhere, but if the breasts are heavy and pendulous suitable support is necessary.

A simple routine of hygiene should include daily washing with soap and water, careful drying of the nipple afterwards, and removal of any crusts that may form by bathing with warm olive oil each night. By this means the need for hardening agents during the last weeks of pregnancy is avoided, and a general stimulus to breast feeding—so largely a matter of will-power—is maintained.

Depressed nipples should be gently drawn out by finger and thumb, held for a moment, and then relaxed. Other recommendations for rectifying this include suction through the vaselined bowl of a clay pipe, or placing the unstoppered mouth of a warmed bottle over the nipple and holding it until a vacuum is formed by cooling and suction exerted, or the use of an electric breast pump.*

Insufficient lactation and engorgement of the breasts are so often complementary that they may be considered together.

Milk is secreted in the intervals of suckling, and failure to remove it may promote a back pressure in the alveoli sufficient to slow the rate of secretion. The yield of milk, therefore, is controlled to some extent by the demand of the infant. During the period 24 to 72 hours after the initial activity the breasts sometimes become very distended

* Waller has found that defective nipples can be improved in a number of instances by exerting gradual, constant, and painless stretching over a long period. For this purpose he uses a glass shield with a central hole for the nipple, which can be applied and worn under a brassière during pregnancy. A shield of this pattern is made by Messrs. Allen & Hanburys Ltd., London.

and the skin covering them stretched and shiny. When engorgement is severe the outflow of milk becomes scanty and suckling almost impossible, causing considerable pain and not infrequently damage to the nipples. H. Waller regards engorgement as severe in 25 per cent of cases, moderately severe in some 50 per cent—when the symptoms may persist for 1–14 days—while the remaining 25 per cent, mainly multiparæ, have a good flow of milk without distension or other disturbance.

In order to avoid any frustration of breast feeding from the outset, with the consequent engorgement, Waller has organized the following technique at his hospital :—

1. The systematic examination of all patients for structural defects of the nipples early in pregnancy.

2. The manual expression of colostrum is taught to all primigravidæ, who are asked to practise it daily during the last six weeks of pregnancy—as it is considered that this dilates the duct system and enables a primipara to start with something of the advantage possessed by a woman who has already breast-fed a baby.

3. When secretion starts suddenly and threatens to produce engorgement it is controlled by the use of synthetic œstrogens.

4. The importance is emphasized of the manual removal of milk to secure adequate drainage, which the baby is not expected to accomplish at this stage.

From experience of the above régime Waller concludes that " if the start of breast feeding can be made easy and painless, and the woman saved anxiety about her capacity to succeed, and given the assurance that her baby is thriving, she will not lightly give up ".

Insufficient lactation is evidenced by the child crying before and after its feeds, and being restless and fretful ; the reason for which is confirmed at the test-feed. The management of such a case will be along the following lines :—

a. General treatment : The intake of fluids is increased.

As yet the giving of galactogogues, apart from their psychological value, is still in the experimental stage. The avoidance of worry and encouragement to the mother are probably the most important factors.

b. Local treatment : Massage of the breasts for 10–15 minutes should be carried out night and morning when the gland has been emptied : hot and cold applications may be tried alternately for 30 seconds about 15 minutes before the feed.

c. Finally, *Abt's electrical breast pump* has given very satisfactory results in hospital cases.

The treatment of engorgement of the breasts is directed chiefly to relieving the pain, which is usually achieved by the application of large hot fomentations supported by wool and bandage. This may be accompanied from time to time by the stroking of the breasts with warm oil, in the direction of the nipple, and the giving of synthetic œstrogens.

FAILURE OF LACTATION

Although a failure of lactation can be attributed to a number of causes, the most important of these is an initial incapacity of the breast itself. Hormonal deficiency may have failed to promote a sufficient development of the mammary tissue during pregnancy or, alternatively, the pituitary gland may fail to play its part in establishing and maintaining lactation. The thyroid gland is also involved, and a lack of thyroxine may be partly responsible for deficient lactation, as well as other factors not yet understood. Of these causes, an insufficiency of œstrogen or of thyroxine are the only conditions amenable to treatment.

Œstrogen.—How œstrogens promote lactation is uncertain, but, possibly, small doses stimulate the pituitary gland to yield the necessary hormones. This action is reversed by larger doses and lactation is consequently suppressed. It seems likely that the variations in response are due to individual differences in the threshold between stimulant and suppressive doses of œstrogens. In some of the experiments on cows (Hammond and Day, 1944) failure was attributed to the persistence of corpora lutea from which, presumably, enough progesterone was produced to suppress the action of the pituitary gland.

Folley and his colleagues have shown that virgin goats can be made to lactate profusely by the inunction of stilbœstrol into their udders. Later, the implantation of pellets of synthetic œstrogens into heifers and dry cows, or their administration by mouth, was found to produce lactation, but in none of the experiments was any relationship noted between the yield of milk and the dose administered. Numerous workers have confirmed and extended these observations in various mammals.

An œstrogen deficiency in women may be indicated by lumpy, tender, and engorged breasts. If sufficiently large doses of œstrogen are given to inhibit lactation temporarily, the state of the mammary tissue is improved and comfortable lactation can be expected to follow cessation of treatment.

Prolactin.—The role of prolactin in lactogenesis and galactopoiesis is not precisely known, but this hormone does not appear to play the important and specific part hitherto assigned to it.

While prolactin, when highly purified, is almost certainly useless, the possible ill effects of crude extracts emphasize a need for caution. Moreover, the recent work of Margaret Robinson (1943, 1947) has shown that the daily milk yield of lactating women is not increased by the use of even crude extracts of the anterior pituitary gland of oxen.

Clinical reports on the use of prolactin in women have been contradictory, but a study of both the " successful " and " unsuccessful " series of cases is not encouraging, and at present no indications appear to exist for the use of prolactin or any other pituitary preparation.

Thyroxine.—For some years it has been known that the administration of thyroxine increases both the yield and the fat content of the milk of cows. Thyrotropin from the anterior pituitary gland has the same effect.

The practical difficulties of exploiting this knowledge have been largely overcome by the discovery that the iodinization of proteins rich in tyrosine, such as casein, produces substances possessing the biological action of the thyroid hormone and from which thyroxin can be isolated after hydrolysis. Iodo-casein is cheap to produce and has a useful galactopoietic effect.

Further observations, however, have shown that more satisfactory results can be obtained by giving Lugol's iodine solution in a daily dosage of 12 drops. This procedure is based on the hypothesis that an iodine deficiency rather than a defective thyroid gland is responsible for a lack of thyroxine. The use of iodine in this manner is inadvisable if the breasts are tender and 'lumpy'. If under these circumstances stilbœstrol, 5 mg. 4-hourly, is given, the breasts can be rendered soft, when iodine will increase the output of milk without a return of engorgement.

SUPPRESSION OF LACTATION

Although, as already mentioned, the exact manner of action of œstrogens is still a matter of doubt, their use for the suppression of unwanted lactation has become established. Of the many synthetic varieties now invariably used none, so far, appear to have any real advantage over the original stilbœstrol. This is usually given in a dosage of 5 mg. t.d.s. for one day and thereafter in decreasing doses for a further two or three days, although a few women may need a somewhat larger dose. A return of secretion can at once be arrested by a further course of treatment. If stilbœstrol causes nausea and vomiting, this should be taken as an indication for a smaller dose, which will as a rule prove effective.*

On the assumption, perhaps an incorrect one, that œstrogens suppress lactation through action on the anterior pituitary, androgens have been tried for the same purpose. Although possessing the advantage of not causing unpleasant symptoms, the suppression of lactation is effective in a much smaller proportion of women. Usually a course is recommended of 5 doses of 25 to 50 mg. of testosterone propionate given intramuscularly, at 12-hourly intervals. It seems probable that a corresponding amount of methyl testosterone, given orally, would have a similar effect.

CRACKED NIPPLES

Cracks are found, more often in primigravidæ, at the apex or base of the nipple ; the lesion is either a small but deep fissure or a loss of surface epithelium and the formation of a raw tender area. Both types may occur together, causing exquisite pain. Insufficient colostrum in the first three days, too vigorous suction by the baby's gums, suckling too frequently or too long, and in some instances thrush, are contributory causes. Waller emphasizes the association of cracked nipples and defective protraction or mobility of the nipple.

Some cracks heal quickly, within 24–48 hours, but others become infected, and the infection is apt to extend into the mammary tissues. A deep crack may bleed readily, when the blood swallowed by the infant is usually vomited, causing concern to the mother.

At any suggestion of cracking, feeding should be limited to a few minutes six-hourly during the first two days, and the child should not be allowed to go to sleep with the nipple in its mouth. If a crack appears the affected breast is rested for 24–48 hours. When both nipples are affected suckling is held up, but the milk can be

* Ethinyl œstradiol, originally prepared in 1938, only became commercially available in England during 1948. It possesses the typical physiological and therapeutic activities of œstrogen in general with the advantage of great potency when administered by mouth. Even by this route it is the most potent œstrogen yet discovered.

When judged by its capacity to relieve menopausal symptoms, estimates of the strength of ethinyl œstradiol range from five to twenty times that of stilbœstrol, and in the suppression of lactation—according to Jeffcoate and his colleagues—at least fifty times. A dose of 0·75 to 1·3 mg. spread over a week gave good results in 21 out of 22 cases. The toxicity is probably of approximately the same order as that of stilbœstrol.

expressed by hand and given by spoon, though additional feeding will probably be necessary. The use of a breast pump, with its tendency to maintain the condition and cause pain, should be avoided. At the same time patience is required to ensure that the baby maintains an interest in suckling from the breast and does not acquire a lazy preference for the bottle.

TREATMENT.—After the customary bathing with sterilized water or boracic lotion—or, alternatively, with a 1–1000 perchloride of mercury lotion or a weak solution of flavine—before and after each feed, the nipple is covered with a sterilized dressing until the next. A fissure or excoriation can be dressed with a mercurial ointment or compound tincture of benzoin, though the latter is perhaps too sticky and apt to cause damage when the dressing is changed. Alternatively, silver nitrate is painted on the crack and the breast firmly bound up in a lying down position.

The most careful cleansing of the nipple is essential before feeding is recommenced. An easily sterilizable nipple-shield may be advisable and, if this is used, the breast should be emptied by massage rather than by a breast pump, and the child fed by spoon. (*See also* Chapter VII, p. 154.)

ACUTE INFECTIONS OF THE BREAST

The risk of acute mastitis appears to be increasing with the tendency to deal with maternity cases in hospital. Fulton's series of 8·91 per cent in 43,000 confinements showed a higher incidence among women delivered in hospital. In his opinion the following were important contributory causes:—

1. The presence of micro-organisms in cases of infection, in carriers (patients, staff, and visitors), in dust, etc., to which the newly delivered woman has not acquired an immunity.

2. The possibility that in overcrowded nursery conditions the infant acquires micro-organisms which are later transferred to the mother. Of the micro-organisms the *Staphylococcus aureus* is most commonly present, and with it may be associated *Staphylococcus albus*, *Bacillus coli*, and the streptococcus.

3. The prevailing tendency to overcrowd institutions.

4. A rigid hospital routine of feeding with unduly long intervals (often four hours) between feeds, thus encouraging stasis.

5. Mal-nourishment of the mother, which predisposes to infection.

The prevention of mastitis, which supervenes by way of stasis, engorgement, and an ascending infection, is of the utmost importance.

H. Waller stresses that cleanliness of the nipple and the measures to express the preliminary secretion are the first steps to prevent mastitis, and the control of engorgement and protection of the nipple from trauma the next. The state of the woman's health, the quality of her food, and the avoidance of severe anæmia or dental sepsis are factors of great importance.

Acute infections of the breast can occur at any period of life but are mainly associated with lactation.

The inflammation may be limited to one constituent of the breast such as the nipple (e.g., cracked nipples as mentioned above), the subcutaneous areolar tissue, the gland substance, or the retro-mammary tissue between the breast and pectoral muscle. The intra-mammary variety is by far the most common.

Infections of the Areola

The areolar glands of Montgomery are liable to cyst formation similar to sebaceous glands elsewhere. A simple cyst may require removal by dissection under local anæsthesia.

An infected cyst, which causes a superficial circumscribed inflammatory swelling near the nipple, either resolves or more commonly discharges through the skin leaving a persistent sinus. In order to clear this, the debris and cyst lining are removed under general anæsthesia.

Sub-areolar Infection of the Breast

When the connective tissue deep to the areola becomes infected, an abscess, if it forms, is superficial to the breast tissue and points under the areola. Pus is liberated through a small radial incision, after which healing, in most instances, is straightforward. Chemotherapy (penicillin) is indicated in the event of severe constitutional disturbance, which is unusual, but in any case resolution is probably hastened by its use.

Intramammary Infection

The incidence of acute infections of the breast during lactation has diminished mainly, no doubt, as a result of more routine ante-natal and postnatal care. The actual numbers are difficult to assess, since those treated at home are not recorded, and acute puerperal mastitis is not notifiable unless fever is prolonged beyond the 24 hours ; but cases, mostly sporadic, or occasionally in epidemic form, still occur. In the event of the latter, the incidence may rise to 1 in 25 of the women delivered, and among those in an institution the primiparæ are found to be mainly affected (Annual Report of the Chief Medical Officer of the Ministry of Health, 1938).

Bacteriological investigations have suggested a means of spread of infection in institutions by showing that organisms (staphylococci), similar to those in the pus of a mammary abscess, have been found in the nasopharynx of the mother, infant, and nurses, as well as in the fomites, feeding utensils, breast pumps, etc. Also a woman with mastitis who is a donor to the milk pool is a potential source of infection, since the collected milk, unless boiled, is contaminated with *Staphylococcus aureus* (Joyce Wright, 1947). Such conditions as pemphigus neonatorum and infantile diarrhœa may be conveyed to the infant in this manner.

In sporadic cases of breast infection primiparæ and multiparæ are affected in about equal numbers, and conditions of the breast itself are occasionally responsible. The cracked or fissured nipple provides a point of entry for infecting organisms, while a painful or deformed nipple which prejudices emptying of the breast, with consequent stagnation of milk, increases the chances of an infection.

An intramammary infection may assume the form of an acute puerperal mastitis or an intramammary abscess, distinguished by the mode of onset, clinical course, and treatment.

Puerperal Mastitis.—With the onset of lactation, some 3 to 4 days after childbirth, the breasts become heavy, engorged, sometimes very painful and tender, with, perhaps, a slight rise of temperature (99°–100° F.) and general malaise. Normally, any disturbance subsides after suckling for a few days.

This physiological state may be complicated by a superimposed inflammation. The recognition of this can be difficult but with the onset of puerperal mastitis, usually about the 8th to the 12th day of the puerperium, the systemic disturbance is increased, with complaint of shivering, headaches, and malaise, a rise of temperature (102°–104° F.) and increased pulse-rate. Apart from a general engorgement, one area of the breast becomes hard and increasingly painful and tender. As a rule one breast and one segment only is affected.

Treatment.—With conservative treatment and chemotherapy* these infections, in most instances, subside in a few days, but close

* *Staphylococcus aureus*, which is penicillin-sensitive, is the organism most commonly found in these infections. Immediately the signs of an acute infection are manifest, systemic penicillin is recommended. The dosage may be suited to the severity of the infection, but, in most cases, intramuscular injections are given 3-hourly of 60,000 units, or more massive doses of 200,000 units twice in the 24 hours. The latter produces effective concentration and is less disturbing for the patient. Sulpha drugs have not been found reliable in these cases.

observation is required during the early puerperium to note their onset and institute treatment immediately. Since with early chemotherapy the milk is rendered organism-free, feeding can and should be continued if the breasts are not too painful, but if emptying is incomplete the residue should be expressed manually or drawn off by means of a breast pump. Undue engorgement can be relieved

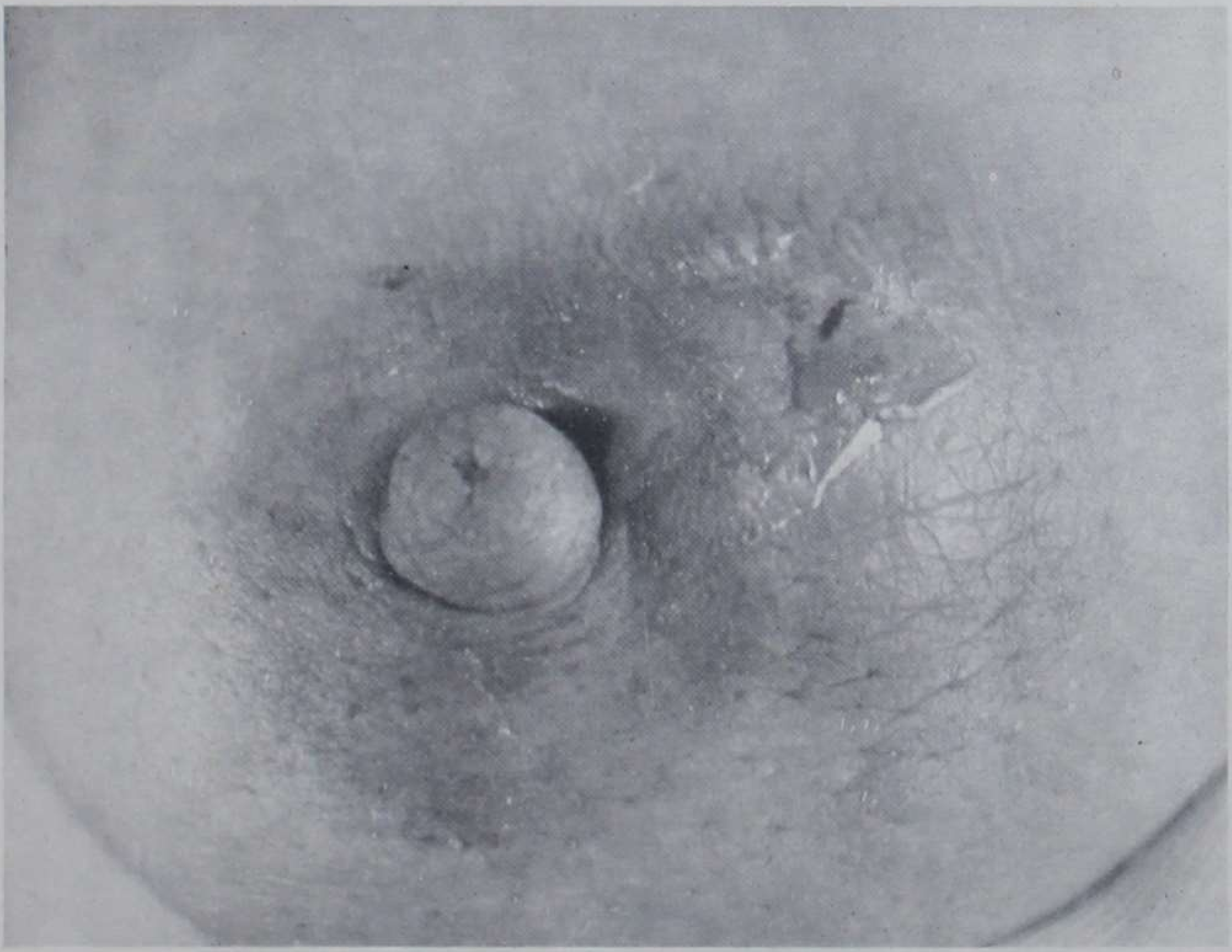

Fig. 58.—Acute suppurative mastitis after a week's treatment with penicillin. The inflammation has become localized to a superficial abscess. Note the *peau d'orange* appearance.

by stilbœstrol 1 mg. 4-hourly for 24 hours, and between feeds the breasts are elevated by a firm, comfortable support.

To sum up, the treatment of acute puerperal mastitis includes complete emptying of the breast, preferably by continued suckling, the early administration of large doses of systemic penicillin, and sedatives to ensure sleep. Apart from support for the breasts by a firm, comfortable binder, local treatment is not required. Most cases are clear of signs and symptoms in about seven days and infection does not recur, but occasionally an abscess forms (Taylor and Way, 1946).

Case.—Woman aged 32. Four weeks after childbirth (3rd child) she developed an acute inflammatory condition in the substance of the right breast. She was treated with 200,000 units of penicillin b.d. for six days, and a breast support. For emptying a pump was required. After a week the inflammation was localized to a superficial abscess (*Fig.* 58). This was drained through a small incision and healed rapidly.

The *peau d'orange* appearance seen in *Fig.* 58 should be noted. Œdema of the skin from an acute or chronic inflammation of the breast, especially the latter, may cause this appearance.

Intramammary Abscess.—The onset of an intramammary abscess varies with its site and the severity of the infection. The mother complains of discomfort and, later, pain and tenderness of the whole breast, more pronounced perhaps in one segment. The constitutional disturbance is marked—temperature 101°–105° F., and the pulse-rate raised, with, not infrequently, a rigor. The surface veins are engorged, and the breast feels heavy and is exquisitely tender, preventing suckling and emptying of the milk.

After a few days the infection becomes localized, and the skin over this part appears tense, red, and glistens with a peculiar greasy sheen. The abscess is recognized as a soft circumscribed swelling in an area of induration, but when suppuration occurs deep in the breast the whole gland is swollen and much of the breast tissue may be involved before fluctuation is evident.

TREATMENT.—

Prophylactic.—Many cases of breast infection can be attributed to lack of care in the postnatal period. Nourishing food, rest and sleep, with, if possible, freedom from worry, are essential in maintaining the health of the mother. Careful supervision of the nipples and of breast feeding are necessary in the early days of lactation in order to maintain the output of milk and prevent pooling of the secretion. Some mothers, in the early puerperium, require encouragement to continue breast feeding, especially if it is inconvenient or difficult to do so.

Established Case.—General surgical principles should be observed throughout. Rest in bed, though not always possible, is advisable and doubtless hastens recovery. Local rest to the breast is given by a well-fitting support or a firm binder.

Dry heat is applied to the affected breast by warm wool, an electrically heated pad, or an electric cradle. Short-wave diathermy is also recommended. Frequent applications of hot fomentations are disturbing and interfere with sleep. Sedatives are prescribed for the relief of pain and to promote sleep; morphine may be necessary in some cases.

To avoid stagnation of milk, the affected breast is emptied by means of the breast pump, while the flow is maintained by suckling from the other side, and in this way the baby suffers no ill effects. When the abscess has healed, normal feeding is resumed from both sides, but if the infection has occurred late in the postnatal period near weaning time, the suppression of lactation by œstrogen is advisable. The dosage of stilbœstrol should be prolonged and reduced gradually, otherwise the breasts will soon fill again.

To suppress the flow, stilbœstrol 5 mg. 4-hourly is given for three days, followed by 5 mg. 8-hourly for a further three days.

Chemotherapy : Penicillin, as a result of its specific action on the *Staphylococcus aureus*, decreases the general constitutional symptoms, and in some cases, as in puerperal mastitis, may abort the local infection and promote resolution, or in the early stages aid localization and early abscess formation. Local penicillin alone is insufficient ; systemic administration in addition to local surgical measures is essential. The injections should be continued for the full course, as the patient's improved general appearance under chemotherapy may belie the state of the focus of infection. (*See* footnote, p. 78.)

When an abscess has formed, it can be treated by aspiration followed by the instillation of penicillin. Repeated aspirations are tedious, uncomfortable, and usually end in a discharging sinus. In practice, once an abscess is evident it should be opened and drained. Under general anæsthesia and the usual aseptic precautions a radial incision (1–2 cm.) is made with a narrow-bladed scalpel or tenotome over the centre of the abscess, avoiding the nipple area and subsequent painful scars. After division of the subcutaneous tissues pus will be liberated and a specimen should be taken for bacteriological examination. When most of the pus has drained out, the skin at the periphery of the abscess is gently pressed, when any residual exudate and a few small sloughs are expelled through the opening, and larger sloughs can be removed by means of sinus forceps. Insertion of a finger into the abscess cavity " to break down septa " is unnecessary and harmful, as uninfected tissue is thus exposed to infection, and the radial interlobar blood-vessels, causing perhaps troublesome hæmorrhage, are needlessly damaged. A minimum of interference inside the abscess cavity encourages rapid healing and restoration of function.

A small length of rubber drain is inserted, the wound dressed with sterile gauze smeared with penicillin cream or acriflavine, covered generously with wool, and bandaged. The tube is removed after 48 hours, and usually healing is rapid and the wound dry in about two weeks. The breast should be re-examined at intervals in case of any residual infection.

COMPLICATIONS.—A *recurrence of inflammation*, or a *secondary abscess*, may occur at the same or another site—rarely on the opposite side—weeks or even months after the initial infection. A *residual mastitis*, persisting possibly for some years, with brawny induration and œdema of the skin, very occasionally follows an acute infection. Sometimes such a condition is localized to the dilated ducts immediately deep to the nipple, causing redness and œdema, and eventually perhaps, some retraction of the nipple.

Such complications are for the most part the result of either inadequate drainage or, nowadays, of insufficient dosage of penicillin for too short a time, or the use of sulpha drugs which are not so effective. Also a 'dried-up' breast, necessitating too early weaning, is apt to become re-infected.

Treatment is the same as for the primary condition, with the addition, in the case of residual mastitis, that a biopsy may be required to determine the nature of the tissue.

Axillary lymphadenitis is liable to occur at any stage of a breast infection but in many cases subsides with treatment of the breast lesion. If suppuration follows, drainage in the usual manner will be required.

A *milk fistula* develops in some cases when the discharge of pus is followed by a persistent flow of milk from the wounds; the continuation of the breast feeding, after subsidence of the inflammation, usually arrests the discharge. If this does persist, as a last resort the administration of a lactostatic drug will be needed.

Persistence of wound infection is usually due to the introduction of secondary organisms into the wounds; each case is treated on its merits.

Secondary hæmorrhage is rare, but can occur, especially if the breast tissue is damaged by too extensive surgery.

Severe scarring can cause retraction of the nipple, and thus making subsequent breast feeding difficult.

AFTER-RESULTS.—With attention to detail of treatment of breast abscesses in the first instance and as little disturbance to the breast tissue as possible, healing will readily occur. After a time the site of the lesion becomes indiscernible except for a small surface scar, and breast feeding after subsequent pregnancies will be unaffected by a previous breast abscess, a point on which the mother can be reassured.

GALACTOCELE

A galactocele, a rather uncommon complication of lactation, is the result of blockage of the excretory ducts by scarring or local inflammation. This may happen in the second or third month of normal lactation or when the milk has been scanty from the beginning. The milk secretion collecting in a loculus and rapidly increasing in amount causes an obvious rounded swelling in the breast recognizable by the size and smooth tenseness of the walls (*Fig.* 59), with

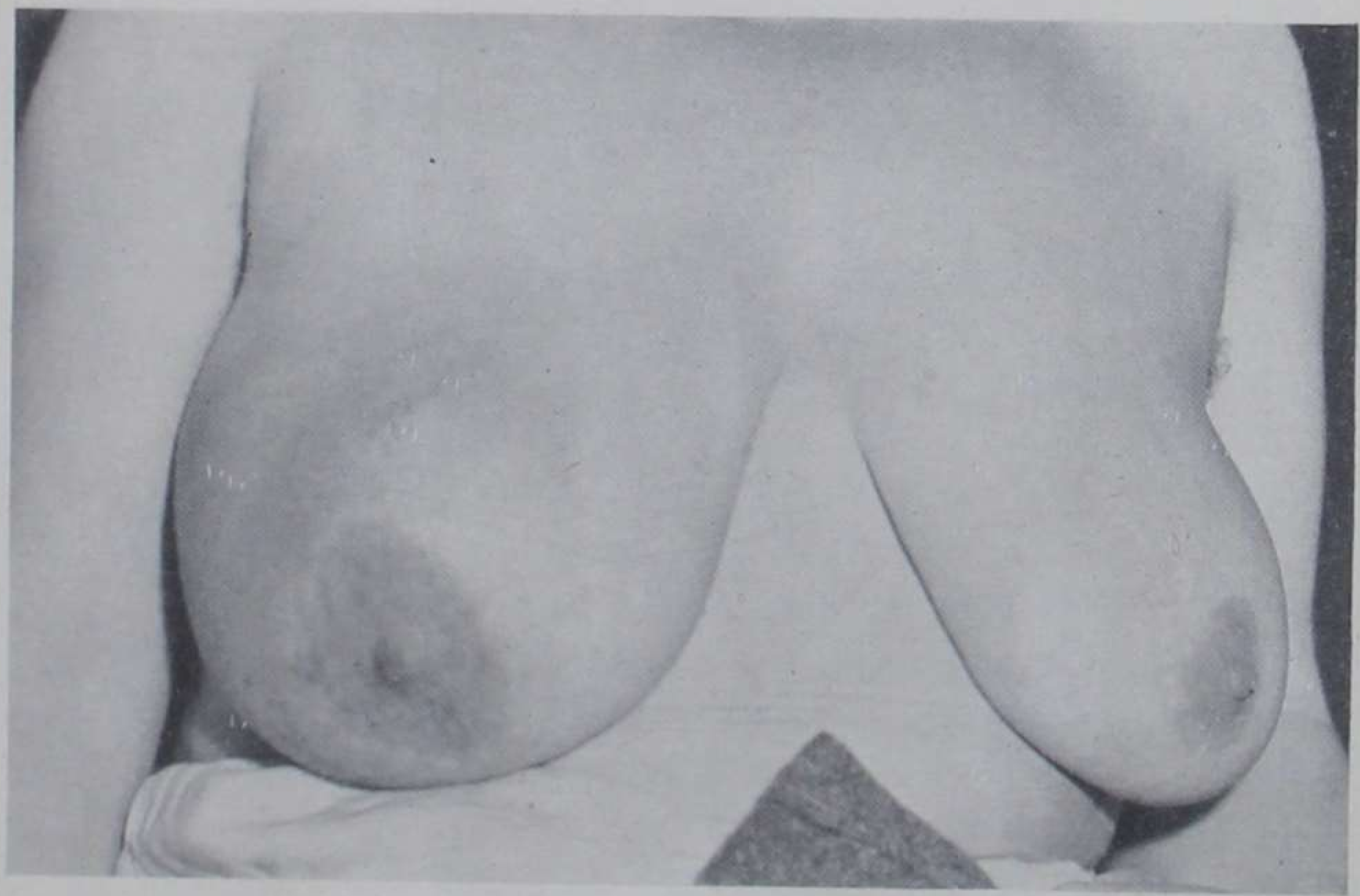

Fig. 59.—Galactocele of right breast in a woman aged 27. Normal lactation of both breasts. Swelling in right breast 2 months after confinement. Treated by aspiration.

occasionally subsidiary swellings close to or separate from the main collection.

Treatment.—A galactocele should be treated by aspiration, and though the fluid may re-collect, repeated aspiration is usually successful. A varying quantity, up to several ounces, of a thin milky serum is drawn off, and, if desired, penicillin is injected into the cavity. Afterwards the breast should be supported and very slightly compressed by a pad and bandage or strapping.

Coloured or thickened fluid may be indicative of infection when the condition has become, in effect, an intramammary abscess. Aspiration of the infected fluid, however, and partial replacement by penicillin, a procedure which is repeated if necessary, may be sufficient to initiate resolution and eventual clearance.

If aspiration is unsuccessful after two or three attempts, the cyst is exposed through a small incision, opened, and a tube inserted for about 48 hours. When this has to be done stilbœstrol should be given to arrest secretion and avoid the formation of a milk sinus.

A galactocele can be associated with or confused with a malignant state. An account of a rare case of this type is given in Chapter X.

GALACTORRHŒA

As the name implies, galactorrhœa is a persistent discharge of milk or milky serum from one or both breasts. Gårdlund (1916) found that 46 per cent of 400 women were still secreting milk a year or more after weaning, some 20 per cent at the menopause, and 15 per cent of women who had not borne children. Geschickter's figure of 2–4 per cent of adult women with persistent lactation is probably more correct for England and the U.S.A. Grunbaum (1907) reported that milk was present in the breasts of 14 out of 21 women who had been recently castrated.

In Geschickter's view the secretion of milk is due to a fall in the output of œstrogen, with, consequently, a withdrawal of pituitary inhibition. It seems certain that sometimes this is true, as at the menopause or after castration. This explanation does not, however, account for those cases in which lactation continues for many years. In the condition known as Chiari and Frommel's disease, persistent lactation is associated with ovarian and uterine atrophy. A fall in the output of œstradiol may be assumed, but an explanation is still required of the failure of the pituitary gland to adjust itself to the new level of circulating œstrogen.

Galactorrhœa is symptomless, and mainly embarrassing rather than harmful. The breast is normal in appearance and to touch, and without evidence of infection, which has been mentioned as the cause. In most cases persistent lactation eventually ceases by itself, and apart from scrupulous cleansing of the nipple no treatment is indicated. Drugs such as stilbœstrol will, in a number of instances, arrest the discharge, though this is apt to return as soon as treatment is stopped. Stilbœstrol is usually given at first in a high dosage of, say, 5 mg. t.d.s., and the dosage gradually reduced over a period of weeks. In some cases œstrogens prove entirely ineffective.

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CHAPTER III

ABNORMALITIES OF STRUCTURE AND FUNCTION

By L. R. Broster and Raymond Greene

I. FAILURE OF BREAST DEVELOPMENT

Failure due to Hypogonadism: Hypomastia.—Abnormal smallness of the breasts may be associated with the general stigmata of hypogonadism—the eunuchoid figure, deficient growth of pubic and axillary hair, and hypoplasia of the uterus.

In the class of general hypogonadism, treatment by means of œstrogens is usually successful in producing a nearly normal development of the breasts (*Figs.* 60, 61). The treatment of hypomastia is, in fact, the treatment of hypogonadism.

Failure due to Insensitivity of Breast Tissues.—Hypomastia may be a single abnormality in an otherwise normal physical make-up. In such cases it is assumed that the breasts, for a reason not yet known, are less than normally sensitive to the growth-promoting activity of the ovarian secretions.

In this class of local insensitivity to œstrogenic stimulation, the results of treatment with œstrogens are far less satisfactory. Attempts to 'boost' a normal output from the ovaries by general treatment either orally or parenterally are usually unsuccessful, presumably because the resulting pituitary suppression causes a diminution in the endogenous production of œstradiol. Local treatment has not the same theoretical objection, and is in practice more efficacious. An ointment containing an œstrogen is applied daily to the breasts, the amount needed being usually in the neighbourhood of 1 mg. to each dose. Results may be improved by the inunction also of an ointment containing progesterone, the dose being approximately 5 mg. daily. In many patients the results are disappointing or, in those in whom it is effective, only temporary.

Failure due to Intersexuality.—Failure of breast development is sometimes an expression of intersexuality, in which characteristics of the opposite sex are superimposed on the normal ones. A striking example of this is Group 1 (prepuberal) virilism due to bilateral adrenocortical hyperplasia in which the cells take up the fuchsin stain and a marked excess of androgens is found in the urine. In these cases the breasts either fail entirely to grow or remain rudimentary and there is an associated primary amenorrhœa. A moderate degree

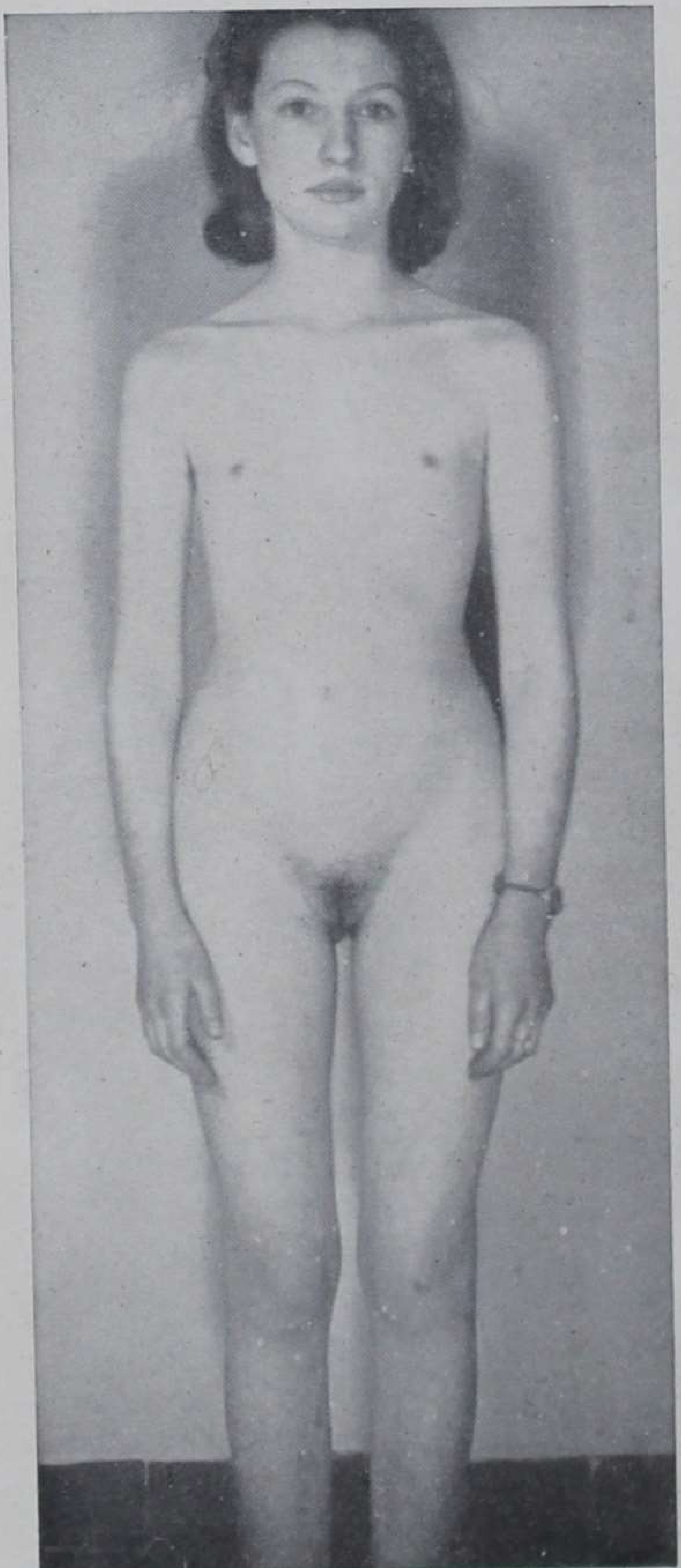

Fig. 60.—Hypomastia in a case of hypogonadism, before treatment. (*Figs.* 60–62 *from Greene's 'Practice of Endocrinology', Eyre & Spottiswoode.*)

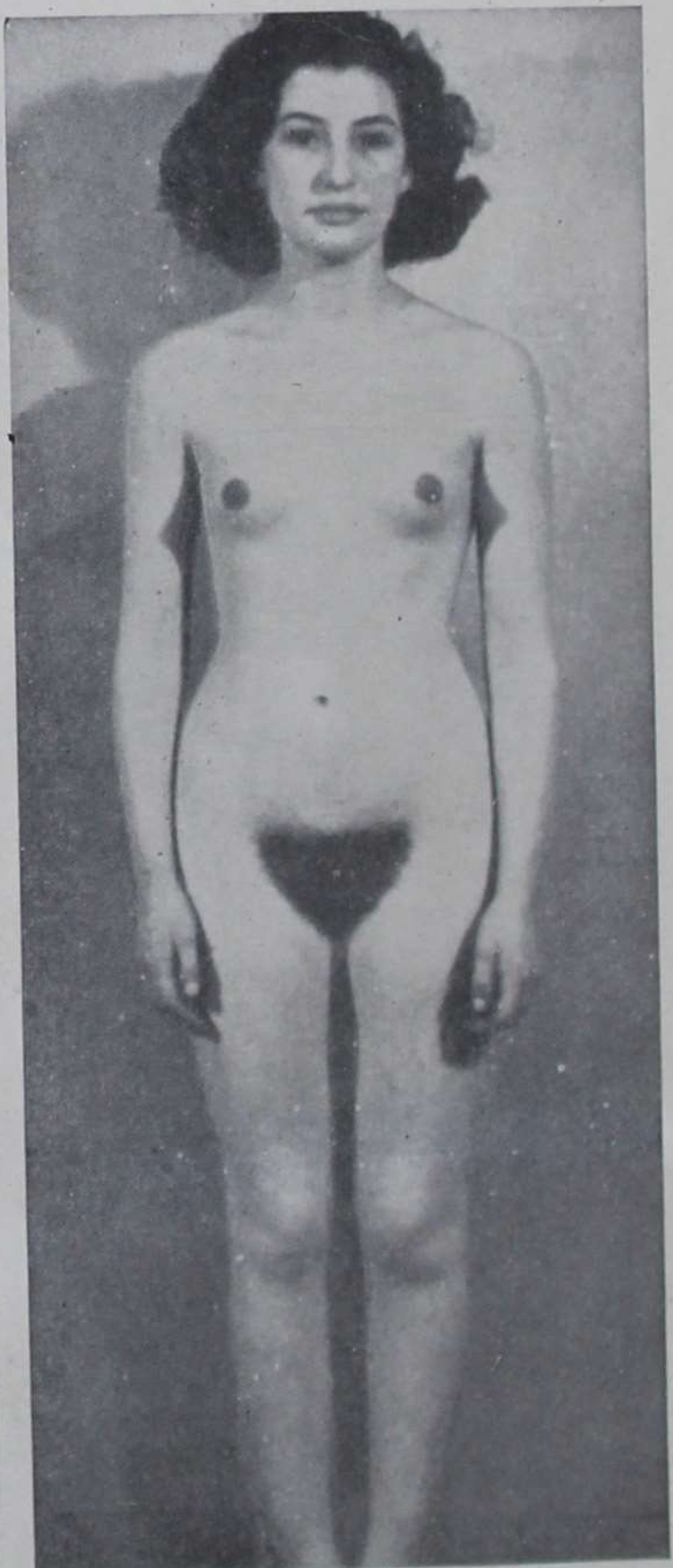

Fig. 61.—The same case after treatment by œstrogens.

of growth can be stimulated, in some cases, by the administration of stilbœstrol, implants of œstradiol, or unilateral adrenalectomy.

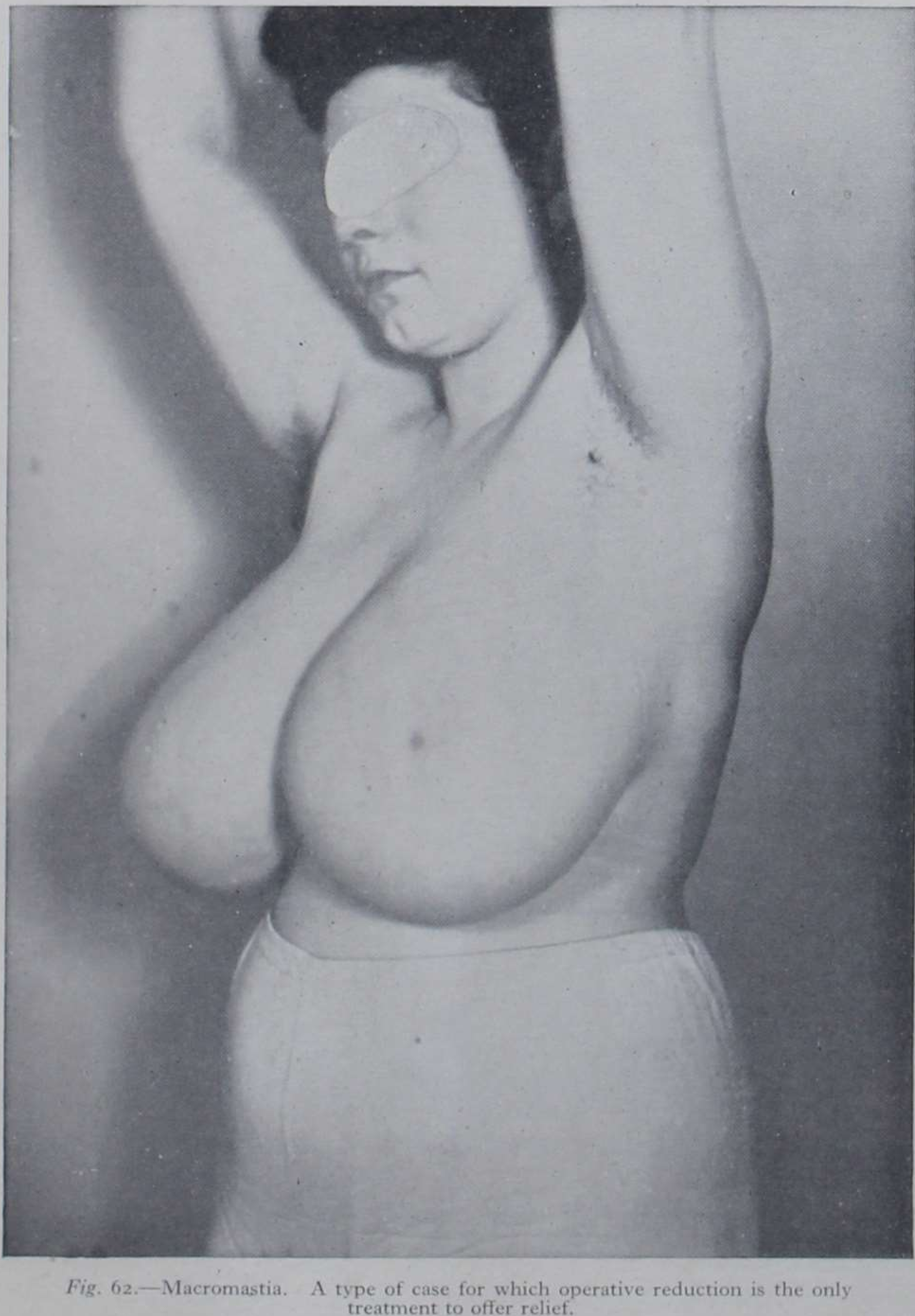

Fig. 62.—Macromastia. A type of case for which operative reduction is the only treatment to offer relief.

The same principle holds true in Group 2 virilism, when, after a varying period of normal feminine development from puberty, a similar syndrome starts. With the onset of the condition the growth of the breasts may be retarded or may actually regress. Unilateral adrenalectomy lowers the urinary androgens by 50 per cent and may at least temporarily improve the tone of the subcutaneous tissue and general contour of the breasts.

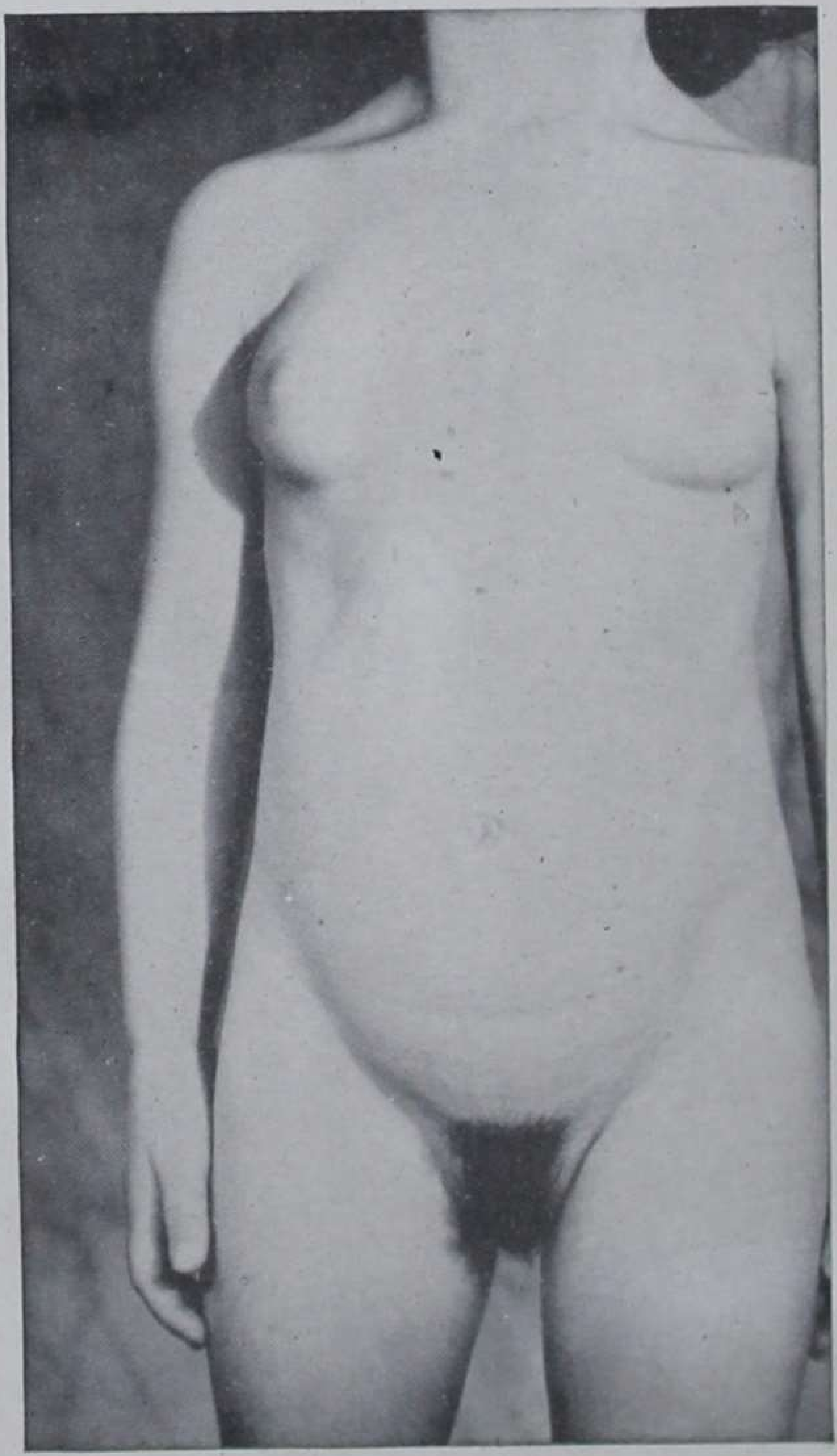

Fig. 63.—Precocious puberty in a girl of 5.

II. EXCESSIVE BREAST DEVELOPMENT

Macromastia.—Simple macromastia may occur without any general endocrine disturbance. Occasionally the breasts become enormous (*Fig.* 62) and cause considerable discomfort by their sheer weight. In such cases a plastic reduction of the breast is the only treatment of any avail (*see* Chapter XII).

III. PREMATURE BREAST DEVELOPMENT

A. CONSTITUTIONAL PRECOCITY

This group, by far the largest, is sometimes difficult to distinguish clinically. There is no demonstrable cause and the prognosis is good. Novak calls this the constitutional or genetic type and considers that early puberty is an example of biological scatter. Children in this group start by growing faster than is normal (*Figs.* 63, 64), but eventually are below the average height. They differ from the patients whose precocity is due to ovarian tumours in that true ovulatory menstruation occurs. This accounts for the extraordinary and rare cases of pregnancy in young girls which are reported from time to time. An adult woman of this type, married to an achondroplastic dwarf, conceived and was delivered by Cæsarean section of a daughter who at the age of 12 was apparently a normal girl in size and development.

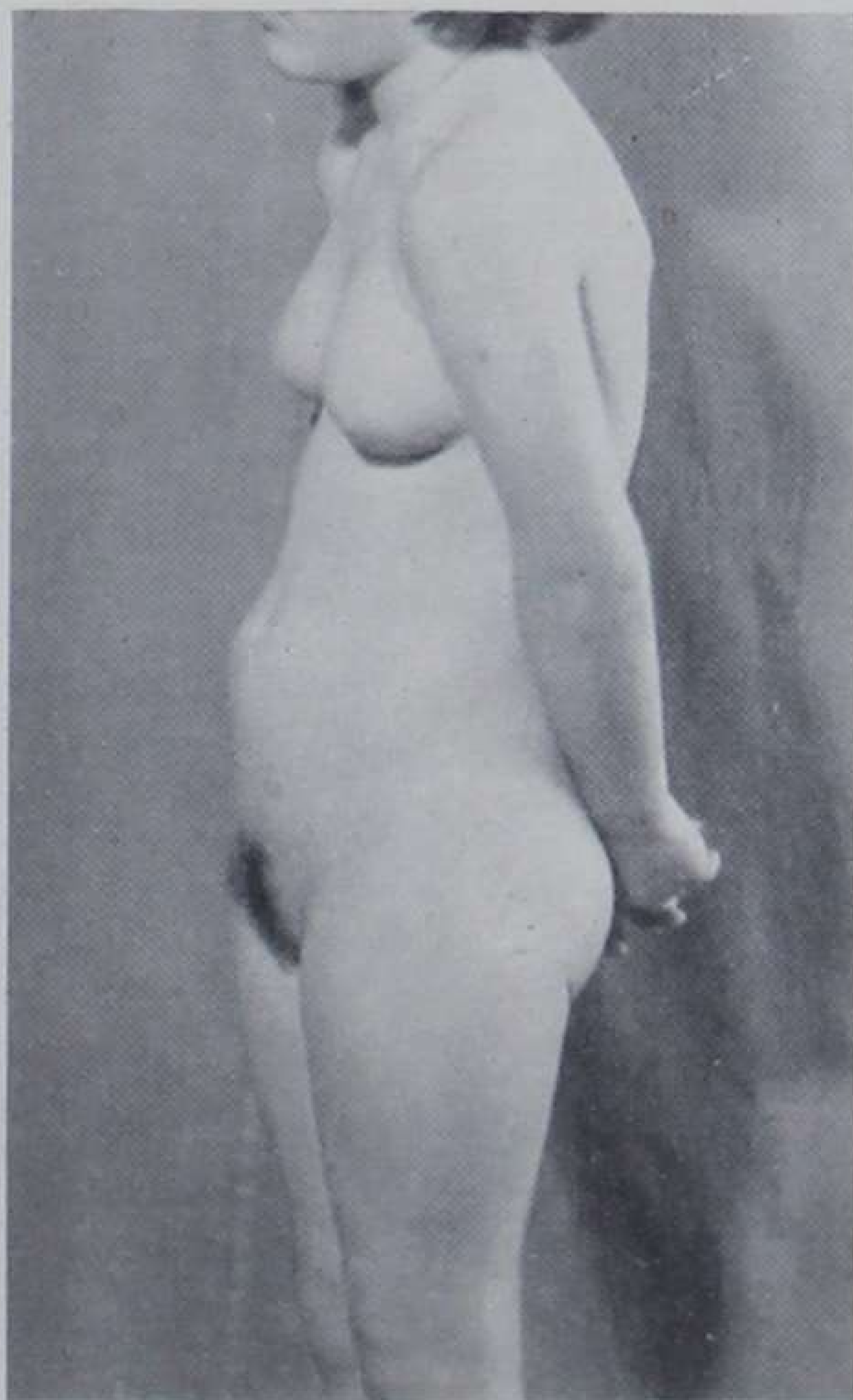

Fig. 64.—Precocious puberty in a girl of 7.

B. PATHOGENIC PRECOCITY

A rare type of abnormality is an isosexual precocity of young girls which may occur as a result of several different pathological conditions. In these cases the breasts develop prematurely in conformity with early maturity of sex and its function. These cases of precocity due to disease usually have a bad prognosis as a result of the pathological lesion itself or of some intercurrent malady to which a special liability seems to exist.

1. Precocity due to Adrenal Tumour.—Isosexual precocity can occur in either sex as the result of an adrenocortical carcinoma which, it should be emphasized, may arise in a solitary adrenal gland. From this children develop the plethoric ruddy complexion and trunk adiposity of the Buffalo type—the so-called 'brewers' draymen'. Operation is useless, and indeed fatal, when the absence of the other adrenal gland has been established by a laparotomy.

Three different clinical types of abnormal breast development due to adrenal hyperplasia are found in girls : (1) The type described above, with adult breasts ; (2) The typical postpuberal virile type, with small breasts ; (3) The intersex prepuberal virile type with no breasts. (In one case a tumour weighing 6 lb. was found and the colossal amount of 2000 units of androgens was excreted in the urine per diem. Death occurred in coma due to hypoglycæmia.)

In the male adult an adrenocortical carcinoma may produce feminizing symptoms with enlarged breasts and hypertrichosis.

2. Precocity due to Granulosa-cell Tumours of the Ovary.—These tumours of the ovary are derived from the granulosa cell rests left over from the formation of the follicular apparatus and are either benign (adenomata) or of low-grade malignancy (carcinomata). The tumours produce female hormone in excess, exert a strongly feminizing influence, and, in children, occasionally cause an isosexual precocity. Œstradiol is increased in the blood and decreases after removal of the tumour, but a recrudescence of symptoms follows the occurrence of secondary deposits. E. Novak has reviewed a number of these cases. The breasts are enlarged. Pseudo-menstruation occurs ; in other words the menses, which start at an early age, are anovular. The breasts remain unduly large after removal of the tumour. A similar effect is produced by cysts of the ovary lined by granulosa or theca lutein cells which secrete œstradiol.

Geschickter regards abnormality of the pituitary gland as the cause of the abnormality of the ovary. He reports that a positive Friedman test, gonadotropic hormone in the urine, and increased eosinophils in the pituitary have been found in some of these cases.

3. Precocity due to Hypothalamic Tumour.—The signs of precocity in these cases are similar to those already described. The main difficulty is one of diagnosis, since no satisfactory endocrine test is available, neurological symptoms are conspicuous by their absence, and the urinary androgens are normal (1·5–3·0 mg. a day). The author (L. R. B.) has seen several children of this description, ranging mainly from 3 to 8 years of age. The youngest, however, was a girl of nine months with downy hair on the pubis and enlarged breasts. Menstruation occurred at 3, 6, and 9 months. The child showed intelligence, was vigorous and active, could stand up, and attempted to talk.

The explanation of precocious puberty associated with hypothalamic lesions lies in the control which the hypothalamic exerts over the pituitary gland. Isosexual precocity, and other endocrine abnormalities, have been known to follow not only the development of hypothalmic tumours but also other diseases affecting the hypothalamus, notably encephalitis lethargica.

Cases of sexual precocity associated with a tumour of the pineal body have also been described; this exerts its influence probably by pressure on the hypothalamus rather than by any intrinsic activity of the tumour itself.

The exact area of the hypothalamus which controls the output of gonadotropic hormones has not been located with certainty. In David Flicker's case of precocity in a girl of 3, a cyst was present in the third ventricle and was removed by operation. Four years later the breasts had enlarged only slightly, but the genitalia and hirsuties had assumed adult proportions.

4. **Albright's Syndrome.**—This excessively rare syndrome occurs in both sexes and is characterized by localized osteitis fibrosa, skin pigmentation, and precocious puberty. When it occurs in girls the breasts are abnormally enlarged. Falconer, Cope, and Robb-Smith have described a male patient with signs of feminism, including gynæcomastia.

IV. GYNÆCOMASTIA

Swelling of the breasts of male infants is recognized as fairly common, and is ascribed to the influence of the female hormones of the mother circulating in the fœtal blood. Cases of lactation from the male infant breast have been described.

A slight enlargement is not uncommon at puberty (*Fig.* 65). Appearing from the 13th to 16th year it should have regressed by the 17th and persistence after this may be accompanied by a mild degree of feminism. A sudden increase in the circulating testosterone, or of œstrogens, is regarded as a possible but incomplete explanation of this enlargement, and it is suggested that as the breasts normally become less sensitive as age advances the swelling regresses. On the other hand a few are benefited by androgenic treatment.

Gynæcomastia, by which is meant a true hypertrophy of mammary tissue as apart from an enlargement due to a deposit of fat, a dermoid cyst or neoplasm, is not a common condition. In the U.S. Army Karsner found 16 cases per 100,000 men. In this series 12 out of 284 were bilateral; in the remainder the two sides were affected with the same frequency. Equal sensitivity of the two sides to circulating hormones is, as has been mentioned, the exception rather than the rule.

Cases of gynæcomastia fall into two main groups; (1) Cases in which there is an obvious testicular abnormality; (2) Cases in which no such abnormality is found. (*Figs.* 65, 66.)

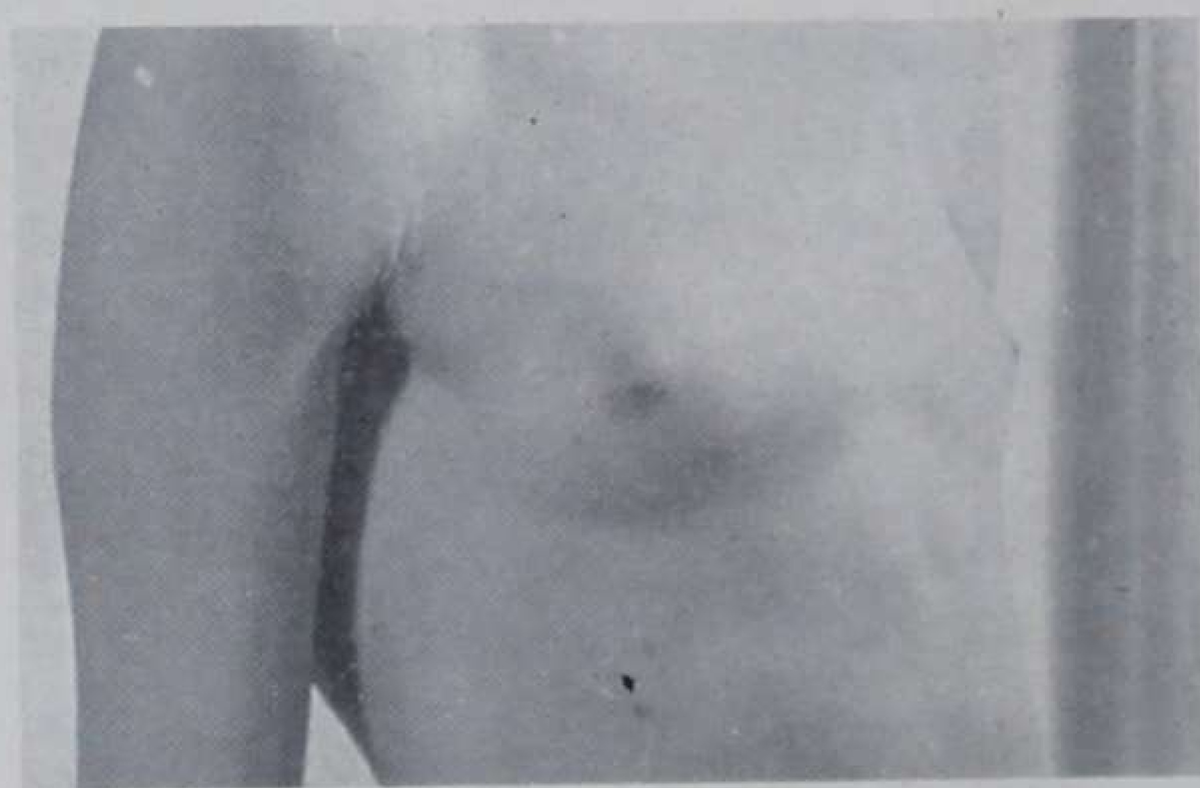

Fig. 65.—Gynæcomastia in a boy of 15.

1. In the first group testicular neoplasia, atrophy, and orchidectomy are included. Of the neoplasms, teratomata are the most common, followed by chorion-epitheliomata and carcinomata. Mammary hypertrophy has also been reported in association with atrophy of

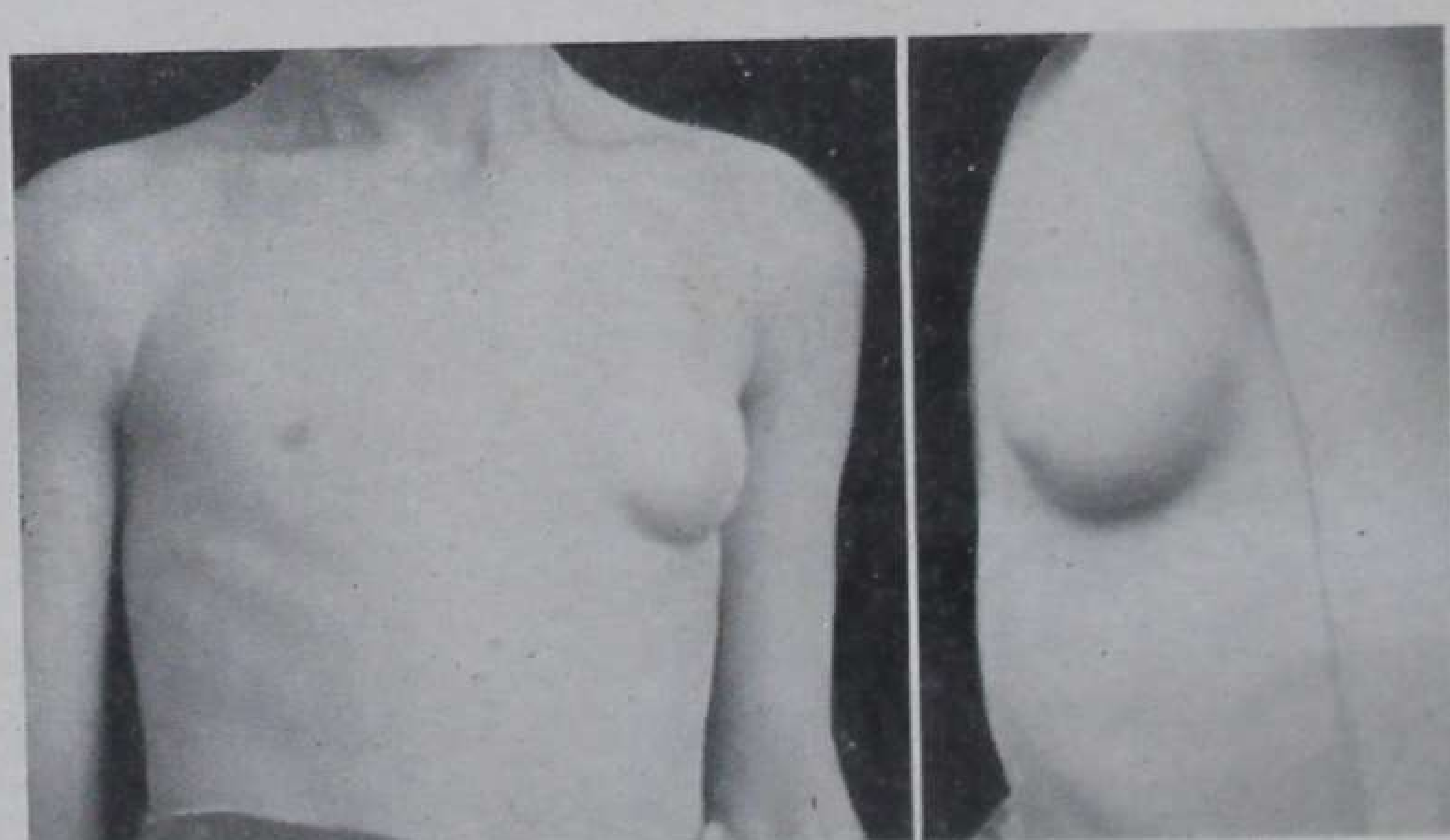

Fig. 66.—Unilateral gynæcomastia. (*Mr. D. Levi's case.*) (*By kind permission of 'The Lancet'.*)

the testicles from various causes such as trauma, epididymitis (B. Kriss), mumps, orchitis (L. Lereboullet), pulmonary tubercle (Woodham), and lesions of the central nervous system. A case after damage to one testicle during an operation for hernia has also been reported.

Klinefelter and others have reported a series of nine cases of gynæcomastia associated with varying degrees of androgenic deficiency, aspermia, and an increased output of urinary follicular stimulating hormone. In some of the cases biopsy disclosed hyalinization of the seminiferous tubules with normal Leydig cells. The authors suggest that this syndrome arises through deficiency of a hormone secreted by the seminiferous tubules, possibly an œstrogen. An unexplained increase in the œstradiol–testosterone ratio seems, perhaps, more likely, especially as the administration of œstradiol aggravates the condition.

2. In the second group are included cases of gynæcomastia without obvious testicular abnormality or endocrine disturbance of any kind, although investigation might disclose that a number, certainly not all, are suffering from Klinefelter's syndrome (J. L. Richardson). Gynæcomastia is reported in cases of neoplasm elsewhere than in the testicle, e.g., teratomata (M. Elzas), renal hypernephroma (B. Kriss, 1930), and adrenal cortical tumours. The latter do not commonly cause changes in the breasts, though the rare feminizing tumours may do so. Also gynæcomastia has been observed during the treatment of Addison's disease with cortical extracts which contain, probably, substances of œstrogenic and androgenic activity. Its occurrence after the administration of synthetic desoxycortone is more difficult to explain (R. D. Lawrence).

Gynæcomastia has been reported in one case of Graves' disease (Starr), which could perhaps be explained by liver deficiency associated with thyrotoxicosis (*see below*), and in a number of cases of leprosy (N. P. Jewell and Kauntze). Another curious group of cases has been ascribed to liver deficiencies as the result of nutritional disturbance in which the condition was corrected on a return to normal diet (R. E. Hibbs, and G. Klatskin, W. T. Salter, and F. D. Humm). In some 10 per cent of men 20 to 30 years of age in a Japanese prison camp, a transitory gynæcomastia was noted. Of the cases in whom the condition persisted for a time after release, enlargement and impaired function of the liver was found in over a third of the cases and atrophy of the testicle in a rather lesser number (G. Klatskin, W. T. Salter, and F. D. Humm).

Cases have been reported in association with acute hepatitis (H. Gilder and C. L. Hoagland) and cirrhosis of the liver. Diminution of liver function, whether from disease or malnutrition, appears to permit an excess of œstradiol to accumulate in the circulation, with a resulting increase in the œstrogen-androgen ratio.

Gynæcomastia, then, may be the result of an excess, absolute or relative, of œstrogen, an increase in the œstradiol-testosterone ratio, or undue susceptibility of the tissue to œstrogenic stimulation.

PROGNOSIS.—This depends on the cause of the condition. If this is amenable to treatment a complete remission may be obtained. Gilbert found 9 instances of carcinoma in 47 cases of gynæcomastia. Karsner, with a far larger experience, concluded that the tendency to malignant change was negligible, and Geschickter in a study of 108 cases supported this view.

TREATMENT.—Treatment is directed to the cause, if discernible. In cases of unknown origin a trial of treatment by androgens is justifiable and occasionally successful. Methyl testosterone may be given by mouth (5 mg., t.d.s.) or testosterone propionate by intramuscular injections (25 mg. twice weekly). Surgical removal of mammary tissue, leaving the nipples intact, is required in some instances (*see* PLASTIC SURGERY, Chapter XII).

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CHAPTER IV

EXAMINATION AND DIAGNOSIS

By F. D. Saner and Anthony Green

EXAMINATION OF BREAST CASES

A routine inquiry and examination of breast cases should include :—

a. The nature of the immediate complaint, e.g., pain, alteration in the skin or size of one or both breasts, the discovery of a lump or discharge from the nipple.

b. History of injury to the breasts and its relation to the present condition : severity of the pain at the time of injury and the presence of bruising.

c. The history of cancer in other members of the family.

d. Menstruation. Irregularities of the cycle and the condition of the breasts before, during, and after the periods.

e. Pregnancy. The number or absence of pregnancies and the likelihood of an existing pregnancy.

f. Lactation. Difficulties with the nipples or with suckling. Whether one or both breasts used. History of inflammation during lactation.

g. Menopause. Age of onset and relation to present condition. Gradual or sudden cessation of periods. General disturbance.

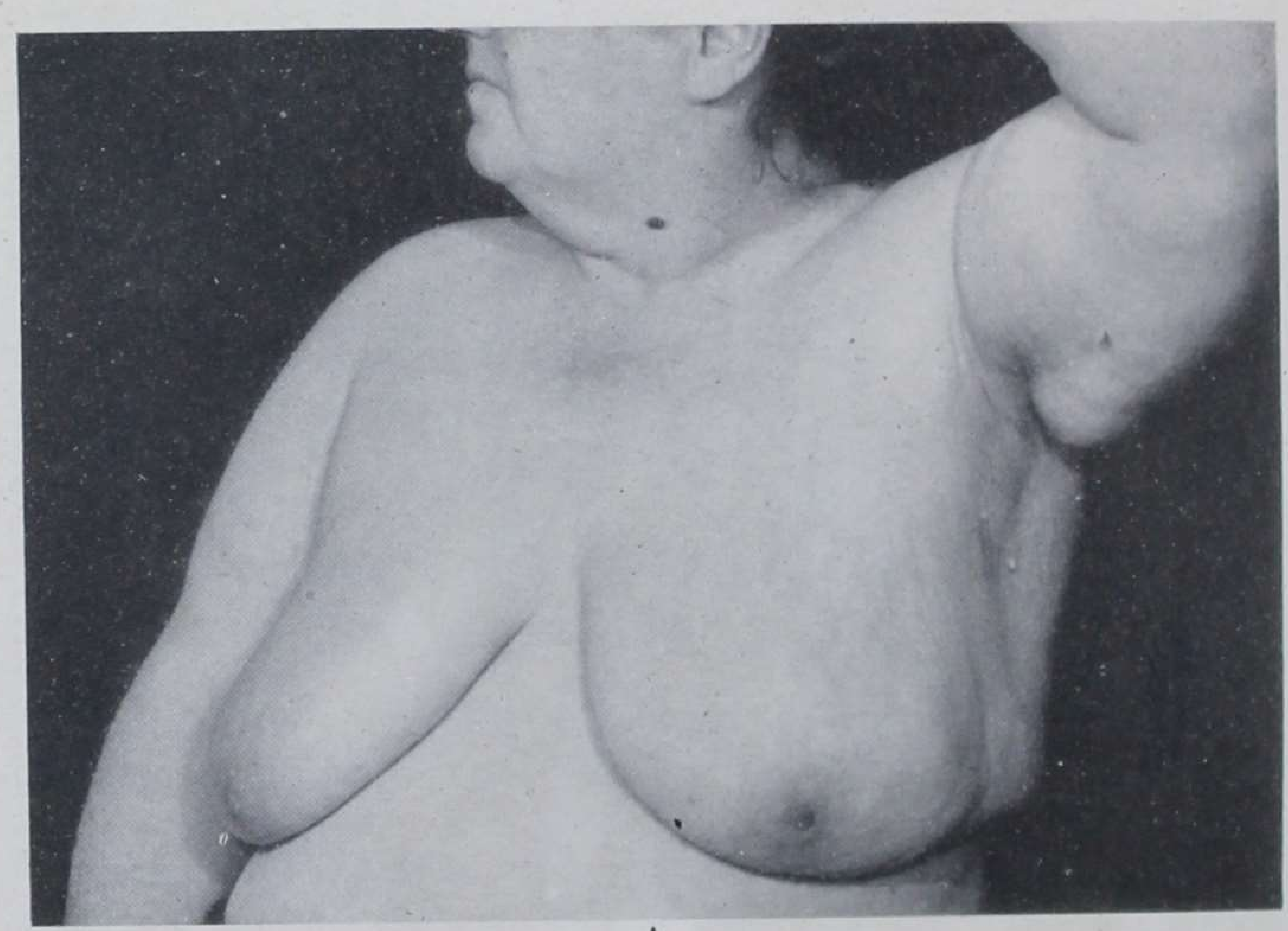
h. Previous operations. On the breast, pelvic organs, or elsewhere.

i. Complaints of cough, pain in the back or down the legs, and for how long.

j. Loss of appetite or recent distaste for any particular foods, especially proteins.

Examination of the Breast.—For examination the patient is stripped to the waist and lying down with the arms abducted from the side and elbows flexed to about a right angle. The breasts, chest wall, axillæ, supraclavicular regions, and neck can then be visualized and palpated.

In a full light comparison is made of the size and contour of both sides, the condition of the skin, of the surface veins, and of the under-surfaces of the breasts. An area of œdema, the raising or discoloration



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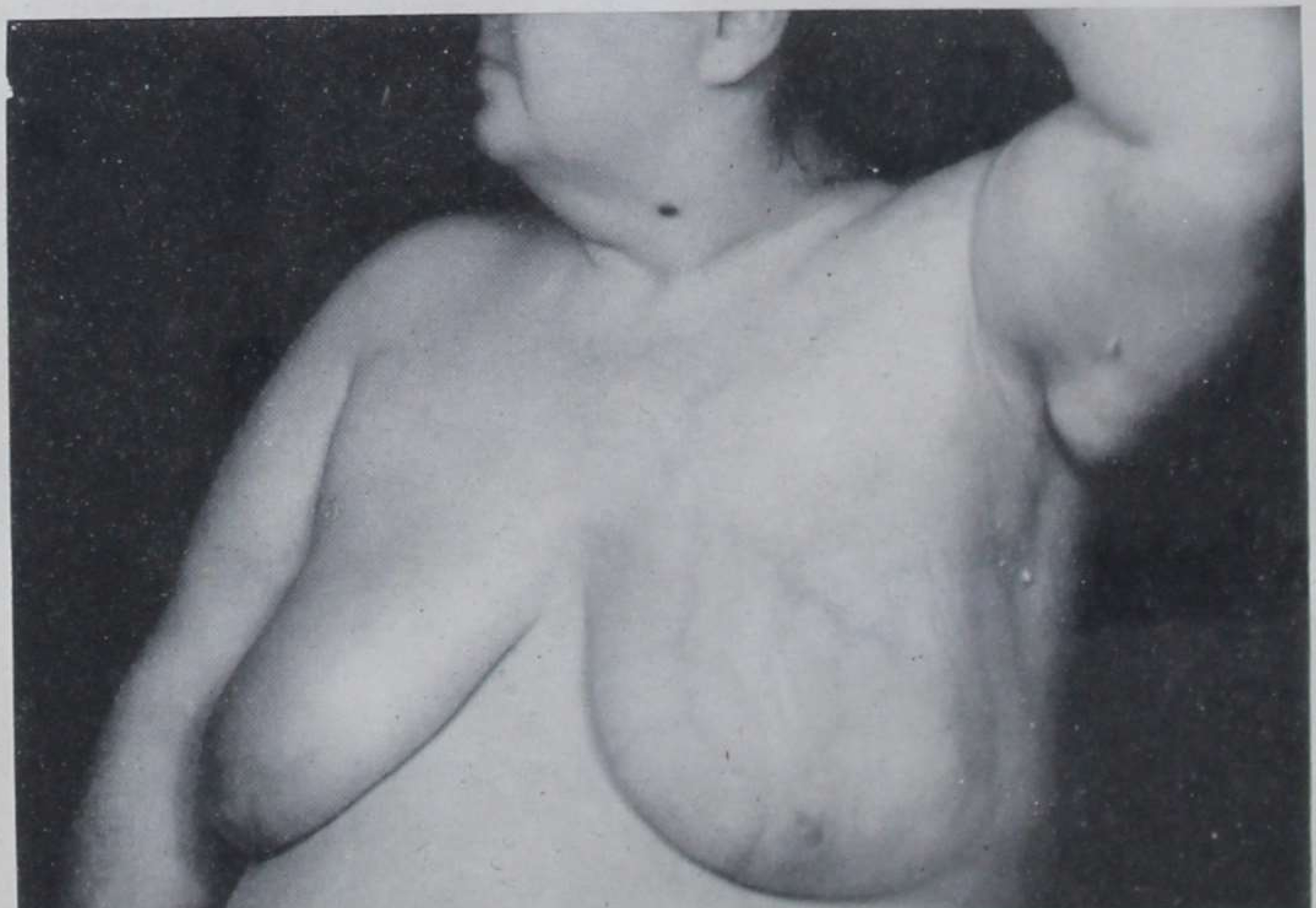

B

Fig. 67.—A case of photographic interest. Woman aged 55 with history of long-standing (some 15 years) pain and tenderness in the upper medial quadrant of the left breast. Intermittent serous discharge from the nipple. Clinical diagnosis indefinite. All operative measures refused. A, Normal photograph. B, Infra-red photograph. This shows the superficial venous system to be more clearly marked in the affected breast and converging at the site of pain and tenderness. At this point some thickening of the mammary tissues was palpable. (*Mr. G. Cruickshank's and Mr. A. Green's case. Photography by Mr. D. Stevenson Clark.*)

of a patch of skin, may be a primary indication of a malignant infiltration. Malignant disease is not always manifested as a mass. Dimpling or retraction of the skin, if not obvious, is sometimes revealed by stretching the arms above the head, or found by 'pinching' the skin from the breast tissue.

The nipples and areolas are examined for eczematous or ulcerative lesions or for fissures. Retraction and alteration in the shape or

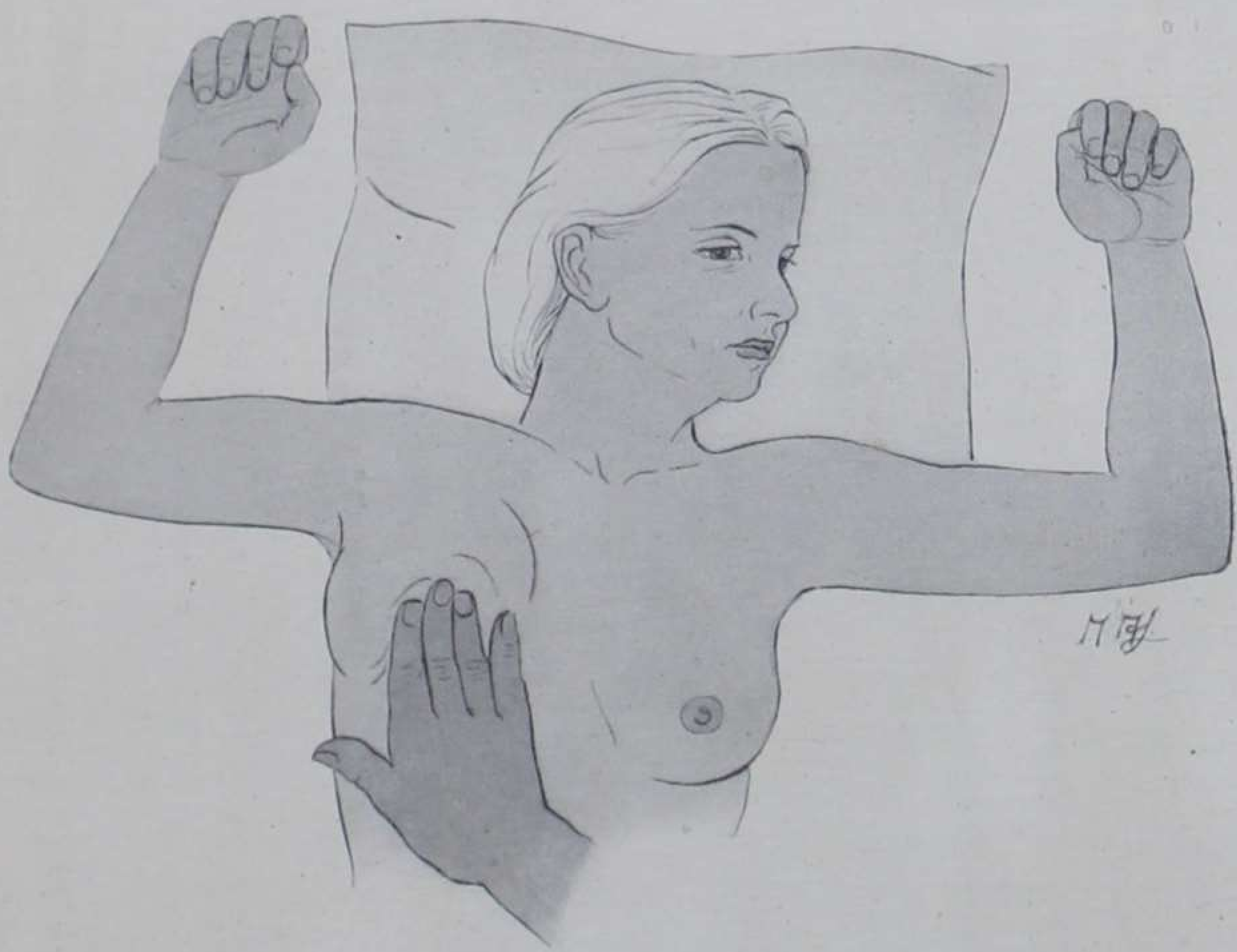

Fig. 68.—Examination of the breast against the chest wall with the patient lying down.

angle of projection of the nipple, if unusual and persistent, are signs of great importance. If a discharge from the nipple is present the fluid should be collected for microscopic examination. Pressure over a defined area of the breast may produce a discharge, but localization of the site may not be possible. The finding, however, of a small ovoid tumour in the central area of the breast, over which pressure causes a discharge of blood or blood-stained serum, is almost diagnostic of an intraduct or intracystic neoplasm.

Next, both the breasts are palpated with the tips of the fingers, by pressure between the fingers and thumb and between the flat of the hand and the chest wall (*Fig.* 68). Mammary tissue is normally rather tough and nodular to the touch, although in most cases a covering of fat gives the impression of a smooth surface. Tumour formation does not alter on pressure, but mastitic tissue, in the absence of marked fibrosis, gives the sensation of becoming flattened. The examination of solitary tumours in a large and pendulous breast is sometimes facilitated by lifting and supporting the breast between the hands of a nurse or by the patient herself.

To test mobility the patient is asked to press her hands against her hips, or the sides of the examining couch, when the comparative mobility of each breast on the chest wall and of a tumour within the mammary tissue can be estimated. The site of a tumour should be noted, and the size of a malignant mass gives some indication of its age. The measurement of mammary tumours and an assessment of their size should be part of the routine of examination.

Transillumination of the breast, to be effective, has to be done in a dark room, a point which limits its use for ordinary examination. A lamp is required from which the light is concentrated and can be varied in intensity by attachment to a rheostat. With the patient sitting, the lamp is placed on the under-surface of the breast, and the light directed upwards through its substance; for the flat breast with scanty tissue this method of examination is of little value. The transillumination of normal and abnormal mammary tissue varies, of course, quite considerably with the intensity of light transmitted. Also, similar conditions in different people can each give a varying depth of shadow, so that interpretation depends much on the experience of the examiner. A tumour, if found to be translucent, is likely to prove cystic; a collection of blood is opaque. When, in a case of bleeding from the nipple and absence of localizing signs, a small opacity is discovered by transillumination, this method of examination has probably its greatest value.

Straight radiographs give some indication of the density and extent of a tumour. Dye injections through the nipple into the mammary tissue may increase the value of radiographic examination (mammography). For immediate purposes, however, neither trans-illumination nor radiography have more than limited scope and afford no genuine help in distinguishing between benign and malignant tissue.

Examination of the Axilla.—The axilla is examined with the arm abducted to about a right angle and brought slightly forwards in order to relax the pectoralis major muscle. The apex of the axilla is more easily examined from the opposite side with the first and second fingers in the axilla and the thumb on the anterior chest wall (*Fig*. 69), or, again, by standing behind the patient and pressing the fingers up-ward towards the apex of the axilla.

The main object is the detection of enlarged lymph-nodes and, if found, an estimate of their site, extent, size, consistence, fixity, and degree of tenderness.

With the same object in view the neck and supraclavicular regions can be conveniently examined by standing at the head of the patient. Examination is facilitated by lateral flexion of the head towards the side to be examined and its rotation towards the opposite side. Enlarged supraclavicular nodes tend to be found most frequently in

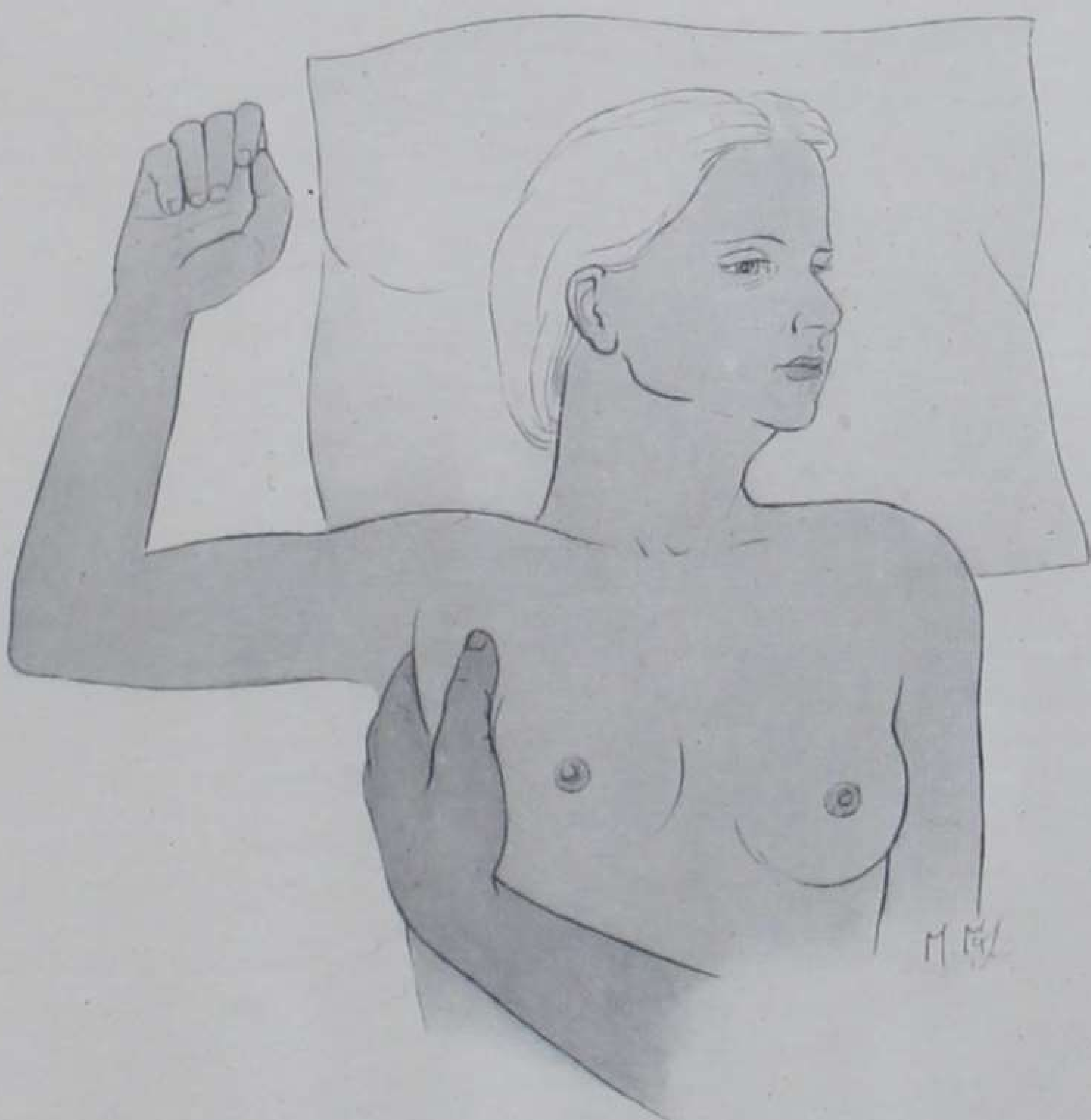

Fig. 69.—Examination of the axilla from the opposite side.

the space between the medial end of the clavicle and the clavicular origin of the sternomastoid muscle.

A general examination, including the pelvis, and other routine investigations are made as thought necessary. A Wassermann reaction should be done in all doubtful cases, especially if during lactation an ulceration of, or blood-stained discharge from, the nipple is noted.

If, by clinical examination, a diagnosis is made of malignant disease of the breast, radiographic examination of the chest, lumbar vertebræ, pelvis, hip, and shoulder regions should be included in the routine. If negative in the first instance, in spite of symptoms suggestive of secondary deposits, the control radiograph is filed for later formation does not alter on pressure, but mastitic tissue, in the absence of marked fibrosis, gives the sensation of becoming flattened. The examination of solitary tumours in a large and pendulous breast is sometimes facilitated by lifting and supporting the breast between the hands of a nurse or by the patient herself.

To test mobility the patient is asked to press her hands against her hips, or the sides of the examining couch, when the comparative mobility of each breast on the chest wall and of a tumour within the mammary tissue can be estimated. The site of a tumour should be noted, and the size of a malignant mass gives some indication of its age. The measurement of mammary tumours and an assessment of their size should be part of the routine of examination.

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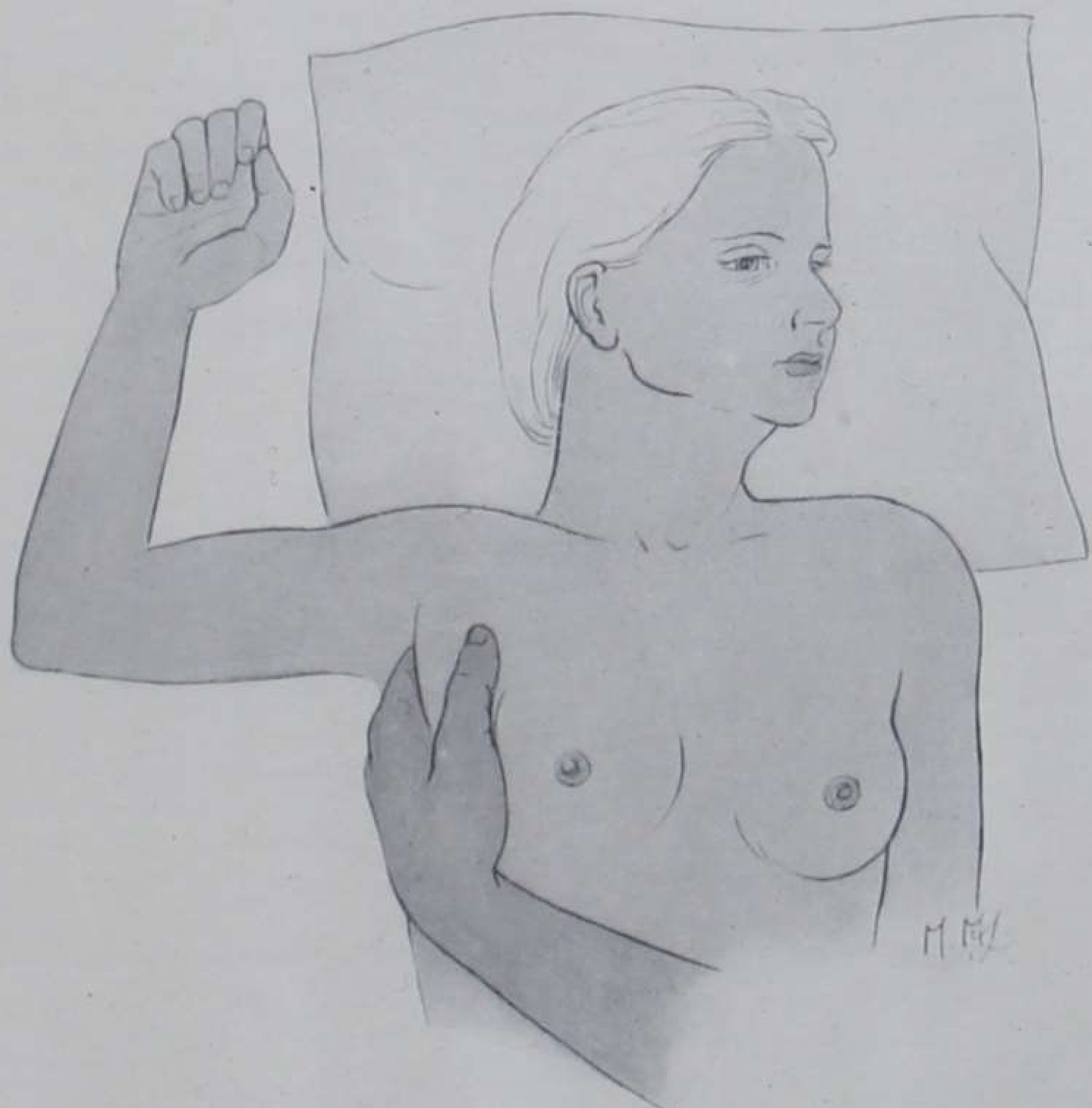

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If, by clinical examination, a diagnosis is made of malignant disease of the breast, radiographic examination of the chest, lumbar vertebræ, pelvis, hip, and shoulder regions should be included in the routine. If negative in the first instance, in spite of symptoms suggestive of secondary deposits, the control radiograph is filed for later reference with the technique recorded on the filing envelope. A repeat film at a later stage, say 6 weeks, can then be made under identical conditions, and in a doubtful case comparison with the control film may be of considerable value. (*See* Chapter XI.)

DIAGNOSIS OF BREAST CONDITIONS

The natural history of the breast falls into three periods : the first, the years up to puberty ; the second, the period of activity, which extends roughly from 15 to 45 ; and the third, the period of regression beginning at the menopause and continuing into old age. The individual and racial variations and comparative age of a breast, the prematurely old and persistently young, call for a separate assessment in every case.

The lesions of the first period include developmental failures or abnormalities which are usually self-evident. Rarely one or both breasts are entirely absent ; more common are various deformities of the nipple, mainly of inversion or indrawing. Abnormalities such as supernumerary breasts (*polymastia*) or nipples (*polythelia*), or ectopic nipples (*Fig.* 70), may be situated along, and occasionally outside, the length of the original milk line. These generally require removal in the woman at some time before lactation. The so-called ‘ mastitis neonatorum ’, an indication of mammary activity, is not uncommon nor actually abnormal, and a similar process may be seen in a boy at puberty. Such conditions as areolar eczema and abscesses are apt to occur in both sexes during adolescence. Precocious development of one or both sides sometimes takes place in the first period. Precocity is associated, in certain instances, with benign or malignant neoplasms of the glands controlling mammary growth.

The primary clinical entities of the second and third periods are the different phases of chronic mastitis, benign tumours, and malignant disease. A further group is comprised of the acute infections of lactation, galactocele, chronic infective mastitis, and other miscellaneous conditions. In round figures malignant neoplasms constitute some 45 per cent of all mammary lesions ; chronic mastitis of all types 25 per cent, benign tumours 15 per cent, and the last group—including abnormalities of form—also some 15 per cent.

Physiologically, the second period is the most important, when the mammary tissue becomes subject to a menstrual routine and undergoes a gradual preparation for its prime function of secreting milk. Changes in its structure varying in time of appearance and extent, usually called chronic mastitis or mammary dysplasia, represent probably a measure of ineffectiveness rather than any pathological process. Of these a hypertrophic form (adenosis), distinguished clinically by mainly 'gritty' tissue, often tender and painful, may develop at any time during the menstrual cycle. Hyperplastic cystic disease, the least common manifestation of dysplasia, though alleged

Fig. 70.—Ectopic nipple on the medial aspect of the right upper thigh of a man aged 42.

to be potentially the most dangerous, is seldom noticed before the middle thirties; typically it is found as a lump of indurated nodular tissue, but sometimes because of symptoms. Involutionary changes with small to medium-sized single or multiple cysts (fibrocystic disease) not infrequently occur in the middle thirties and onwards, more especially perhaps in the single, spare type of woman.

Clinically, two forms of benign neoplasm, the fibro-adenoma and the intracystic papilloma, are the only more or less routine tumours, of which the former is much the more common, in a proportion of roughly 3 to 1. A fibro-adenoma is essentially a tumour of a young woman (16 to 30). These tumours also appear, though much less frequently, between the ages of 30 and 50. The intracystic papilloma, on the other hand, is usually found at the menopause, but sometimes in much younger women. Other benign tumours, such as lipomas and the giant tumours associated with the fibro-adenoma, are comparative rarities. Malignant disease of the breast rarely develops before 30, not often before 40, except for the occasional pregnancy-lactation carcinoma, and then the liability rapidly increases. Among other lesions of this period can be included abnormalities of growth, acute and chronic infections, and various minor complaints.

In the third period an occasional benign neoplasm or fatty tumour (fat necrosis) is found, but the primary tumours of the mid-forties to fifties are malignant neoplasms, essentially carcinomata, and involutionary cysts, in a proportion of nearly 5 to 1. These cysts, often large and solitary, sometimes called the blue-domed cysts of Bloodgood from their colour on exposure if superficial, and seldom actually quite solitary—are a manifestation mainly in a large fatty breast of involutionary changes, and are benign in character. Cyst formation consequent on malignant disease, an actual cystic degeneration of a neoplasm, is a process quite distinct from that of the involutionary type, and although comparatively rare can be dangerously confusing.

In this country the incidence of mammary cancer reaches its peak at about 55, but from then on continues to be by far the most common lesion of the breast and practically the only one of old age.

A malignant state is most often revealed as an ill-defined, craggy, and unmistakable mass, or as a plaque of indurated tissue isolated or superimposed on an area of chronic mastitis; sometimes as a small, rounded, discrete, and softish tumour (early encephaloid carcinoma), thus liable to be mistaken for a cyst, or as an area of induration on the surface of the breast or patch of discoloured skin.

On the other hand, mastitic tissue because of its density, a fibro-adenoma in a middle-aged woman which from fibrosis in its capsule has lost elasticity and mobility, or an involutionary cyst placed deeply in a large breast, can all be difficult, or impossible, to distinguish from a carcinoma by palpation alone.

The problem of diagnosis in breast cases is mainly two-way, and between a benign and malignant state, since no pre-cancerous stage is recognizable. If after ordinary clinical examination a condition can be labelled benign the advantage to the patient needs no emphasis, but to make a confident diagnosis of malignancy the disease has to be well established with, in consequence, immediate doubts of its localization.

A carcinoma of the breast at its inception is most unlikely to cause an awareness of its presence. Symptoms, if any, are for the most part unimportant at any stage, and signs become typical only when the disease is advanced. The first indication of trouble is, in most cases, the chance finding of a lump—the size of the breast may influence the timing of a discovery—which, if found to be clinically doubtful, is that much to the advantage of the patient. Such signs as have to be enumerated and taught for the diagnosis of cancer of the breast are, in fact, but a measure of its advance, and the greater the certainty of these the less favourable is the outlook.

Long experience, it has been said, teaches the distinction between a benign and malignant breast. This perhaps is partly true, but among the lessons of experience may be included: the need for palpation of the breasts as part of the routine of examination, especially in older women; never to dismiss lightly any change of structure in mammary tissue or in the skin covering it; never to await diagnostic signs; not to neglect the importance and correctness of biopsy.

BIOPSY

Biopsy will be considered under three headings: (A) Certain evidence in favour of biopsy; (B) Conclusions from clinical experience of 500 biopsies; (C) The description of cannula biopsy.

A. Evidence in Favour of Biopsy

There are certain cases in which the result of the biopsy should be considered along with the clinical evidence and not alone, otherwise appropriate treatment may be delayed until the case is hopelessly advanced.

In 1888 the distinguished pathologist Virchow issued a warning which was based largely on an unfortunate experience with the second German Emperor. Virchow had three specimens of tissue submitted on different occasions from a laryngeal tumour in the patient, and no cancer was diagnosed histologically. Von Bergmann had correctly diagnosed cancer on the first visit. Pathology has advanced greatly since this day, but an old lesson should not be forgotten. A positive biopsy is invaluable, but a negative biopsy should be considered with the clinical evidence and, if necessary, repeated.

Pathological evidence is more accurate than clinical evidence as a rule. Horder stated at the International Cancer Conference in 1928 that there is in biopsy a diagnostic means approaching nearer to certainty than any other. Fischer found that in 1700 surgical specimens the pathologist was correct in 91 per cent and the clinician in 68 per cent of cases, i.e., 23 per cent more accurate. This means that the clinician makes one mistake in four. In 14·5 per cent of cases the clinician had pronounced the growth malignant while the pathological examination revealed a benign condition.

Early diagnosis by biopsy results in the early application of the correct treatment, which is vital to success in cancer. McCarty reviewed the material of the Mayo Clinic and found that, of 1213 surgical cases, 16·4 per cent came to operation with a doubtful clinical diagnosis, 12 per cent required biopsy, and in 17·5 per cent the histological diagnosis made from frozen sections during operation changed the prognosis and operative treatment.

In order to estimate the risks of biopsy, Wood inoculated 400 animals with Flexner rat carcinoma, which metastasized to the lungs in 20 per cent of cases ; 200 were kept as controls ; 200 had a specimen of tissue removed and the skin sutured. Several months later all the animals were killed. There was no increase of metastases in the animals after biopsy. Wood and Tyzzer did a similar experiment massaging tumours, and metastases were almost doubled. The experiments suggested that repeated clinical examination is of greater danger than biopsy.

Bloodgood, with his unique experience, observed no difference in five-year relief rates with and without biopsy, provided an operation was carried out *immediately* afterwards. It is his opinion that badly performed biopsy should be condemned ; he is in favour of X-ray therapy beforehand and the use of endothermy to seal lymphatics. Copeland and Geschickter believe that biopsy does not necessarily affect the prognosis of Ewing's sarcoma of bone, provided immediate operation or X-ray treatment is instituted. The Committee of the American College of Surgeons on the Treatment of Malignant Diseases endorsed the rapid microscopical methods with the following advice : " In order that in patients with cancer the possibility of cure shall not be jeopardized, an exploratory operation should be conducted only under such conditions that the appropriate treatment by surgery or by radiation may be carried out immediately when the diagnosis is established by the pathologist by means of frozen sections".

If the decision is taken against performing biopsy, other conditions should be excluded by performing a Wassermann test, bacteriological examination, noting the response to treatment, and a readiness to revise the diagnosis in the light of the clinical progress of the case and to reconsider biopsy.

B. Conclusions from an Experience of 500 Biopsies

The bulk of cases have been mouth, throat, and breast cancer, and in these situations both the tumour and the gland sites are readily observed and any harmful effects detected. The most outstanding fact is that *the author* (A. G.) *has not been convinced that in selected cases and with careful technique biopsy has resulted in the dissemination of metastases.* The importance of avoiding trauma to the tissues as a whole is not usually emphasized, nor are the risks of low-grade sepsis from organisms present in an infected growth. Sepsis of low grade is not stimulated by the careful removal of an excrescence, but by cutting deeply into the tissues below the normal surface. This is especially so when the growth is largely covered by mucosa or skin. Manipulation of an infected growth is liable to produce a low-grade connective tissue infection—e.g., forcible endoscopy in advanced growths of the hypopharynx may produce a phlegmon-like condition of the neck adjacent.

Choice of Method.—The choice of the method of biopsy depends on the size and site. For extremely small growths, biopsy by excision is attractive pathologically. It is, as a rule, also sound treatment provided the whole of the suspected area of tissue can be removed entire together with a margin of normal tissue. Endothermy loop removal from an excrescence of an ulcerated tumour is a safe procedure. Deep and encapsuled tumours should be hesitantly attacked by incision, and can be done more safely by aspiration or cannula biopsy. If radiotherapy is contemplated as a method of treatment, biopsy will in many cases be desirable in expert hands and after some radiation has been given.

Minimizing the Risks.—The risks of biopsy may be lessened by :—

1. Avoiding deep biopsy when *latent sepsis* is suspected. The sepsis should be cleared up first and the biopsy treated as a serious surgical procedure with full aseptic precautions.

2. *Choosing methods* inflicting the minimum of trauma and using extreme gentleness and precision. The diathermy loop slides gently into the tissue of an ulcerated growth and a piece falls out without any manipulation or tugging, which is so very important.

3. *Practising well* in the post-mortem room, and on hopeless cases first, when a new technique is tried.

4. *Use of radiotherapy beforehand.* In order to avoid histological changes of a marked degree as a result of radiotherapy, the specimen should be taken not later than three days after treatment is given, and, in the case of radio-sensitive tissues, on the same day. The time of biopsy and dosage depend on the experience of the pathologist in interpreting histological changes due to radiotherapy. The magnitude of the dose and the area treated are a matter of importance. In slowly growing tumours 600 r may be given, whereas in the radio-sensitive tissues 200 r to the whole area is often a high dose because the rapid lysis of malignant cells may cause a high temperature from the absorption of breakdown products suddenly produced. High doses seem undesirable because at the most this pre-biopsy dose can only affect the most radio-sensitive and rapidly growing cells which, it may be argued, are most liable to produce metastases, and large doses also damage the connective tissue. If biopsy is long delayed, or the dose too large, the cells may be undiagnosable on account of the radiation changes. It would appear reasonable that radiated cells, released into the circulation, would have mitosis inhibited, and so give the defensive mechanism time to act before tumour propagation occurs from rapid cell division. Experimental evidence, however, is complex.

5. The use of *diathermy* seems to have two advantages. Firstly, it seals minor vessels as it cuts, both vascular and lymphatic, and so minimizes spread. Secondly, it kills the adjacent cells which are loosened. The minimal cutting current is used, in order to avoid thermal destruction of the specimen.

6. The use of *general or surface anæsthesia* inflicts less trauma than the injection of local anæsthetic into the tumour.

The Role of the Pathologist.—There is need for improved tumour pathology. Knowledge of the single cell changes produced by radiotherapy, and structure, are important. The radiotherapist is very dependent on biopsy and requires the following information :—

1. *Type of cell* {
Mitotic figures
Hyperchromatism
Size of cell and nucleus
Degree of differentiation (Broders' classification)

2. *Tumour structure*
- Arrangement of cells, formed or primitive
- Proportion of cells to stroma
- Type of stroma
- Vascularity
- Lymph spaces
- Presence of infection or œdema

3. *Tumour bed*
- Vascularity
- Fibrous, fat, bone, or loose connective tissue
- Natural barriers and defence
- Presence of infection or œdema

A tumour is more radio-sensitive when the cells have many mitotic figures and are hyperchromatic, and also if the size of the cell and nucleus is large and the degree of differentiation poor. When tumour structure shows a primitive arrangement of cells with a high proportion of cells to a vascular stroma, radio-sensitivity is usual. Large lymph and vascular spaces, with the cells forming the walls, indicate tendencies to metastasize, especially if cells are seen within them. If a tumour bed is very vascular and made of loose connective tissue, this is of assistance to radiation treatment. The presence of œdema or infection are unfavourable signs. Sometimes a natural defence mechanism is seen whereby the host reacts by forming fibrous tissue tending to limit the spread of the tumour.

Aspiration Biopsy as a Diagnostic Procedure.—The practice of aspiration biopsy was first described in the *Annals of Surgery* by Martin and Ellis of the New York Memorial Hospital, in 1930, as the withdrawal of fragments of tissue for microscopical study by means of an ordinary needle and syringe.

The method described by these workers is as follows. Using a 20 c.c. syringe with a wide-bore Gauge 18 Record needle attached, a piece of tumour is obtained through a skin puncture. For this purpose, the needle is introduced into the tumour and the piston of the syringe is withdrawn to its full extent and the needle is pushed further into the tumour. By this procedure, a thread of tumour is drawn into the needle. Maintaining the suction in the syringe, the needle is withdrawn a little and then pushed forward again at an angle to its previous direction so as to cut off the thread of tissue in the needle. The tension on the syringe is then released completely and the needle withdrawn from the tissues. The syringe is next disconnected from the needle, filled with air, re-attached to the needle and the contents of the needle expelled. The entry of the needle into the tumour tissue is usually quite obvious from the change in resistance to the progress of the needle. Martin and Ellis deal with the thread of tissue by making a smear and staining it, or by fixing and embedding in paraffin as for an ordinary piece of tissue.

Biopsy by surgical excision has dangers, disadvantages, and limitations which are not shared by aspiration biopsy. Hospitalization of the patient, general anæsthesia and a relatively time-consuming operation involving several people are necessary. The wound may heal cleanly and yet malignant cells may be set free in the cellular connective tissue and can grow with little restraint being imposed on them by the body defences. The wound may heal but cancer *en cuirasse* result, or healing of the wound may not occur and a sinus persist. In certain cases surgical biopsy is not expedient by reason of the nature or inaccessibility of the tumour. Aspiration biopsy offers a rapid and effective method which can be safely carried out without admitting the patient to hospital. The time taken in the Out-patient Department is very short. A tray with the necessary articles having been prepared, the time taken, including washing out the syringes, administering the local anæsthetic, and introducing the tissue into the fixative, rarely takes more than a few minutes. Tumours are often found surprisingly to contain fluid or pus, and aspiration biopsy reveals this more safely and with less trouble than a major procedure.

In some cases, however, aspiration biopsy, although apparently quite a safe procedure, has proved a failure. As Dr. Ellis has pointed out, failure occurred in 27 per cent of cases, and especially when the tumour was of a very firm consistency, such as scirrhous carcinoma of the breast.

C. Cannula Biopsy

An instrument has been designed by one of the authors (A. G.) to overcome the difficulty just referred to.

After taking experimental biopsies with cork borers, which closely resemble the outside sheath of a trocar and cannula, this method was found, although providing excellent biopsies in some instances, to be capricious, and rough and ready.

The next stage was to design a pair of forceps which would pass down the centre of a small trocar and cannula to bite a piece right out of the centre of the tumour. The small trocar and cannula is inserted into the middle of the tumour, which can be felt to move when the point is engaged. The trocar is then removed leaving the cannula in place. The forceps is inserted and while it is moving forward, the jaws are slowly opened in the tumour tissue. A bite is made and the cannula is then pushed forwards. The cutting edge of the cannula shears off the specimen. A satisfactory piece of tissue is obtained, even in hard tumours, with a little practice and if the forceps is kept sharp. After removal of the forceps a specially constructed diathermy electrode is inserted into the cannula and the site of the biopsy electro-coagulated. The diathermy is then touched on the cannula so that the track is also slightly coagulated before withdrawal of the instrument.

The first choice lies with aspiration biopsy, and if that fails, or if a larger specimen is required, the cannula biopsy should be used to avoid the trauma of an incision. It should not be used, however, unless a definite lump can be felt and can be engaged in the point of the instrument. Vague thickening in tissue has provided unsatisfactory specimens.

Summary

In conclusion, the safest and most useful methods of biopsy are :—

1. Diathermy loop removal of an excrescence in ulcerated tumours.
2. Punch biopsy with cutting forceps in ulcerated tumours for speed.
3. Aspiration biopsy in deep or non-ulcerated tumours.
4. Cannula biopsy with diathermy in similar cases and when aspiration fails.
5. Biopsy by incision may be almost limited to breast cases on the operating table provided the operation proceeds forthwith.

Aspiration and cannula biopsy should be employed more widely and in preference to incision wherever possible.

DIAGNOSIS OF CANCER OF THE BREAST BY RADIO-ACTIVE PHOSPHORUS

Radio-active substances should be used with caution in a woman during the child-bearing period on account of their genetic effects on the germ cells. They may be given in patients over 40 years of age, but any late effects from the use of these substances have not yet been fully determined. On the other hand the dose is exceedingly small, and may be compared with the exposure necessary for a full set of diagnostic X-ray pictures, which are ordered without hesitation.

The method is now being developed for trial with biopsy material and in estimating the presence of secondary deposits.

A dose of 300–500 microcuries of radio-active phosphorus is given intravenously as isotonic di-sodium hydrogen phosphate, 24–28 hours before investigation. (Work is also proceeding with fluorescein linked with radio-active atoms.) A shielded counter tube is pressed firmly over the site of the tumour, which exerts a greater effect if near the surface. Deeply placed tumours may produce little change in counter rate, since the range of penetration of the beta rays from radio-active phosphorus in tissue is limited to about 1 cm. This difficulty may in future be overcome by an interstitial measuring device.

Counting rates made over many areas of the breast show a significant (25 per cent) increase of radio-activity when a malignant tumour is present: with a benign tumour the counter rate is little different from normal tissue.

The method has the disadvantage that acute inflammatory conditions, with the consequent vasodilatation and increased blood-flow, lead to a rise in the counting rate comparable to that obtained with malignant tissue.

(For workers using this method protection is essential for the hands by gloves and the eyes and face by a cellophane drop-sheet attached to a head mirror. A gown should always be worn. The cleaning of syringes, dealing with swabs, etc., requires expert supervision. It is advisable that such work should be confined to a radiotherapy team.)

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CHAPTER V

MAMMARY DYSPLASIA : CHRONIC MASTITIS

By P. O. Ellison, Raymond Greene, and F. D. Saner

Nomenclature and Classification.—The term chronic mastitis, with the implied suggestion of an inflammatory or pathological process, is misleading as a descriptive title ; nevertheless its adoption is useful as a general term to cover certain states of the mammary tissue. Whether these states ought to be regarded as distinct or not is still speculative, but as a working hypothesis, rather than an expression of opinion, all are reckoned here as variations of a basic deviation from the physiological normal.

As clinical entities the phases of chronic mastitis shade one into another, but, for descriptive purposes, they can be roughly separated into three :—

	Synonyms
1. Adenosis, including Mastodynia	Chronic interstitial mastitis
2. Hyperplastic Cystic Disease	Schimmelbusch's disease Adenosis (Geschickter) Chronic cystic mastitis Adenocystic disease Chronic cystipherous hyperplasia, etc.
3. Involutionary Mastitis or Fibrocystic Disease	Cystic disease Bloodgood's cysts

This suggested nomenclature and classification is based mainly on histological appearances which have been assumed to show the main types of structural alteration. Many, too, if not most, of the clinical cases can be included under the same headings.

GENERAL CONSIDERATIONS. RELATIONSHIP TO CANCER

Mammary dysplasia, distinguished mainly by knotty, nodular, cystic, and often painful breasts, does not appear before puberty, is prone to exacerbations before each menstrual cycle, is ameliorated by pregnancy, and regresses in old age. These outstanding features are suggestive of an endocrine influence. Again, intense and prolonged stimulation by œstrogens has been found experimentally in certain animals to produce hyperplastic, cystic, and finally carcinomatous changes in the mammary tissue. In this respect, incidentally, Geschickter distinguishes between the effect of an intense but short and a moderate but prolonged œstrogenic stimulation, and regards the latter as potentially the more dangerous.

Further, the following observations suggest that an absolute or relative preponderance of œstradiol over progesterone may be partly responsible for initiating tissue changes :—

1. At puberty, before ovulation has begun, the œstrogen-progesterone ratio is high. At this time mammary pain, indicative of physiological hypertrophy, is not an infrequent complaint.

2. At the menopause, when ovulation ceases, a temporarily high œstrogen level may be responsible for mastitic changes.

3. Chronic mastitis is often most painful at the peaks of œstrogen excretion, i.e., at the time of ovulation and in the premenstruum.

4. Painful breasts are sometimes associated with the condition of endometriosis when there is reason to surmise an absolute or relative œstrogen excess.

5. Mastodynia is often produced in men undergoing treatment with œstrogens for prostatic cancer.

The hypothesis, therefore, that an excess of œstradiol, with or because of a deficiency of progesterone, is an influence in chronic mastitis seems, at least, not unreasonable. But the investigation of these aetiological hints is not easy. Assays of the œstrogenic output in the urine are not reliable ; those of pregnanediol are difficult to apply because of the very small amounts of the substance found in the urine of non-pregnant women, even in the luteal phase of the menstrual cycle. It should be mentioned, however, for what it is worth, that Geschickter found a low excretion of pregnanediol in all groups of mastitis with a normal, or occasionally high, œstrogenic output.

But these endocrine variations are unlikely to be more than a part of the whole story. Inherited differences in the quality of tissue in a breast, mainly but not altogether coincident with its form, must surely have considerable bearing on an easy or uneasy association with endocrine action both during the menstrual cycle and on its cessation at the menopause.

Mammary dysplasia appears to be a result of an inadequacy of the breast itself and of endocrine disorder. Both these factors in varying proportion are present in many women probably from puberty, and are produced occasionally in others by circumstances affecting the general health. If in some such manner the routine of the menstrual cycle is deranged, mammary tissue has the capacity to promote changes in its structure with the object, presumably, of maintaining its predestined activities at an effective level.

Such changes, for the most part, are manifested as a hypertrophy of functional tissue (*adenosis*), in which the routine processes can be carried on, albeit imperfectly, and perhaps painfully.

Far less often an epithelial hyperplasia (*epitheliosis*) becomes evident with cyst formation and fibrosis (*hyperplastic cystic disease*); here, however, it is more difficult to recognize what useful purpose, if any, is being served.

A further form of structural change is associated with the cessation of functional activity of the breast and is referred to as *involutionary mastitis** or *fibrocystic disease.* Fibrosis and cyst formation, the latter probably from incidental difficulties in drainage, are predominant features, coincident with a general atrophy. These changes would appear to be within the framework of a normal regression or may be a development, at the menopause, from a pre-existing condition such as adenosis.

Chronic mastitis, in any phase, becomes a clinical entity when symptoms or nodularity of the breast are sufficient to attract notice, but even so it belongs mainly to the category of minor ailments. Yet because of the alleged association with malignant disease, and the difficulty, very real on occasion, of differentiating between mastitic and malignant tissue, either by clinical or even by histological examination, all these phases have assumed an importance in the mind of the clinician probably far beyond their deserts.

Hyperplastic cystic disease is especially suspect. A number of authorities regard this state of the mammary tissue as potentially, if not actually, a pre-cancerous condition. Janet Lane-Claypon writes: " If there is transition from hyperplasia to cancer in one case it is probable that it occurs in others—it could hardly be regarded as a special phenomenon but as an example of a pathological process ". Cheatle and a number of others are suspicious of all cystipherous lesions.

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* Some authors, notably Geschickter, prefer to segregate cystic involutionary changes as, clinically, a condition distinct from chronic mastitis, under the heading of cystic disease.

Geschickter in a large series of cases of mammary dysplasia and cancer found that the two diseases coexisted in twice the expected number of cases and that cancer developed in breasts with 'adenosis'* three times as often as should be expected.

Response to a functional difficulty or failure, or to an abnormal agent, apparently varies in different areas of the same breast, which are at different levels of activity, and the tissues react, become altered, or, presumably, remain unaffected. Fibrosis, it has been suggested, may be a response to a carcinogenic agent, but it is also the common accompaniment of any persistent structural change in the mammary tissue. A condition of adenosis can, in general terms, be regarded as a specific manifestation of a deficiency or an instability of function of varying duration, and hyperplastic cystic disease of an irritation or disorder affecting one or more areas of the parenchyma of the breast. This evidence of derangement between structure and function is given during the period of preparedness of the mammary tissue for its prime function of secreting milk. Malignant disease, on the other hand, in the great majority of instances is associated with the period of regression of the whole organism from its fertile state to final quiescence, although regressional changes in the breast, or elsewhere, are likely to be at varying levels and may be premature in one area or, in another, delayed. In this manner a combination of unaltered and various types of altered tissue and carcinoma when present at the same time could be accounted for without implying that one is a grade of or a sequel to the others.

The coexistence of mastitic and malignant tissue is not unusual, but, from clinical evidence especially, a direct transition from one state to the other appears to be unlikely. If mastitic changes beginning in the thirties or forties are liable to provoke malignant disease in the fifties, the evidence by now should be more convincing than in fact it is; in the majority of cases of carcinoma a relationship is not even suggested. If and when such transition does occur it seems less likely to be a sequel of mammary dysplasia *per se* than of the inevitable course of regression affecting mammary tissue, unaltered or altered, and the degree of disturbance created.

Two questions appear to be relevant:—

1. Does a carcinogenic agent, if such exists at all, find more suitable soil in normal or abnormal tissue?

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* 'Adenosis' is here used as in Geschickter's nomenclature, but is the condition described in the present chapter as 'hyperplastic cystic disease'.

2. Does the cessation of routine functional activity, and occasionally the state of pregnancy and lactation, create the liability to a disturbance of the balance between structure and function sufficient, in some instances, to permit or provoke an immature and finally autonomous process? Primarily such an incident could be an attempt to redress the balance or to restore a previous activity, and thus far the conception of a neoplasm may not be without purpose.

The causation of both mammary dysplasia and carcinoma appears, in many respects at any rate, to be closely associated with the rise and fall of mammary activity. Dysfunction and disturbance is revealed by the formation of altered tissue. The minute structure of the latter has been studied at different stages under the microscope in numbers of still pictures which show, for the most part, remarkably uniform patterns without obvious transitional stages between them.

ADENOSIS

Pathology.—The name adenosis is used here to denote an exaggerated physiological state or a hypertrophy of functional tissue, initiated and influenced perhaps by an imbalance, either of hormone control, or of tissue response, yet comparable histologically to the state of the breast in early pregnancy. Adenosis waxes and wanes during the menstrual cycle and may cause symptoms but often disappears spontaneously. The condition is essentially benign, though a pathological process can be superimposed or coexist in the same breast.

On macroscopic examination, the pea-like nodule, or the breast tissue with small knotty areas which are lost immediately on cutting with a scalpel, are typical. In sections, the lobules are enlarged owing to the marked increase in the number of acini,* together with a varying hyperplasia of the peri-acinous fibrous tissue and possibly an infiltration of a few plasma and small round cells. (*Figs.* 71, 72.) The histological picture, then, is that of a physiological state for which the term adenosis seems appropriate.

Clinical Aspects.—Adenosis, with or without symptoms, is common in the woman of poor physique and rare in a well-developed breast or one in which lactation and regression have proceeded uneventfully. Healthy mammary tissue, however, can be depreciated by a general metabolic disturbance, e.g., a continued nutritional deficiency (*see Case* 1).

* Although histologically the terms alveolus and acinus are synonymous, here *acinus* is used when the small tubules tend to form clusters, and *alveolus* for the larger bundles.

The 'lumpy'—but not cystic—sometimes painful and pendulous breast of a woman at or near the menopause can be included as a late manifestation of adenosis, though, histologically, fibrosis and atrophy are often the predominant features.

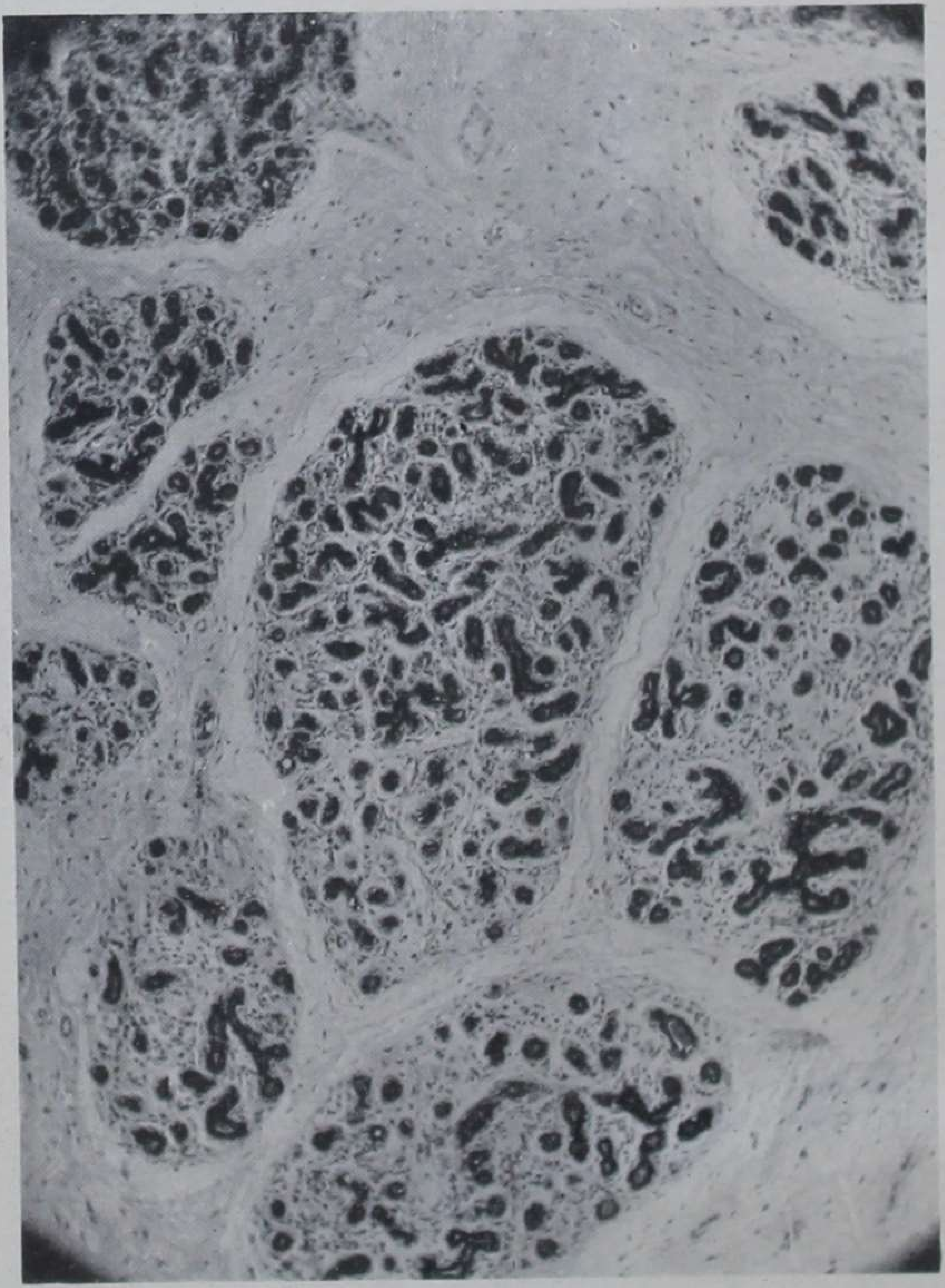

Fig. 71.—Adenosis. Note the lobular hypertrophy as is shown by the increase of the number of tubules. There is also an increase of fibrous tissue. This illustration should be compared with that of the lactating breast (*Fig.* 72). (× 60.)

In a different manner, a sudden interruption of activation of the breast by a premature termination of pregnancy may leave, in effect, a state of painful adenosis from which regression is slow but tends eventually to be complete (*see Case* 2). A similar condition very occasionally follows a normal, perhaps prolonged, lactation (*see Case* 3).

The feel of the tissue in adenosis has been given many descriptions—knotty, rubbery, gritty, nodular—depending much on its duration and extent. Ordinary breast tissue, without a covering of fat, is somewhat nodular to feel. If limited to one small area, hypertrophic

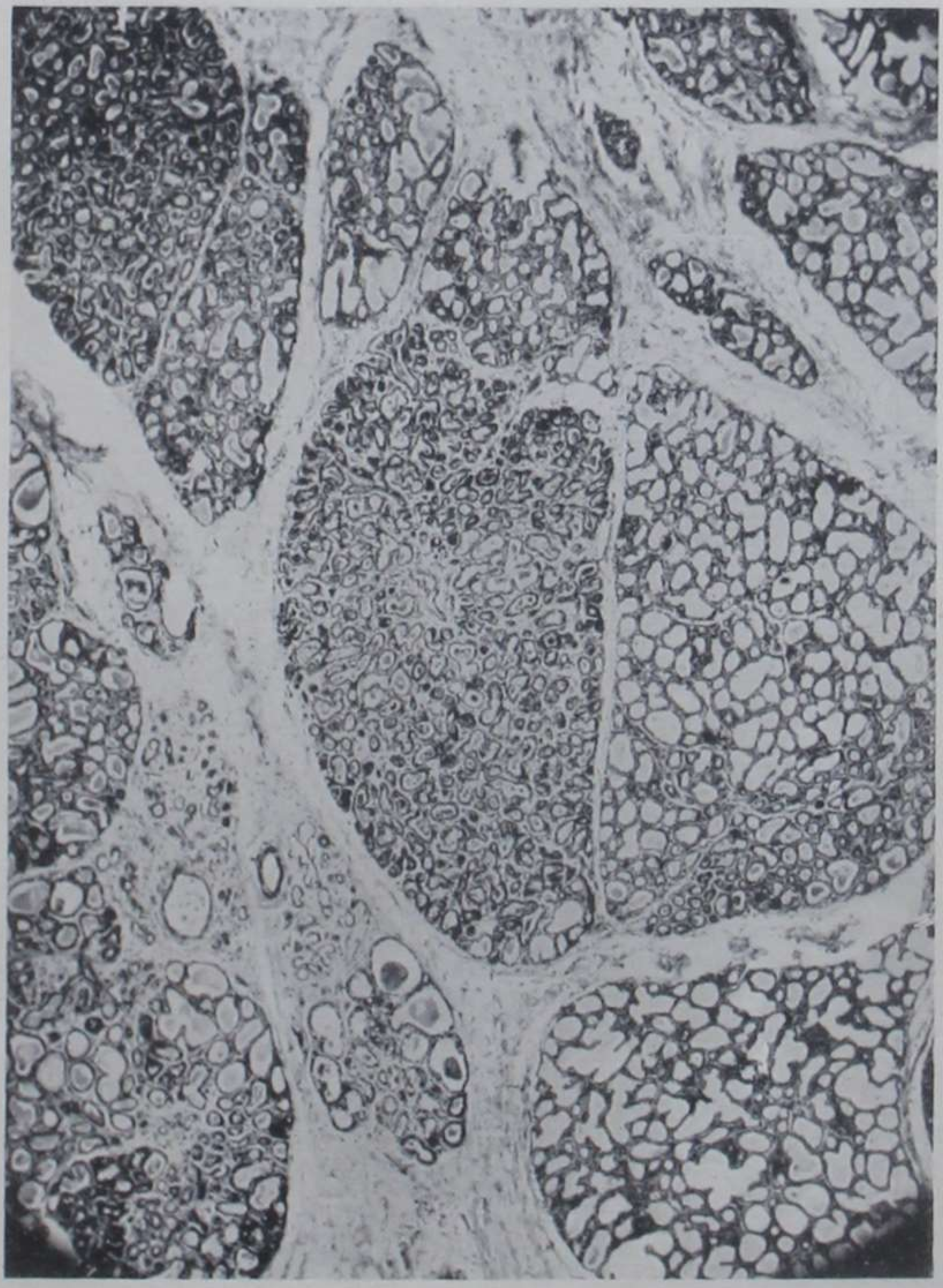

Fig. 72.—Lactating breast. The section shows the structure of a lactating breast four days after childbirth. The patient died of acute anterior poliomyelitis. This section should be compared with *Fig.* 71, showing the condition of adenosis. (× 30.)

tissue may produce a solitary pea-sized nodule, often painful and tender, or a number of scattered nodules, or patches of knotty tissue involving much of the substance of one or both breasts. The extent of the changes has no apparent bearing on the severity of the symptoms. The ratio, in fact, is not infrequently inverse.

The skin, the position of the nipple, and the outward appearance of the breasts is unaffected, though a slight difference in size between the two sides may be noticeable (*Fig.* 73).

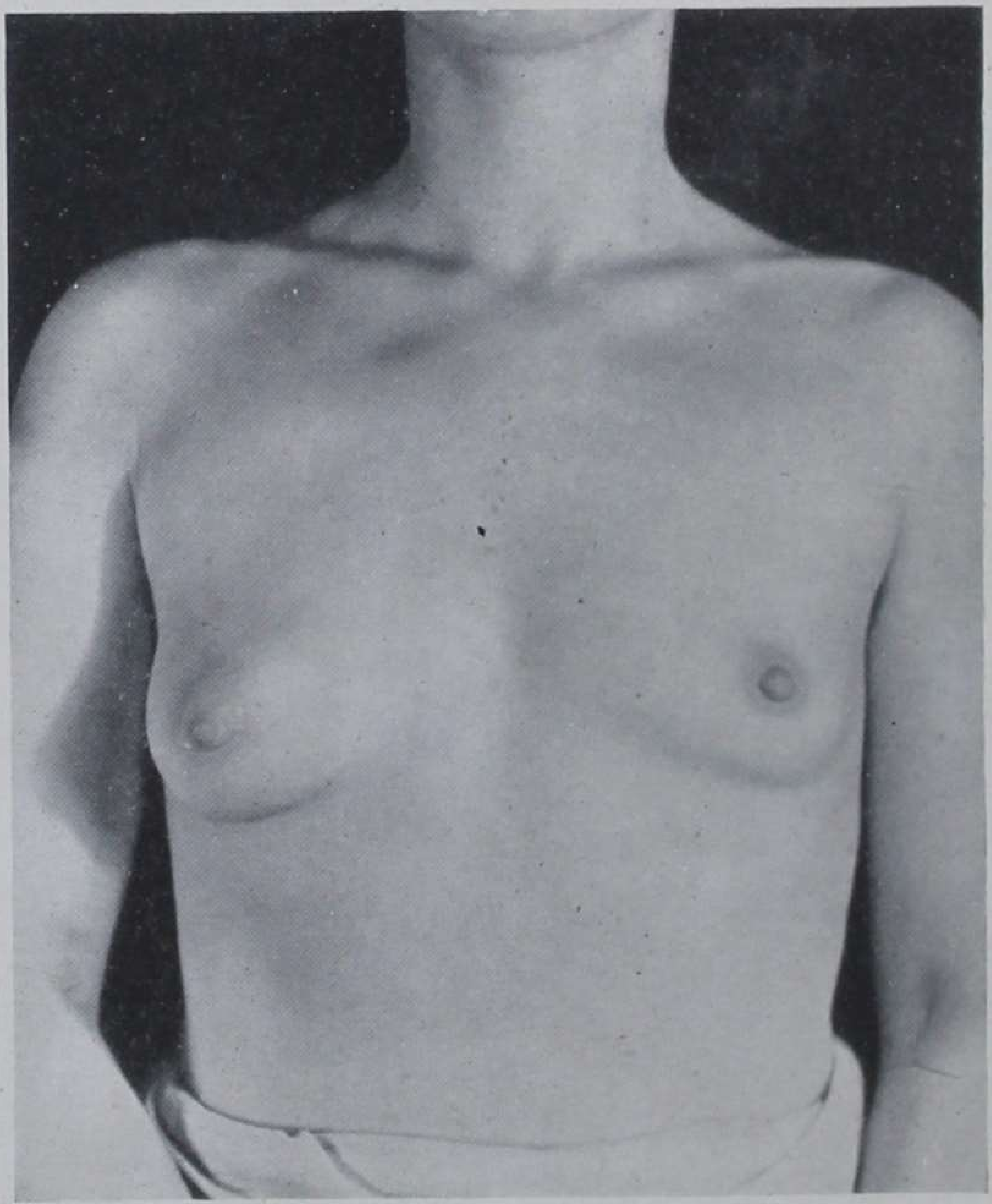

Fig. 73.—Adenosis of the right breast. Married woman, aged 25. Two months' history of swelling of the right breast. Moderate discomfort before menstruation. Menstrual history normal. Areas typical of adenosis over most of the lateral half of the breast.

Case-histories.—Some of the points mentioned in regard to the depreciation of mammary tissue are illustrated by the following cases :—

Case 1.—Polish woman aged 25. Originally of excellent health and physique. During three years in a concentration camp in the War she lost some $3\frac{1}{2}$ stone in weight. She complained of aching in both breasts, especially, though not only, just before menstruation, which was regular, but scanty. The pain, a feature previously unknown to her, had started about 12 months before release from the camp and had continued without remission for over 2 years. She complained too of the hardness, lumpiness, and "loss of size" of both breasts. Practically all the rather scanty breast substance had been replaced by dense, knotty, and tender adenosis tissue.

Case 2.—Woman aged 28. A healthy, well-built woman. Her first pregnancy was terminated at ten weeks, and later she was sterilized because of the strong history of hæmophilia in her family. Soon after leaving hospital she began to complain of considerable aching in the right breast, less in the left, present most of the time, and sufficient on occasion to interfere with sleep.

Typical tender adenosis tissue was present in the upper outer quadrants and along the lateral borders of both breasts. After about eighteen months the symptoms started to ease and gradually disappeared, with at the same time a marked improvement in the consistency of the breast substance.

Case 3.—Woman aged 26. Two children, aged 4 and 2½. Both had been breast-fed for over ten months without any difficulty. About six months after weaning the second child this patient began to complain of aching, "lumpiness", and "loss of size" of both breasts.

Obvious areas of tender, indurated, and nodular tissue were found, and in view of the unusual history and density of the tissue a biopsy was made from each side. A histological report of hypertrophy of gland tissue was returned. This woman again became pregnant; at the fourth month her symptoms had abated and on examination the breast tissue appeared of normal consistence.

Some observers regard pregnancy as an unfailing remedy for promoting or restoring the mammary tissue to a normal, balanced state, but lactation—although perhaps satisfactory for a short period—is usually limited. Nevertheless, the effect is mainly beneficial, and as a rule any symptoms and signs are difficult to distinguish after about the third or fourth months of pregnancy.

Mastodynia (Painful Breasts).—The main feature of mastodynia is severe pain with few, if any, physical signs.

The pain is usually an exaggeration of the more normal sensations in the breast which precede menstruation, but instead of easing with the onset of the period, it continues with varying intensity. Changes in the breast tissue, when present, are those of adenosis, from which there is no genuine distinction except in the severity of the symptoms.

Mastodynia, which is not a common condition, occurs mainly in women of 20 to 30 years of age, of poor physique, and not infrequently in this type in the early months of marriage. The condition may be transient or intermittent, affecting one or both sides, and in some instances it is stated to be continuous over a period of years and in the extreme case till the menopause. Sensations of differing degree, variously described as throbbing, burning, or stinging, and exaggerated by a sudden jar or noise, are complained of, and in severe cases extend over the chest wall to the shoulder or down the arm, movements of which aggravate the pain.

Often the whole breast is tender to touch, and in about half the cases small pea-sized nodules or scattered sensitive patches of ' knotty ' tissue are noticed either by the patient or on palpation. In the event, however, of tissue being removed for examination, its naked-eye appearance shows little or no abnormality but hypertrophic changes are generally noted microscopically.

Pain may precede any discoverable alteration in the mammary substance, so that in the doubtful case causes outside the breast have to be considered. Pain from deformities or arthritis of the spine, or an intercostal neuritis, can be referred to the breast area, as well as disease of the ribs immediately deep to the breast.

In another small group of cases of mastodynia the psychogenic factor, nearly always present, predominates. It includes women of ordinary physique, with symptoms varying little in intensity and quite out of proportion to the clinical findings or disturbance of general health.

Case-histories.—The following cases serve to illustrate some of these points :—

Cases 1 *and* 2.—Ages 26 and 30 when first seen. Unmarried. Medium development. Menstrual periods normal. Both these women attended the out-patient department regularly for some 3 to 4 years, one for pain in the right and the other in both breasts. The pain was described as " unbearable " and there was always much wincing on examination, but little could be found except for a few scattered tender nodules, which did not vary. Treatment was ineffectual. Yet both these women, after a week or two of war work, one in a factory and the other in the A.R.P. service, were completely relieved of their pain, and some months later when examined again the breasts were only slightly tender, though otherwise the signs were the same as before.

Case 3.—Age 22. Good health, strongly built, a keen rider, swimmer, etc. This young woman complained of constant and severe pain in the left breast, with a degree of tenderness of the whole gland quite out of proportion to the general or local condition. The origin of the pain was stated to be an injury some two or three months previously, and removal of the breast was " demanded " to give relief. Treatment was of little avail until the story of an unrequited affection was unearthed and dealt with by the parents, when—with the breast still in situ!—the pain was soon forgotten.

A psychogenic manifestation of this type is probably rare, but an anxiety which has become centred on the breast, including the fear of cancer itself, has sometimes to be excluded in the diagnosis of mastitic lesions.

Treatment.—Adenosis is not always painful, often not, but is relatively more prone to cause symptoms, sometimes severe. Differences of tension and circulation within the mammary tissue, personal sensitivity, and anxiety of mind are features which may influence the degree of pain. As part of a general anatomical ill-equipment, though causing symptoms, the condition does not necessarily call for active treatment. An essential, however, in the management of all these cases is reassurance and observation. Apart from this, action is seldom required except, on occasion, to confirm the diagnosis by biopsy.

If consequent on illness or under-nutrition, attention should be directed to the general rather than the local failure. The main reason for treating adenosis *per se* is for the presence of mammary pain severe enough to interfere with ordinary activities or sleep, and the benefits of treatment will be measured by its success in giving relief. Any improvement gained in the state of the breast tissue appears to be but temporary excepting perhaps after a pregnancy.

If pain, making due allowance for a psychogenic factor, is regarded as a manifestation of functional activity under difficulty, a basis is given, theoretically at any rate, for the management of a case. This should include, in most cases, assistance in general nutrition, and, in some, hormone therapy. Radiotherapy and surgery may be used in the occasional case to deal with an isolated area of painful adenosis tissue.

1. *Simple Remedies.*—Support of the breasts.* Ultra-violet therapy, a rest from work, mild sedatives, etc., are often helpful remedies and worthy of a fair trial.

2. *Endocrine Treatment.*—Treatment with œstrogen, progesterone, and androgens has now been tried in a sufficient number of cases to permit of a comparison and assessment of their respective merits.

Œstrogen : Œstrogen therapy, which, at first sight, appears to be irrational, has been shown as a result of experimental work (Hamblen, Cuyler, and Axelson) to enhance the function of the corpus luteum when given in the first half of the intermenstruum. If, as a result, the increased output of progesterone is proportionately greater than the œstrogen administered, such treatment may be effective. The method is indirect in action and consequently uncertain in its results.

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* In order to obtain effective support the breasts must be actually lifted. For this purpose the lower border of a brassière should fit firmly round the chest wall below the breasts, and the main shoulder-straps should act from the centre of its upper border. In addition, elastic supporting straps stretch from the top points of the cups of the brassière to the main shoulder-straps. (This description is based on a model designed by Messrs. Bruce & Evelyn, London.)

Again, the administration of substances, such as œstrogen, which are thought under certain conditions to act as carcinogenic agents, may well appear to be harmful. But if the length of a course of treatment is considered in proportion to the life-span, and the high dosage in relation to body-weight required experimentally to produce cancerous changes in the mouse mamma even in a susceptible strain, the usual amount given to a woman seems unlikely to prove dangerous. (When assessing the results of experimental evidence allowance must be made for the considerable differences between human and animal physiology of mammary tissue.) Nevertheless cancer of the breast has been reported to develop during œstrogen therapy (Allaben and Owen; Auchincloss and Haagensen; Parsons and McCall), and its value in the treatment of mammary dysplasia is scarcely sufficient to warrant any risk. Caution is urged against unnecessary use.

Progesterone: Treatment by intramuscular injections of progesterone—5 mg. twice weekly for two weeks preceding menstruation—was found to give symptomatic relief in a number of cases of various types of chronic mastitis (Geschickter). Often, a higher dosage (10 mg. daily) has been required, but treatment is troublesome and expensive for the patient. In order to overcome these objections the oral use of ethisterone was tried without success.

Androgens: The administration of androgens by mouth (methyl testosterone 5 mg. daily) has generally been found helpful in relieving pain and diminishing nodularity. At this level of dosage there is little risk of masculinization or of causing menstrual irregularities. Androgen therapy needs to be prolonged—4–6 months—and the permanency of its effects is variable.

Inunction of the breasts with testosterone ointment is also sometimes effective. These two methods are preferred to injections of testosterone propionate.

3. *Radiotherapy.*—Deep therapy with its generally beneficial effect on hyperplastic tissue will often relieve pain in cases of adenosis or hyperplastic cystic disease. The induration shrinks after moderate dosage, such as 1000 r tissue dosage in one week, which is insufficient to produce erythema or late effects.

4. *Surgery.*—The small nodule or area of tissue, apparently the source of pain and causing anxiety of mind, may be removed. A local excision of hypertrophic tissue is often successful in relieving symptoms and confirming a diagnosis on which reassurance can be based. If, however, the psychogenic factor is marked, pain is apt to remain unrelieved and to be transferred to the operation scar or elsewhere.

HYPERPLASTIC CYSTIC DISEASE

(*Fig.* 74)

Pathology.—An epithelial hyperplasia, or epitheliosis, with the formation of cysts and a varying amount of fibrous tissue, is an activity of the mammary tissue serving apparently no useful or physiological purpose. The term hyperplastic cystic disease is used as it includes two of the main features of a state potentially neoplastic in design during the years of the menopause. Otherwise, during the menstrual

Fig. 74.—Hyperplastic cystic disease. Radial section through wedge of indurated nodular tissue in situ. Marked fibrosis with few cysts. The latter are somewhat larger than is usual.

cycle, this form of mastitis varies little, except perhaps to increase in extent, while normally regression of the condition is coincident with that of the mammary tissue in general.

Hyperplastic cystic disease is recognizable by the naked eye as, on macroscopic section, a number of small cysts are found which exude a typical inspissated greenish fluid (*Fig.* 75). The mastitic tissue itself feels solid, firmly nodular, and may be up to an inch thick; the whole specimen in its fresh state requires careful palpation for any area suspiciously hard or a nodule larger than the average.

Cysts are always present, usually very small, about ·2 mm., or are seen only on microscopic examination; occasionally in a long-standing case a cyst of some size is found. Cysts are the result of the blocking of the ducts by desquamated epithelium, or, it has been suggested, from strangulation by fibrous bands, or, again, of distension by over-secretion of fluid from œstrogen excess. The microscopic appearances suggest that acini become distended

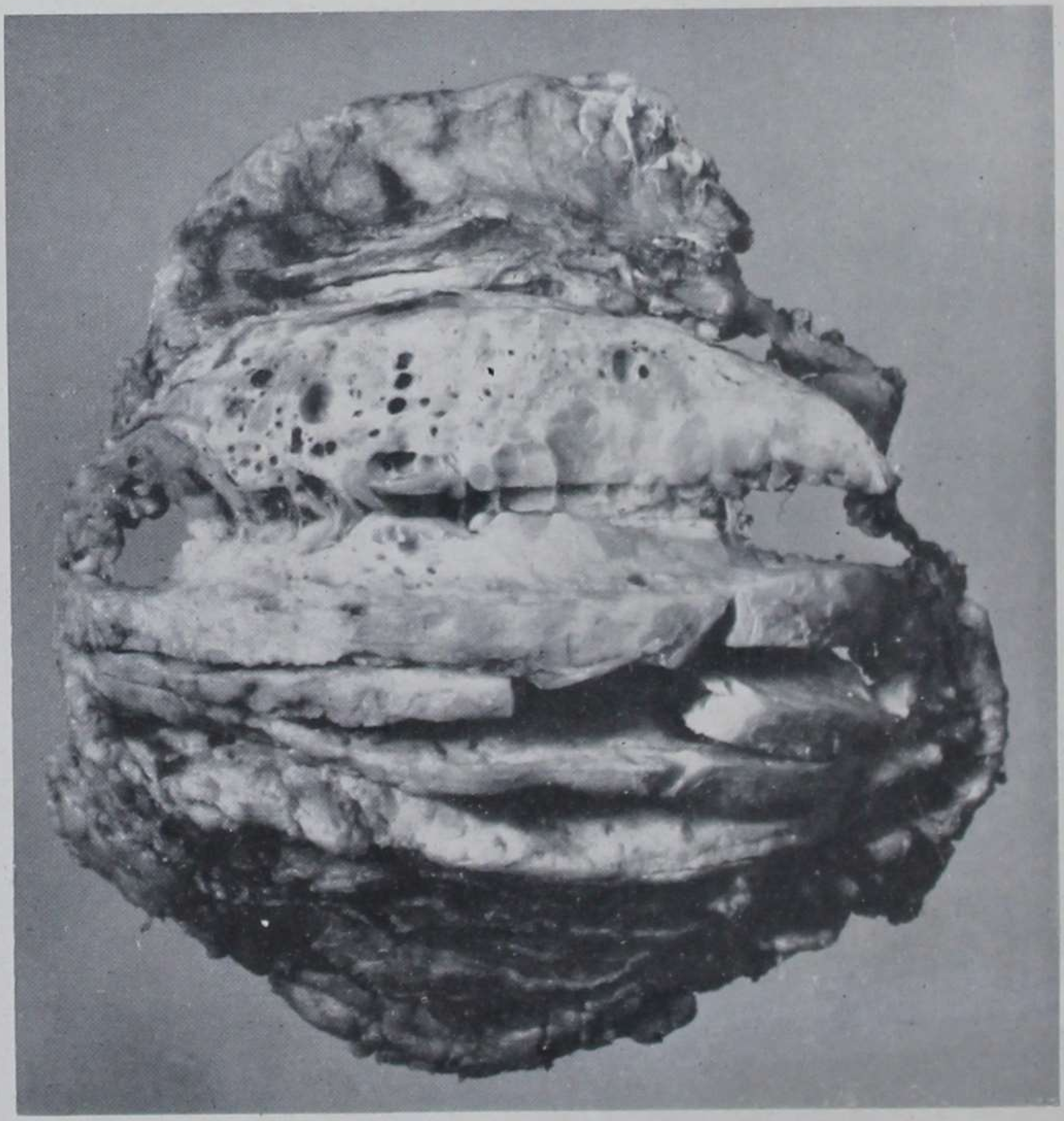

Fig. 75.—Breast tissue showing the typical appearance of hyperplastic cystic disease. The mammary tissue is greatly thickened and contains many small cysts from which thick greenish yellow fluid can be expressed.

into cysts, though these are smaller than those arising from the ducts.

Microscopic Appearances.—Epithelial changes are characteristic and easily detected (*Fig.* 76). Compared with normal areas in the section the acini in abnormal areas are perhaps larger and stain differently, but the most distinctive feature is the presence of cysts and the formation of papillomatous processes or intracystic papillæ (*Figs.* 77, 78). This state has been called a benign neoplasia and probably rightly so, although some of the multi-radicular papillæ may be the

Fig. 76.—Section of specimen from adult male breast. Note the increase in fibrous tissue, the distended tubules, and epithelial hyperplasia. (× 50.)

result of epithelial hyperplasia and atrophy of intervening connective tissue.

More important, though, is the solid epithelial hyperplasia obviously suggestive of a starting-point for malignant change. Rounded cells with deeply staining vesicular nuclei pack the circular spaces (intraduct adenoma), or larger cells with hyperchromatic nuclei (intraduct carcinoma). The former appearance may be merely an epithelial bud, which, not infrequently, is associated with the more ominous intraduct carcinoma.

A well-marked round-celled infiltration of the lobules is frequently in evidence, and a general increase of fibrous tissue as well as peri-acinar fibrosis.

Clinical Aspects.—Hyperplastic cystic tissue forms mainly in the sub-fertile type of woman of about 35–45 years of age. The

Fig. 77.—Section showing the small cysts, epithelial hyperplasia, and multi-radicular papillomatosis of hyperplastic cystic disease. (× 18.)

condition, much less common than adenosis, is usually found as a lump, or because of pain, which is sometimes severe.

Any clinical differences between adenosis and hyperplastic cystic disease are not precise. The setting is often the same and the two conditions not infrequently coexist, but hyperplastic cystic disease is limited more to one type of woman and is more permanent, though, like adenosis, it regresses at the menopause. The differences in the feel of a nodule of hypertrophied tissue and a small cyst, or of the density of 'knotty' and 'indurated' tissue, are too narrow to define.

In a typical case hyperplastic cystic disease is confined to one segment of one or both breasts. The elevated, dense tissue, which

Fig. 78.—Multi-radicular papilloma in a case of hyperplastic cystic disease. Note the broad base. (× 50.)

may form an isolated patch or a roughly triangular or sector-shaped lump of indurated tissue, its base towards the periphery, is easily palpable. When the tissue is taken between the finger and thumb the small nodules are generally obvious, and also, a distinctive feature, the indurated area appears to have a definite margin or edge. When examined with the flat of the hand the induration seems less obvious and the tissue flattened, with the sensation, perhaps, of the skin being

Fig. 79.—Hyperplastic cystic disease. A problem that may arise in the operating theatre is here shown. Is this condition innocent, malignant, or pre-cancerous ? (× 27.)

Fig. 80.—The same more highly magnified. (× 60.)

not entirely free from the underlying tissue, though otherwise there is no fixation.

Treatment.—In many, probably most, cases of hyperplastic cystic disease a biopsy is necessary to establish a diagnosis and exclude carcinoma. This can be conveniently arranged as an operative investigation, with immediate microscopic examination in the theatre by which further procedure is controlled (*Figs*. 79, 80). In these investigations much depends on the views and experience of the examining pathologist. A snap diagnosis between hyperplastic and malignant epithelium is not always justifiable, but a positive diagnosis of benignity and of carcinoma is a great help. If there is doubt, the wound should be closed and a full pathological examination made. Seldom, actually, is the theatre diagnosis reversed.

A local excision of indurated tissue, from its extent, may entail a simple mastectomy, or a pathological report of undue epithelial activity may be regarded as an indication for this operation. Removal of the breast is unnecessary in the absence of malignant change, provided that regular observation can be maintained over a sufficient period of time and a further excision of tissue and examination be made if necessary. Otherwise treatment follows similar lines to those described for adenosis.

Case-history.—The following case illustrates many of the characteristics of hyperplastic cystic disease with unusual and controversial findings:—

Fig. 81. — Hyperplastic cystic disease. Rough sketch of the type of patient whose case is described in the text.

Case. Age 43. Single. Thin, breasts flat and scanty tissue (*Fig*. 81). Complained of pain in the left breast, sometimes sharp and shooting, not associated with the periods, and of hardness in the upper part noticed for about three months. General health unchanged; menstruation was stated to be always irregular and varying in length.

A simple mastectomy was performed and the pathologist's report gives the general picture :—

"The nipple is large and partly retracted. The breast tissue is 1 in. thick, feels rather hard and nodular. The indurated area forms roughly a triangle with the apex at the nipple and the base $3\frac{1}{2}$ in. long at the periphery. Several small cysts are present deep in the breast tissue, the largest being only 2 mm. in diameter.

"*Microscopic Examination*: The sections show well-marked lobular hypertrophy (adenosis) with increase of peri-acinar fibrous tissue and infiltration with small round and plasma cells. Also, there is epithelial hyperplasia (epitheliosis) and duct distension. The epitheliosis varies from a slight degree of hyperplasia of a few acini to massive proliferation of cells which appears to be wholly within the ducts. This almost solid epithelial hyperplasia has multiple lumen formation giving a cribriform appearance (cribriform carcinoma). A favourable circumstance is that no infiltrative tendency has been found.

"The condition is that of hyperplastic cystic disease in which intraduct carcinoma has developed."

About fifteen months later this woman developed a lump in the right breast. A hard, rounded, isolated lump about $\frac{1}{2}$ to $\frac{3}{4}$ in. ($1\frac{1}{2}$–2 cm.) in diameter was obvious on examination in the lower and outer quadrant—a quite different clinical picture to that of the previous occasion and one suggestive of a carcinoma.

After removal the specimen was examined by a different pathologist and reported on as follows :—

"Acinar and polygonal-celled carcinoma arising in breast tissue showing chronic mastitis with cyst formation."

INVOLUTIONARY MASTITIS OR FIBROCYSTIC DISEASE

(*Figs.* 82, 83)

Pathology.—A feature of the regressive changes of breast tissue is dilatation of the ducts and the formation of cysts. The cysts are medium-sized or large and solitary, together with a number of small ones, and embedded in, or surrounded by, dense fibrous tissue. On exposure the wall of a superficial cyst generally has a bluish tint—the blue-domed cyst of Bloodgood—and the dome is covered by attenuated tissue or fat ; the colour disappears on liberation of the fluid, which, though sometimes clear, is more often a cloudy milky serum. The lining of the cysts is smooth and shiny.

The changes are found mainly in a large fatty type of breast, and the cysts are situated at any level of its substance or stand out from the surface of the mammary tissue so as to be obvious or easily palpable under the skin. Dilated ducts are occasionally visible in the nipple area.

Fig. 82.—Fibrocystic disease in a woman aged 48. Large solitary cyst in breast substance—'blue-domed' cyst of Bloodgood. Coloured drawing constructed from biopsy.

Fig. 83.—Fibrocystic disease in a woman, aged 38, showing breast in situ. Multiple small cysts.

Microscopical Appearances.—A cyst may have a lining of flattened epithelial cells or no cell lining. Usually there is fibrous thickening of part of the cyst wall, the remainder of which is very thin (*Fig.* 84). In the thickened part massive cellular areas are not uncommonly found and these are packed with acini so dense as to suggest an adenoma. It is unlikely that this is a true tumour; more probably it is a condition of adenosis. In the remainder of the breast tissue the picture is

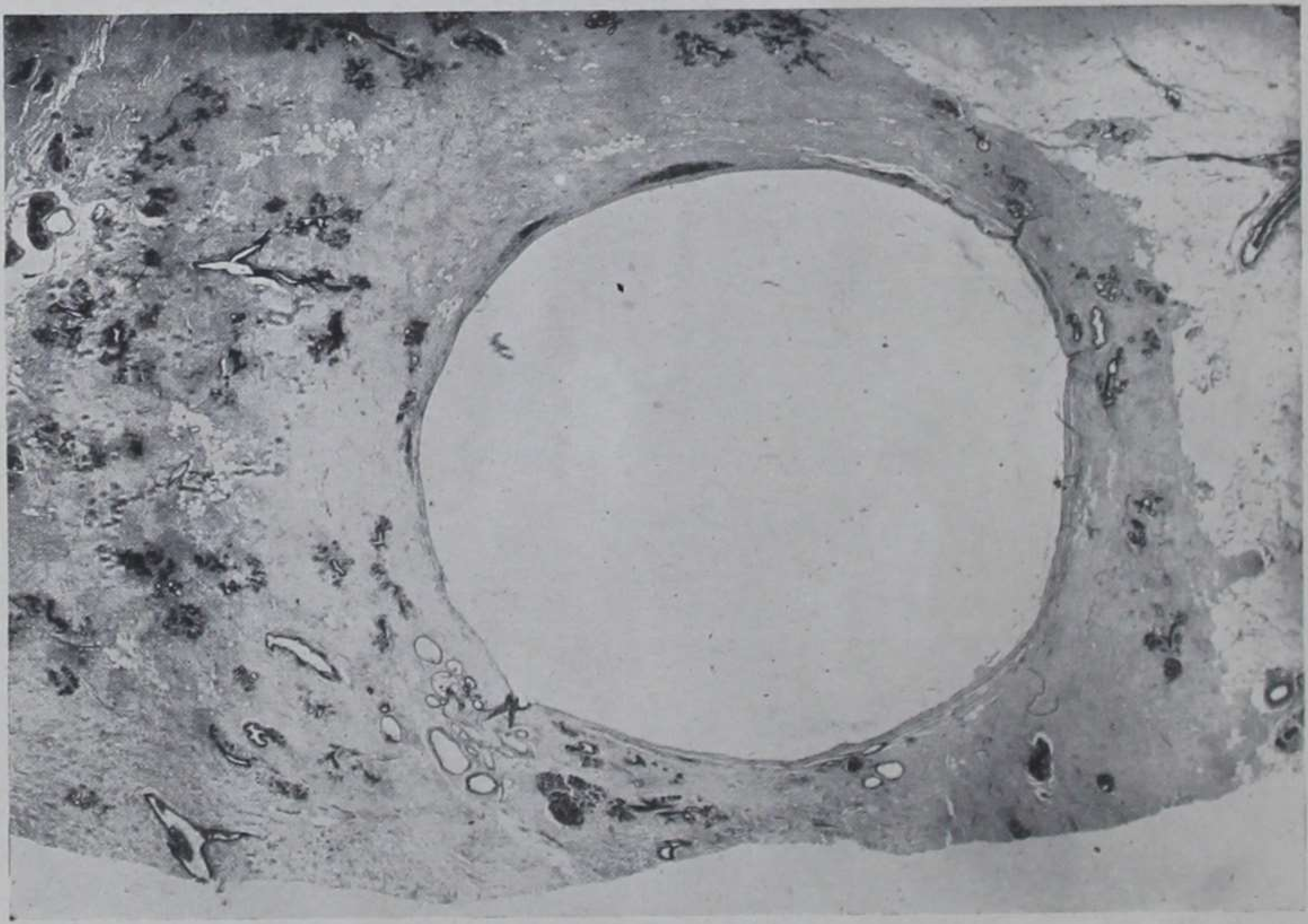

Fig. 84.—Fibrocystic disease of breast. The illustration shows a small cyst, 7 mm. in diameter, fibrosis, and some cystic dilatation of acini. The tissue formed part of the wall of a larger cyst of about 1 in. in diameter. (× 9.)

mainly one of atrophy, viz., a few scattered tubules embedded in fibrous tissue. (*See also* Chapter I, pp. 46-48.)

This state of the mammary tissue, here called fibrocystic disease, conforms probably to a physiological but exaggerated type of involution causing mechanical difficulties in drainage. The changes, which are apt to occur in one or both breasts, tend to persist, but sometimes regress and are benign in character. Inasmuch, however, as a large cyst may have an epithelial lining, a chance of neoplastic growth presumably exists. Judgement, though, has perhaps been influenced unduly against the character of involutionary cysts in general owing partly to clinical difficulties in diagnosis between cysts and carcinomata, more especially during the cancer age, and also because malignant tissue *per se* sometimes undergoes cystic changes.

Clinical Aspects.—Involutionary cystic conditions, which are apt to occur with greater frequency in nulliparæ, fall into two main clinical groups but with no essential histological differences. The heavy type of woman of 45–55 years of age with a large, solitary cyst—most often situated in the upper half of a pendulous breast—comprises one group, the more common. The other consists of younger women of 35–45, generally of spare build, with single or multiple small cysts affecting one or both breasts. Either of these manifestations of fibrocystic disease may be presented as an isolated tumour at any time during the period of regression of mammary activities.

A so-called large solitary cyst—in most cases there are a few small cysts as well—varies in size up to 1 or 2 in. in diameter or more. When near the surface it feels smooth, rounded, and fluctuant, making a diagnosis reasonably certain. On the other hand, if deeply placed in the breast, and the wall is tense and fibrous, a cyst can be very difficult to identify by palpation alone. Carcinoma and the large cyst form the most common mammary tumours of the woman of about 50, but the former outnumber the latter by something like 5 to 1.

In a number of cases attention is attracted by the finding of an obvious lump which has suddenly appeared in the breast. Sometimes it disappears again almost equally suddenly; the lump that is said to have vanished, or to come and go, is generally of this nature. Pain, or dragging, if complained of at all, tends to be associated with the appearance of the swelling. Not infrequently a serous discharge from the nipple is noted during involutionary changes. The discharge may be clear, or a muddy brown or greenish colour, and thickened from stagnation in the ducts.

(A dilated tortuous duct may itself form a visible and palpable tumour in the central area of the breast and cause discoloration and dimpling of the areolar skin. Because of its feel this tumour has been called the varicocele tumour of the breast. Dimpling of areolar skin does not seem to have the same significance as elsewhere.)

Treatment.—Aspiration only of a large cyst is not to be recommended, since the fluid tends to re-collect; but, apart from this, the setting is not known without operative exposure and investigation, which is essential in most cases.

Involutionary cysts may be on the surface of the breast tissue or walled in by dense, rubbery tissue. Provided that their nature is not in doubt—confirmed by immediate microscopic examination—a local removal is all that is required. At the same time the extent of the fibrotic tissue, in which further nodular areas, formed by small cysts, are often palpable, may influence the limits of an excision and encourage removal of the breast.

The other variety of fibrocystic disease is characterized clinically by one or more smooth rounded swellings which may be noted to vary in size and are sometimes slightly painful. When presented as a small, discrete but dense tumour an area of fibrocystic disease can be difficult to distinguish from a neoplasm ; an area of malignant tissue, especially of the encephaloid type, can feel very much the same. An operative investigation is again essential. For the small involutionary cyst a local excision is sufficient. Multiple cysts may be regarded as an indication for a simple mastectomy, perhaps for future peace of mind rather than as a measure of safety.

If then regular observation can be maintained these involutionary cystic conditions of the breast do not actually warrant interference beyond the requirements for a diagnosis. If, however, a new situation arises in the same or opposite side a second biopsy is immediately called for.

Case-history.—The following case was instructive :—

Age 52. Three children. A big, heavy woman. Complained of pain, a sensation of pulling, and a lump in the right breast. On examination the lump, some 2 in. (4–5 cm.) in diameter, situated in the upper central area of a very large breast, was thought to be a cyst. Removal was advised.

At the operation a typical superficial "blue-domed" cyst, embedded in a dense fibrous bed, was found, as well as several minute cysts in the surrounding tissue. A local excision was performed. No evidence of malignancy was found by microscopic examination.

Over a year later this same woman reported again for a lump in the left breast. This time she had found a rounded discrete lump near the margin of the lower outer quadrant which, as a result of the previous finding in the right breast—incidentally the condition of this breast was satisfactory—was thought to be a small cyst, but biopsy was advised. At the operation a circumscribed, softish but solid tumour was removed and found to be malignant.

SUMMARY

Biopsies on the 'lumpy' breasts of the middle-aged woman usually show an histological picture mainly of fibrosis. In some instances this appears to be due to a fibro-adenosis, and in others to hyperplastic cystic disease in which fibrosis rather than cyst formation is predominant.

Three main groups of cystic conditions can be distinguished :—

1. *Hyperplastic Cystic Disease.*—A phase of chronic mastitis associated with scanty breast tissue in a woman of the late thirties and forties. The cysts are very small and often a microscopical finding only. The significant feature, histologically, is epithelial hyperplasia. This condition is regarded by many authorities as potentially dangerous.

2. *Fibrocystic Disease.*—A benign process and within the range of a normal physiological regression of mammary tissue. Two clinical types can be recognized : the large solitary cyst found in a fatty pendulous type of breast ; and the single or multiple small or medium-sized cysts of the small breast.

3. *Malignant Cysts.*—A less common type of cyst resulting from the presence of or as an actual part of a carcinoma.

The average age given for these groups is approximate. Geschickter's figures show a peak for hyperplastic cystic disease (' adenosis ' in his nomenclature) between 35 and 39, and for fibrocystic disease (' cystic disease ') between 40 and 45. Malignant cysts occur mainly in older women. It is probably accurate to say that benign cystic conditions are very rarely seen before the middle thirties, but from then onwards over the next ten to fifteen years they become a more or less routine clinical entity.

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CHAPTER VI

BENIGN TUMOURS. CHRONIC INFECTIVE LESIONS

By P. O. Ellison, F. D. Saner, and Valentine Swain

BENIGN TUMOURS

FIBRO-ADENOMA

(*Figs.* 85, 86)

Pathology.—The fibro-adenoma is a tumour essentially of connective-tissue origin, as this, rather than the epithelial element,

Fig. 85.—Fibro-adenoma of breast exposed. Rapidly growing tumour in a girl of 19, about two months pregnant.

grows in greater profusion. The name, therefore, is not altogether descriptive, but in the young woman the fibrous and glandular elements may be more evenly balanced.

On macroscopic examination the fibro-adenoma is smooth, encapsuled, rounded and lobulated, somewhat tough to cut when its surfaces are convex and its substance homogeneous.

Histologically, two types of fibro-adenoma are distinguishable; the peri-canalicular, showing small tubules surrounded by concentric rings of fibrous tissue, and the intra-canalicular (*Fig.* 87), which consists of lobules of fibrous tissue covered by epithelium. The latter type, found more generally in the older woman, may grow to a

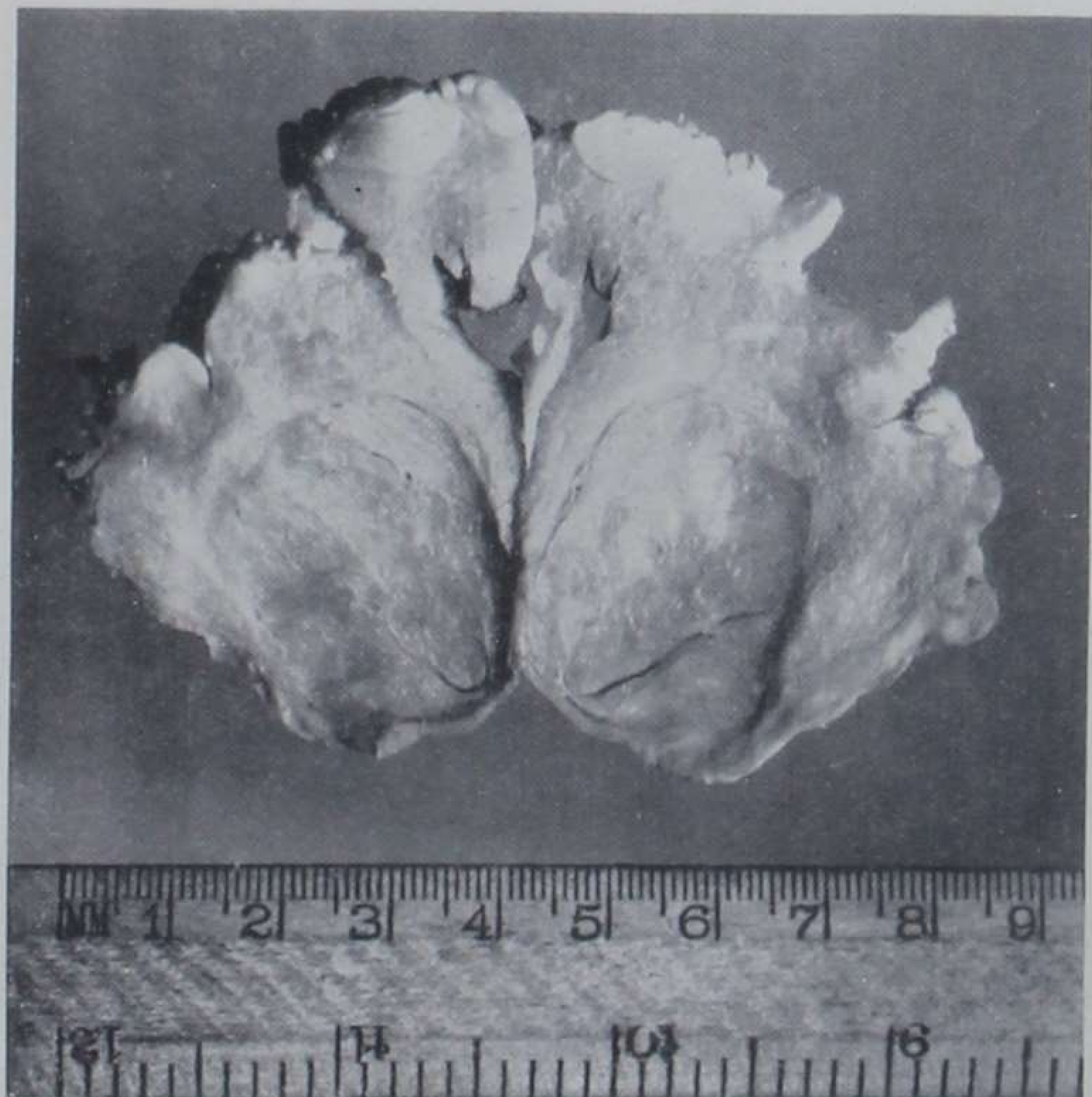

Fig. 86.—Piece of breast tissue showing an oval-shaped fibro-adenoma. Note the cleft running into the base of the tumour.

large size (cauliflower tumour of the breast), or undergo cystic degeneration (sero-cystic or Brodie's tumour—*Fig.* 88), myxomatous degeneration, or assume malignant characteristics of a sarcomatous type.

Any relationship between fibro-adenoma and chronic mastitis is doubtful, though, very occasionally, in hyperplastic cystic disease, a connective-tissue core covered by a single layer of epithelium is seen.

Clinical Aspects.—The fibro-adenoma is the common mammary tumour of the girl or young woman. The majority occur between the ages of 16 and 35, very occasionally before this, but not infrequently in older women.

At first a fibro-adenoma tends to grow rather quickly and then after reaching a certain size to remain stationary ; the small mammary

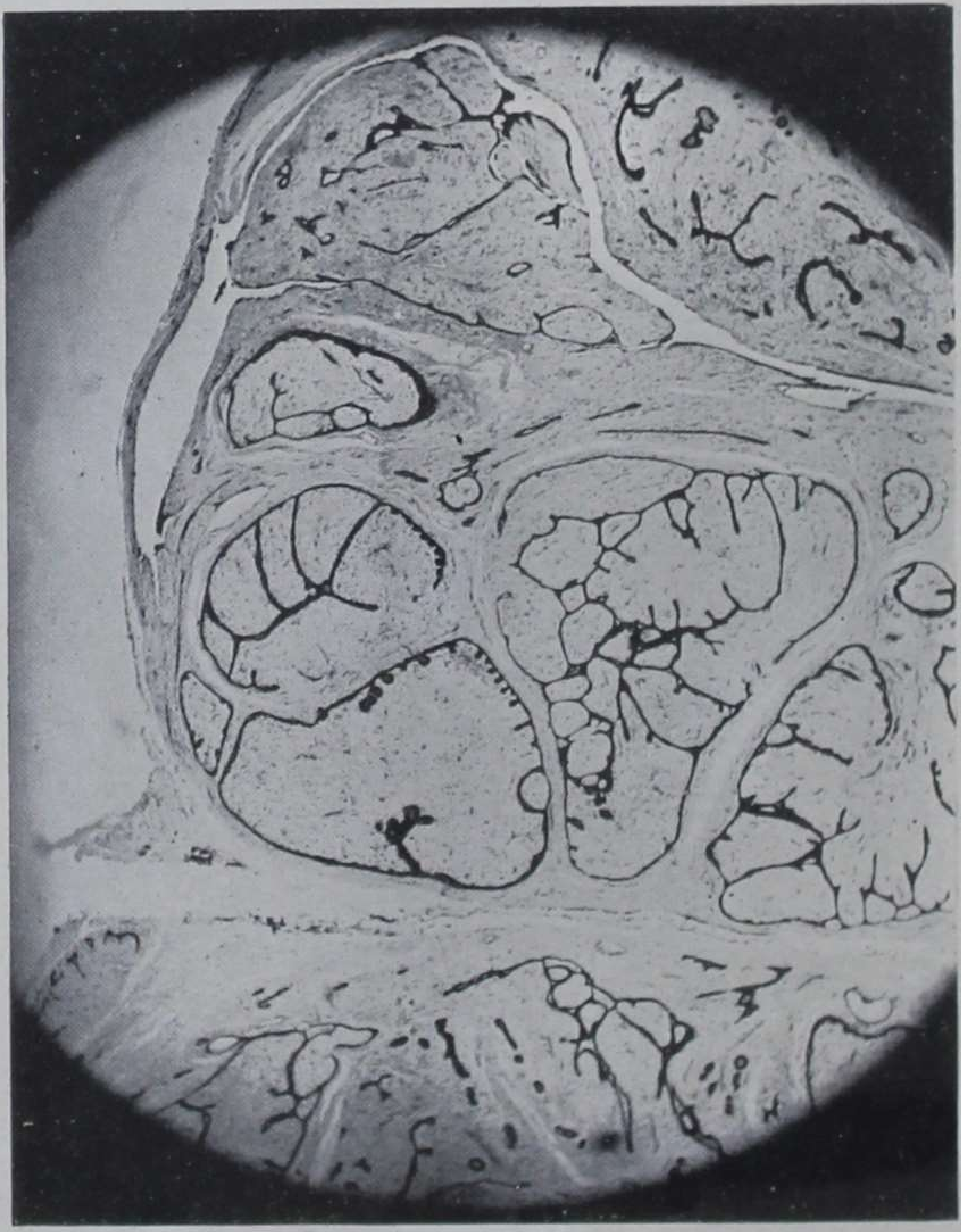

Fig. 87.—Intra-canalicular fibro-adenoma from the breast of a young woman. The tumour was easily shelled out from the surrounding tissue. Note the preponderance of fibrous tissue and the clefts formed by deeply stained epithelial cells. (× 18.)

tumour which has been present and remained unaltered for a number of years is generally of this nature ; it shows no invasive property.

In size, these tumours vary from about half an inch up to three to four inches in diameter, but freak cases are reported of two feet in diameter and weighing many pounds (*Fig.* 89). If a fibro-adenoma is present in the breast at the beginning of pregnancy, its growth is stimulated by the general increased activity of the mammary tissues, though without any change otherwise in its main characteristics.

Fibro-adenomata are most common in the lateral half of the breast, and a lump, as a rule, is the first noticeable feature, though pain is not infrequently associated with this and in the occasional case precedes it.

Case.—Woman aged 31. Unmarried. Music teacher. A tall, spare woman. Complained of pain in the outer half of the right breast, worse

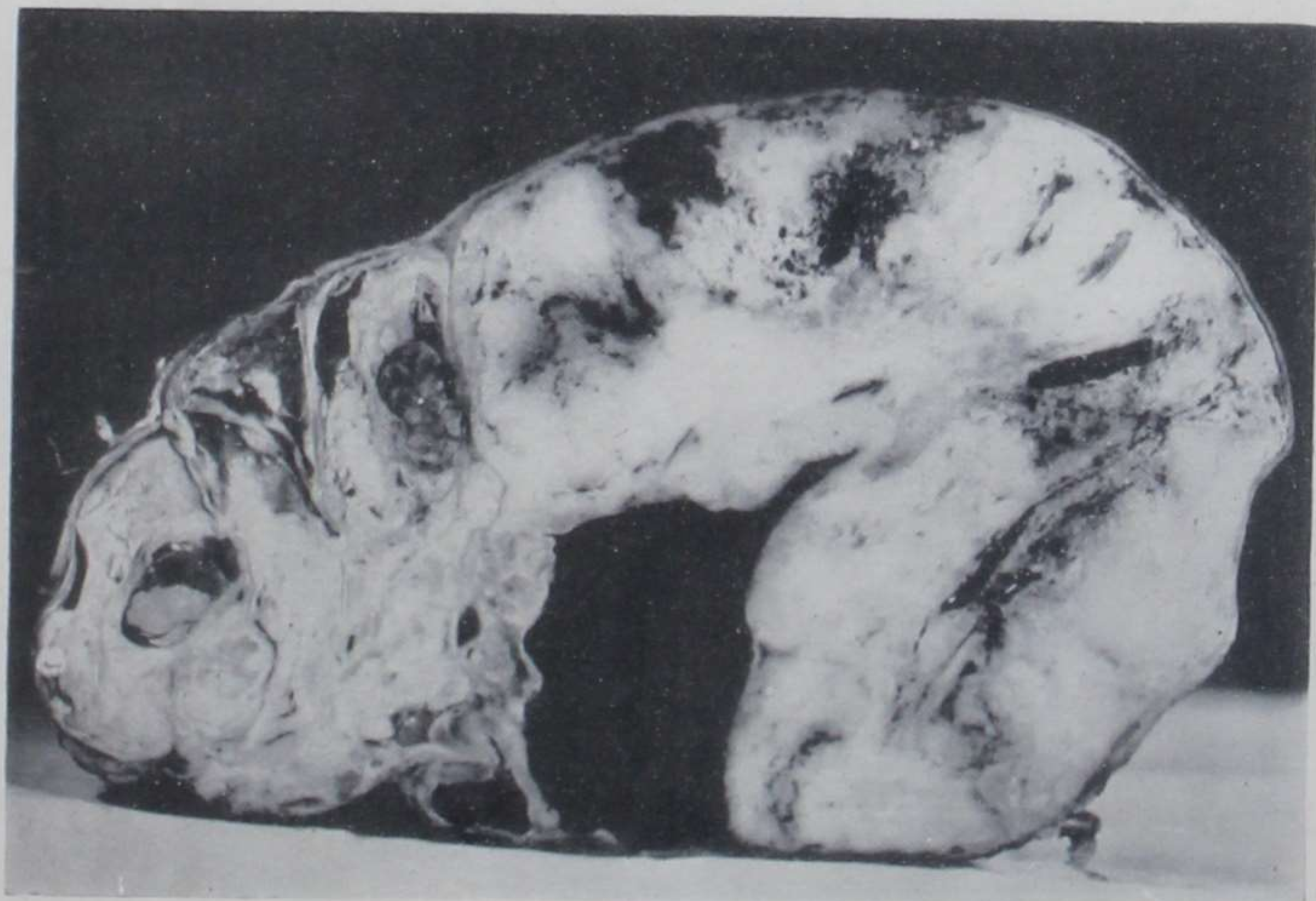

Fig. 88.—Sero-cystic disease of the breast (Brodie's tumour).

before menstruation but continuing after the period, and at times severe enough to interfere with her work owing to aggravation by movements of the arm.

On examination (June, 1934) she complained of tenderness on pressure over most of the outer half of the breast, otherwise no signs could be found. Some eighteen months later—in the meantime the pain had been variable with free intervals—a small lump was found by the patient. This, situated near the outer margin of the breast in the nipple line, discrete, freely movable, and tender, was removed and reported to be a fibro-adenoma.

In the girl or young woman the tumour is smooth, firm, resilient, and freely movable, round or lobulated, but with a well-defined edge; in the older woman, as the result of fibrosis in the capsule, it is often less resilient, more fixed and apt to be mistaken for a carcinoma. Otherwise the breast itself, though perhaps enlarged according to the size of the tumour, is normal without alteration of the skin or position of the nipple. The axillary lymph-nodes are unaffected.

Treatment.—A fibro-adenoma should be removed in order to confirm the diagnosis and to avoid the chance of exceptional growth

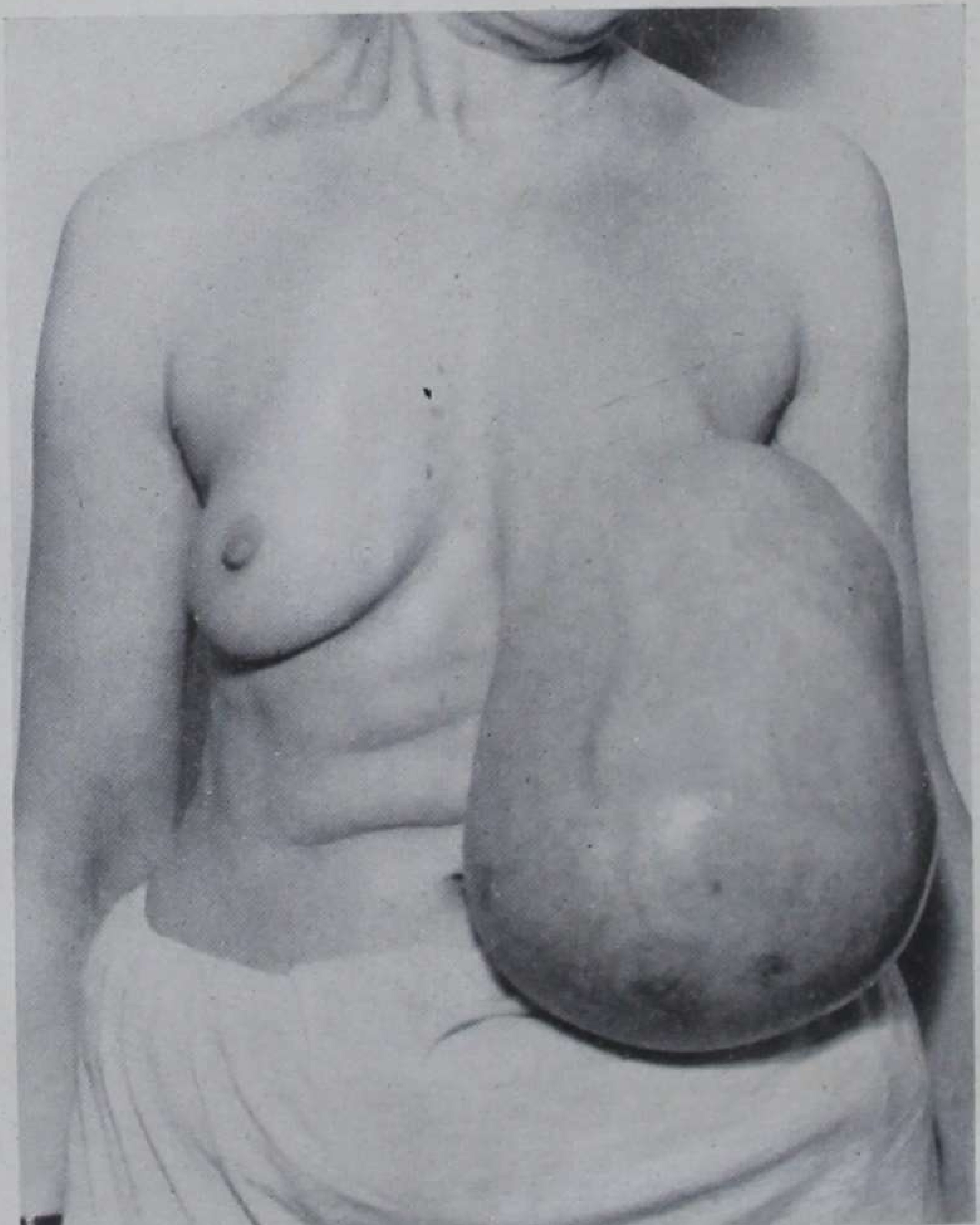

Fig. 89.—Giant tumour of left breast of cyst-adenoma type in a woman aged 55. (*Sir L. Barrington Ward's case.*)

or malignant change. This is done by a radial incision over the site of the tumour or a curved one along the margin of the breast, or—for the rather large tumour—these may be combined, making an anchor-shaped incision.

In the routine case, if growth has been slow or is stationary, there is seldom any call to do more than a local removal of the encapsuled tumour itself, but if growth is more rapid, a margin of a clear half inch of breast tissue should be removed with the tumour. The excision of a wider area than this, up to a quarter segment of mammary tissue, has been advocated in order to lessen the risk of further tumour formation, but fibro-adenomata may grow at a different site in the same or in the other breast. A recurring—or rather, it should be said, more than one—adenoma is found in some 10 per cent of cases.

The giant tumours of the breast, whatever their size, tend to remain encapsuled and can be shelled out leaving a thin layer of mammary tissue. For these, however, a simple mastectomy is usually to be preferred, after which the outlook is mainly favourable, since secondary deposits from these large tumours are rare.

INTRACYSTIC OR DUCT PAPILLOMA

Pathology.—In the section on HYPERPLASTIC CYSTIC DISEASE, p. 125, attention is drawn to the presence, on microscopic examination, of multiple intracystic papillomatous processes (papillomatosis). The solitary—in the rare instance more than one—duct papilloma, sometimes referred to as a single-stalk papilloma (*Fig.* 90), is in a different category. This tumour is situated near the nipple, is fairly superficial, usually of small size—a few millimetres in diameter—with a tendency to bleed on slight trauma.

Under the microscope it is seen to consist of a number of papillary processes with a very vascular connective-tissue core. The larger tumours, microscopically, present a more complicated appearance of multiple small papillary processes projecting into a cyst. Frequently these appear to be composed of a number of small acini in a fibrous-tissue core with an element of solid connective tissue. Vascularity is again a feature.

Clinical Aspects.—The stalked papilloma situated in a cystic dilatation of a duct, though the most common cause of discharge from the nipple, is usually discovered by the patient as a small lump in the central zone of the breast. A tumour or thickening in this position, which may vary from pea size to an inch or more in diameter and over which pressure causes an exudation of serum, blood-stained serum, or of blood, is typical of a rather uncommon condition associated more especially with the years of the menopause, but also with young women.

A history of intermittent bleeding or serous discharge may extend over a number of years. Pain, described as sudden and sharp, is sometimes a feature of these cases, or a persistent discomfort, both of which can be attributed to local distension from bleeding or serous exudate.

The size of the papilloma—usually very small—and the amount of blood—the ratio is often inverse—is responsible for the size of the lump, which may disappear after discharge from the nipple. In a few instances no lump is discovered even on repeated examination, but sometimes pressure over one area causes a bead of discharge to

Fig. 90.—Duct papilloma of breast. Two small ducts containing a section of a simple papilloma. (× 16.)

appear. A papilloma itself is not opaque to transillumination, but if sufficient blood is present a small shadow, or rarely more than one, can be seen by this examination.

The appropriate place for the papilloma—as opposed to papillomatosis—in the catalogue of breast lesions is still unsettled. The tendency to regard all papillomata as low-grade cancers has passed, and, though appearing mostly at the cancer age and suspected by some of being a phase in the progress of mammary tissue from a benign to a malignant state, and carcinoma being apt to arise in the stalk, the papilloma is coming to be regarded mainly as an innocent tumour with the same liability to malignancy as similar growths elsewhere in the body.

Treatment.—The effect on treatment of this change of outlook is of course obvious, as instead of an almost routine mastectomy for bleeding from the nipple, now—provided localization is possible and the lesion solitary—local excision of tissue is performed. In the absence of localizing signs, the case—especially if a young woman—should be kept under observation until the dilated duct or cyst can be found. (In an analysis of 203 cases of intracystic papillomata (Geschickter), 110 cases were treated by local excision, with satisfactory results over a five-year period, 46 by simple and 47 by radical mastectomy, some of which followed a local excision.)

A mastectomy is often unnecessarily drastic and should not be performed in the young woman for mere bleeding from the nipple, though in the middle-aged woman reasons can be urged in its favour. A local excision is the treatment of choice and is performed through a radiating incision over the tumour, and the dilated duct is then opened, the papilloma removed, and the skin incision closed (Wakeley, *Brit. med. J.*, 1945, **1**, 436). (*Fig.* 91.)

Alternatively, and perhaps preferably, the small tumour is removed together with a good margin of normal tissue. An immediate histological examination in the operating theatre is helpful in deciding the scope of the operation.

Case-histories.—Some of the uncertainties are illustrated by the following cases :—

Case 1.—Woman aged 60–61. Four children. The immediate complaint was of a bloody discharge from the left nipple, intermittent for about nine months, and sufficient on occasion to soak through her clothes.

Near the lateral margin of the areola was a small, tender, hard, and somewhat indefinite lump, on pressure over which stale-looking blood exuded from the nipple. Along the pectoral border of the axilla several enlarged though softish nodes were palpable.

A simple mastectomy was performed, chiefly because of the age, and the nodes removed for examination. A report was returned of an intraduct papilloma and hyperplasia of the lymph-nodes, with no evidence of malignancy in breast or nodes.

Case 2.—Woman aged 46–47. Two children. A similar, though rather longer, history to that of the case just described. A small, somewhat tender lump was distinguishable in the central zone of the breast, lateral to the midline, from which on pressure a sero-sanguineous fluid—later proved to contain blood-cells—appeared at the nipple.

Through a radial incision, the small tumour with a margin of surrounding tissue was removed, examined macroscopically, and thought to be a simple papilloma.

Fig. 91.—Intraduct papilloma. Exposure and removal of tumour, with subsequent skin closure. (*After Wakeley.*)

Over two years later, in reply to a letter requesting information, it was stated that this woman had a hard mass in the left breast, deep to the site of a small operation scar, with a few enlarged axillary glands, and that clinically the condition was thought to be malignant.

Case 3.—Woman aged 45. Twelve months history of serous discharge from the left nipple, at times profuse and latterly sometimes blood-stained. Pressure over the lower areolar margin, just medial to the midline, produced a slightly reddish serous discharge. No definite lump could be distinguished. The specimen in this case is shown in *Figs.* 92, 93. (*Mr. Alan Small's case.*)

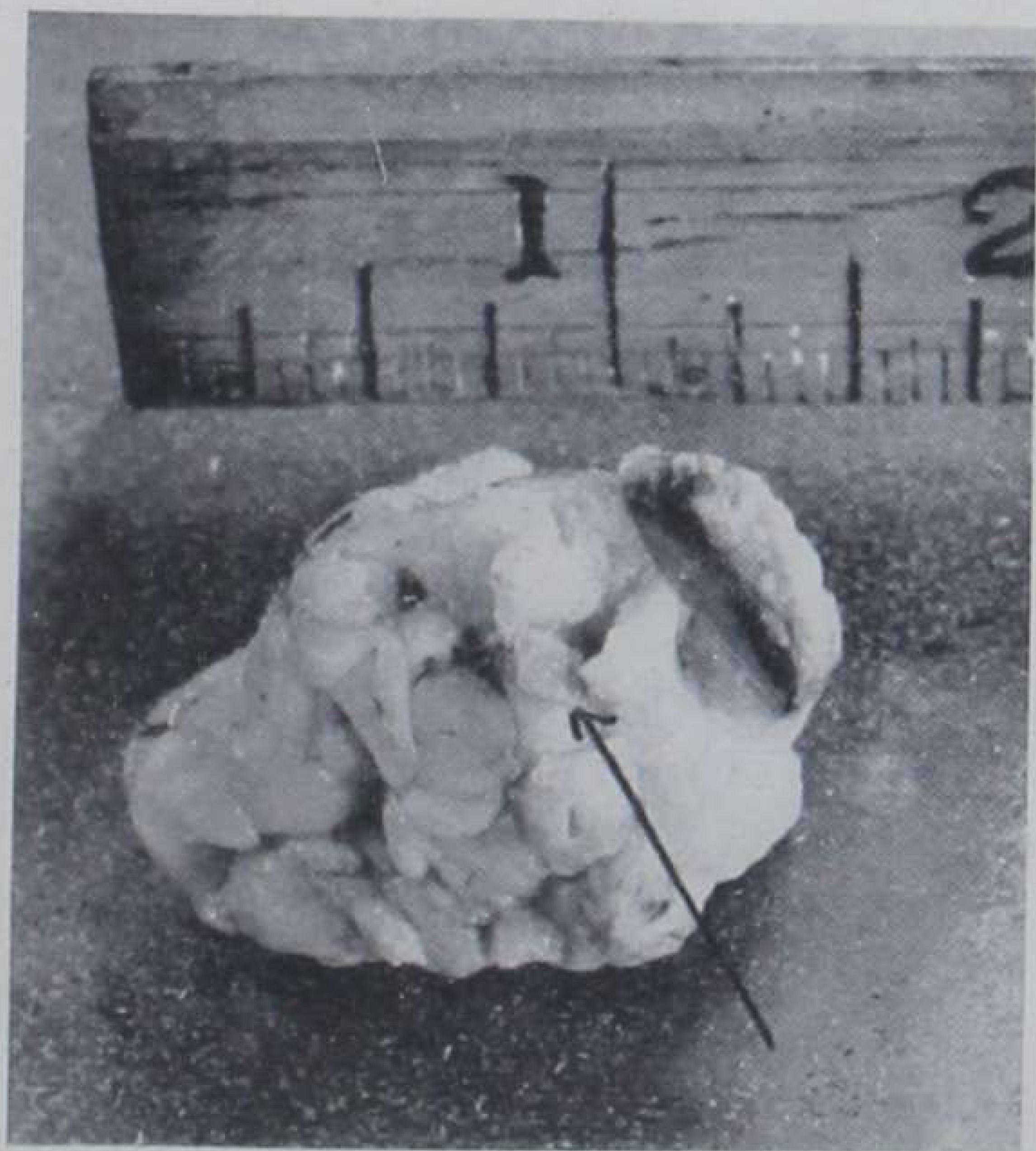

Fig. 92.—Intracystic stalked papilloma. (*Mr. Alan Small's case.*)

Fig. 93.—Intracystic stalked papilloma. Coloured drawing of the same specimen as *Fig.* 92.

LIPOMA

Both in the female and male, uncommon benign tumours are occasionally found in the breast. These may arise from the fat, blood-vessels, muscle, or bone tissue, and are mainly unrecognizable except by removal and histological examination.

A lipoma is not quite so uncommon and appears to originate in the subcutaneous fat over the breast and extend perhaps on to the chest wall, or vice versa, without invading the mammary substance. A retromammary lipoma has been reported.

These tumours, though mainly seen in the middle-aged woman, and occasionally in men, are not necessarily associated with the fatty type of breast and do not as a rule attain a large size. The soft, lobulated fatty tumour, with dimpling of the skin, is characteristic and easily recognizable.

Treatment.—Unless growth is rapid a lipoma can be left in situ, although removal is generally desirable for either diagnostic or cosmetic reasons.

FAT NECROSIS

The condition of fat necrosis, which occurs in the substance of the mammary tissue, is associated with the large, fatty, pendulous type of breast. A minute area, or areas, of fat necrosis may be found incidentally on histological examination of mammary tissue, but if sufficient tissue is involved a small lump becomes noticeable, with, perhaps, enlargement of the axillary lymph-nodes. Such a lump can be hard, especially if of old standing with calcareous deposits in its substance, rather painful, and tender, and can also, if near the surface, cause retraction of the skin. An area of fat necrosis is liable to undergo xanthomatous degeneration (Geschickter).

On clinical examination this condition closely simulates a carcinoma or a cyst. It is, however, rare, and the type of breast may arouse sufficient doubt to suggest a preliminary investigation rather than a primary mastectomy.

On section with a knife the affected area is hard, feels gritty, and has a yellowish or orange colour. The naked eye appearance is distinctive.

Foam cells, endothelial cells, irritation giant cells, cholesterol crystals, round-celled infiltration, and fibrosis, may be found under the microscope.

CHRONIC INFECTIVE LESIONS

RETROMAMMARY ABSCESS

A retromammary abscess is unrelated to lactation and seldom follows an infection of the mammary tissue. It can arise at any age from osteomyelitis of an underlying rib, or more rarely of the dorsal spine with pus tracking along an intercostal space.

Retromammary inflammation, in the early stages, is difficult to distinguish from an inflammation situated deep in the breast. Pain in the chest wall, aggravated by movements of the arm and shoulder, is a primary symptom, together with the signs of an acute general infection. When suppuration occurs the whole breast appears to be raised from the chest wall, though the consistence of its tissue is unaltered. On deep palpation tenderness is elicited and gradually

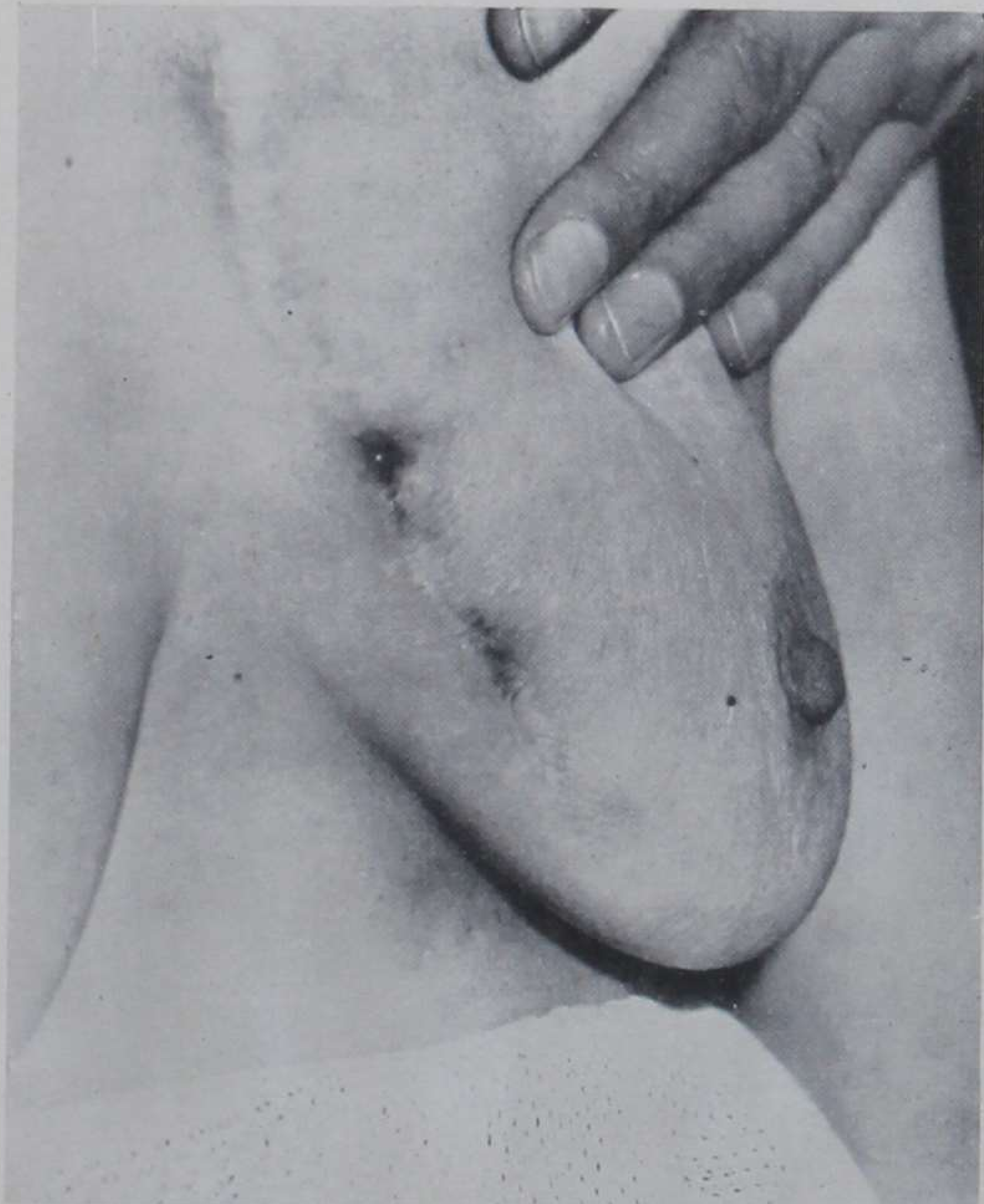

Fig. 94.—Persistent sinus resulting from retromammary abscess due to osteomyelitis of the rib.

becomes more pronounced towards the periphery of the breast, where pus, subsequently, tends to point.

In an old-standing case of osteomyelitis of the rib, now rarely seen, the mammary tissue may become involved and discharging sinuses form through the substance and skin of the breast.

Case.—Woman aged 52. Single. First noted a painful swelling of the left anterior chest wall involving the medial border of the breast, which was due to abscess formation.

The pus was found to originate from the 4th rib, the anterior surface of which was eroded. Resection of area involved was performed. The condition healed, but later a persistent sinus developed (*Fig.* 94).

On bacteriological examination the pus was sterile. Tubercle bacilli were not found.

Treatment.—An abscess of this nature should be drained at the margin of the breast, avoiding damage to healthy mammary tissue. Through a submammary or marginal incision the pectoral fascia is exposed and incised, when pus is evacuated. The abscess cavity is explored to ascertain the original site of infection. If from an osteomyelitis of the rib, the case is treated on its merits, either by drainage of the abscess and removal of a segment of the diseased rib at the same operation, or, and perhaps preferably, by a two-stage procedure. The general infection and local spread is lessened by chemotherapy.

PYÆMIC ABSCESS

A pyæmic abscess in the breast is a rare form of intramammary suppuration, and occurs only in patients debilitated by some chronic

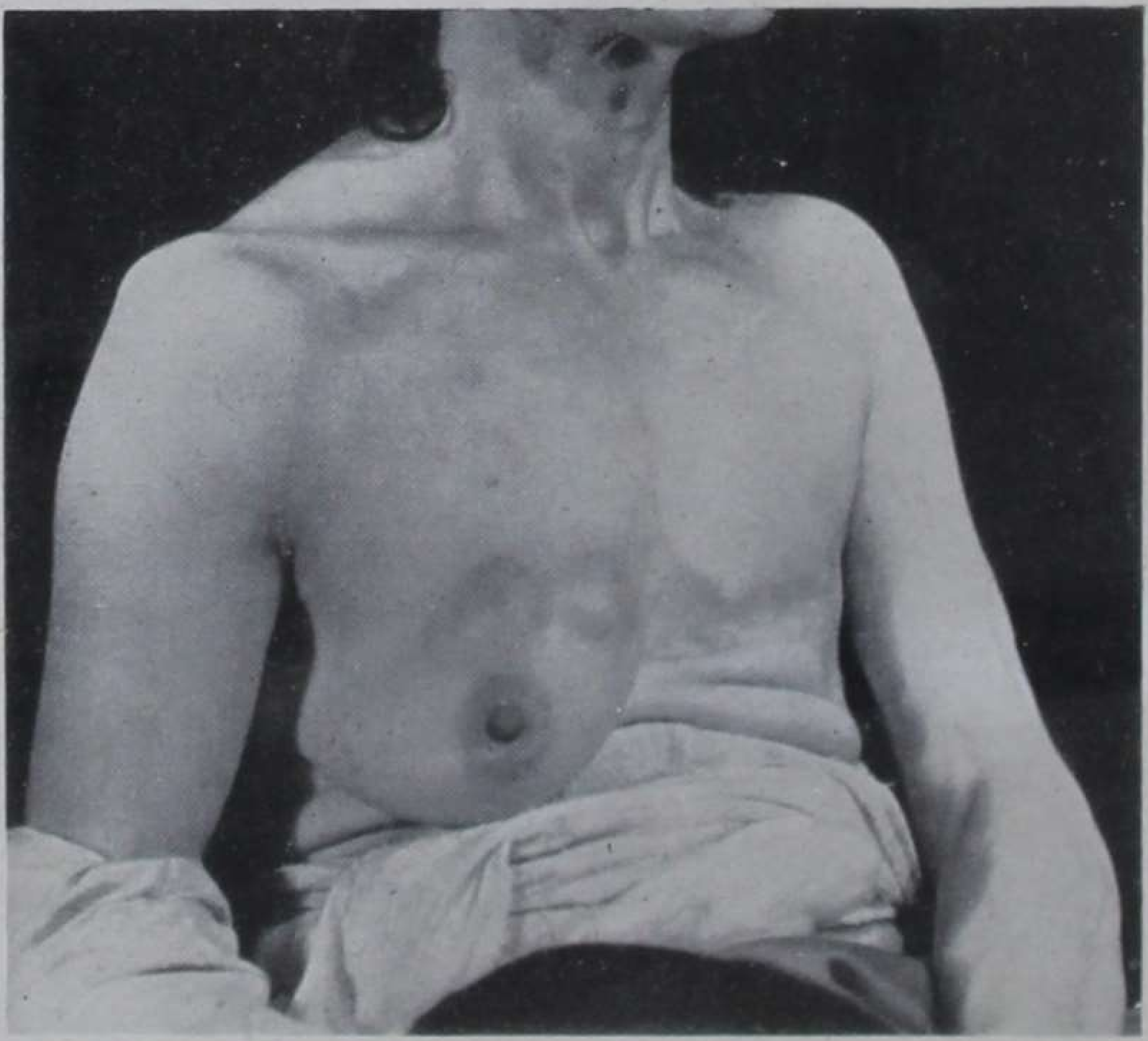

Fig. 95.—Multiple pyæmic abscesses of the breast and other regions.

infective process. Multiple abscesses may form in one or both breasts, and if the condition continues until the abscesses coalesce most or all of the mammary tissue becomes involved in a suppurative process.

Case.—Woman aged 40. Single. Multiple pyæmic abscesses (staphylococcus) involving both breasts. L. mastectomy 1945, R. mastectomy 1947, for multiple abscesses in the mammary tissue (*Fig.* 95). Resistant to sulphonamides and penicillin.

The infection has recurred at intervals over a period of twenty years and involved the face, neck, and left forearm in addition to the breasts. The source of infection is unidentified, possibly bronchiectasis. (*Mr. H. Bailey's case.*)

Treatment.—Treatment should be directed both to the general septicæmia by chemotherapy and to the primary focus. As a result of treatment the formation of abscesses will tend to subside, but in most cases local drainage will be required. In some instances, if multiple sinuses have formed or a large area of the breast is involved, a simple mastectomy may be indicated.

TUBERCULOSIS

This infection is rarely seen in the breast as a primary lesion, but occasionally in association with pulmonary phthisis. An infection may be activated during a pregnancy-lactation period.

The vegetating and ulcerating types do not differ in any way from those observed in other parts of the body, and the prognosis and treatment are the same. The formation of sinuses may suggest the possibility of actinomycosis, in the discharge from which the typical yellow grains of the ray fungus are conclusive evidence. Lupus vulgaris has also been recorded, but merits no special description.

The tuberculous gumma, which originates in the fatty tissue of the dermis, is much rarer than its syphilitic analogue. It may begin as a rounded or lobulated tumour which soon becomes adherent at one or more points to the breast tissue or underlying fascia. The epidermis above it assumes a bluish tint, and somewhere in this area, after a month or more, an abscess will point and discharge the usual grumous or cheesy pus. In contradistinction to the luetic or true gumma, pain is a feature ; the associated lymph-nodes are commonly enlarged in both types.

Treatment is surgical except in lupus. In this type resolution and absorption can be assured in most cases by the oral administration of calciferol, 150,000 units per day (Charpy and Dowling).

Case.—Woman aged 30. A nurse. Complained of a painful tender swelling on the under-surface of the right breast. This, it was stated, had started as a pea-sized nodule under the skin some 4–5 weeks previously. A rounded, hard, tender swelling, rather larger than a sixpence, was situated in the midline just above the areolar margin ; the skin was raised and reddish in colour. Axillary lymph-nodes were not involved.

On admission some two weeks later the area was slightly larger and softening, and under anæsthesia it was excised and the wound closed. In a small collection of granulomatous tissue and pus, tubercle bacilli were found. No evidence could be found of any other focus.

Tuberculous Mastitis.—A tuberculous mastitis starts as a firm swelling in the breast tissue which slowly enlarges. When the axillary

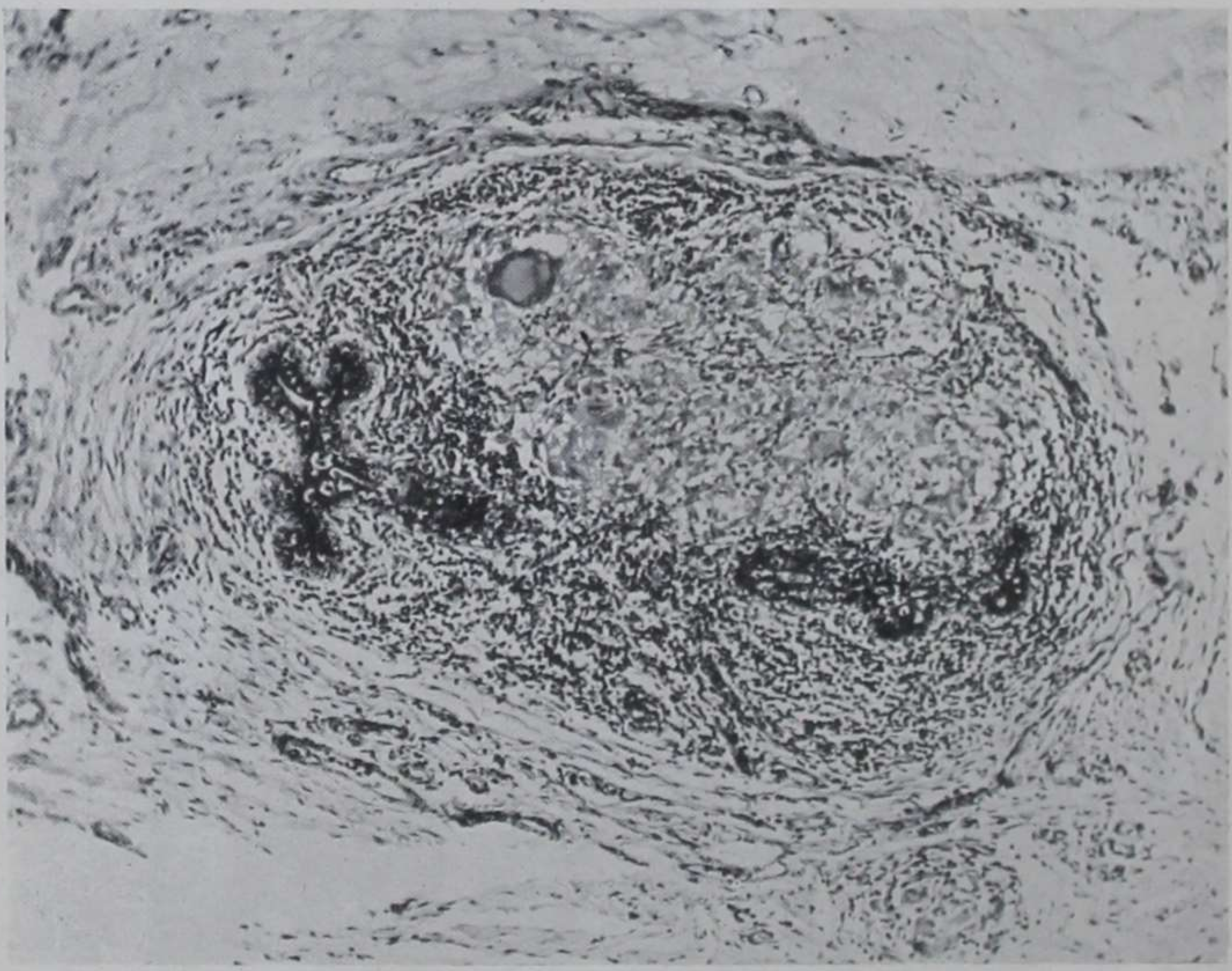

Fig. 96.—Tuberculous mastitis. Mammary lobule showing loss of acini, round-celled infiltration, and tuberculous granulation tissue, with a single giant cell. (× 75.)

lymph-nodes are enlarged, and at some stage these become infected, the clinical resemblance to a malignant neoplasm may be close. Although usually described as painless, a tuberculous mass does sometimes cause pain and is generally tender to touch.

As the mass increases in size liquefaction takes place, the subcutaneous tissues and skin become involved, and multiple sinuses are gradually formed, discharging typical pus. A sclerosing type of tuberculous mastitis, with diffuse induration of the mammary tissue and discoloration of the skin, has also been described ; but in these, as in so many other conditions of the breast, a biopsy is an essential examination for diagnosis, and microscopically the picture is characteristic of tubercle (*Fig.* 96).

The treatment of tuberculous mastitis is controlled by the stage at which the condition is first seen. A small focus may yield to general treatment combined with a local excision of infected tissue or of a localized abscess. In either case a margin of normal skin and tissue should be included in the excision. The wound is closed. When, however, the lesion is slowly progressive with sinus formation, and our experience of a few cases has been mainly of this type, a simple mastectomy, with clearance of the axilla, has been performed.

(*See* Chapter X for a case of tuberculous mastitis during the pregnancy-lactation period.)

PLASMA-CELLED MASTITIS

Attention has been drawn to this very rare condition of a non-lactating breast (Cheatle and Cutler, *Tumours of the Breast*, 1931; Max Cutler, *Brit. med. J.*, 1949, **1**, 94).

Three stages are described. The onset is acute with pain and swelling of the breast, redness of the skin, some rise of temperature, and enlarged axillary lymph-nodes. There may be a creamy discharge from the nipple. The acute stage subsides into a subacute, in which there is diffuse nodularity in the breast, and finally to a chronic stage which is apt to be prolonged. In this the density of the mammary tissue, attachment to the skin, and perhaps retraction of the nipple, make a clinical diagnosis from carcinoma almost impossible unless a precise history of the onset is forthcoming.

The histological appearance of a concentration of plasma cells, the presence of giant cells, and a marked epithelial hyperplasia may also be confusing—especially, the point is made, in an examination of frozen sections.

An explanation of what appears to be an inflammatory process in a non-lactating breast is not obvious. It may be mentioned that a similar microscopic picture of mastitic reaction has been noted in a few instances with a definite carcinoma.

In most cases the condition of plasma-celled mastitis is mistaken for malignant disease and treated as such. When, however, it is recognized and proved by biopsy to be inflammatory, resolution can justifiably be awaited.

CHAPTER VII

THE NIPPLE AND SKIN

By F. D. Saner and H. C. Semon

ABNORMALITIES AND DEFORMITIES OF THE NIPPLE

The lengthy distribution of the milk line in the embryo, extending from the anterior axillary fold to the pubic and inner thigh regions, is responsible for the appearance of supernumerary breasts (polymastia) and nipples (polythelia) which also occasionally appear outside the direct line of its track. The treatment is removal, both for cosmetic reasons and because of the discomfort of a lactating breast situated in an abnormal site.

The nipple of one or both breasts may be completely absent or so small as to be useless, or blind, without communication with the ducts, so that milk if secreted is not excreted.

Inversion or indrawing of the nipples, suggestive of failure to obliterate the nipple pouch, constitutes a constant source of irritation and of difficulty in keeping clean, and causes difficulty or is incompatible with suckling.

Defective protraction and mobility, in varying degree, is the most common nipple deformity and may be sufficient to prohibit suckling or limit it considerably. (*See* Chapter II, p. 71.)

Apart from causing difficulties with lactation, however, these deformities have no particular significance nor apparently any association with the development of malignant disease.

An intermittent retraction of the nipple is noticed occasionally at the menopause from involutionary changes in the breast, but in an adult woman a permanent retraction or deformity, which has not been present before, is nearly always caused by a malignant growth in the mammary tissue. Protrusion can be caused by a neoplasm in the ducts such as a large intracystic papilloma.

Benign warty conditions sometimes follow the cracked or fissured nipple of lactation, which, owing to the bleeding and associated scabbing, simulate, in some instances, a malignant condition. A pedunculated fibroma, seldom of any size, is also occasionally seen.

DISCHARGE FROM THE NIPPLE

A discharge from the nipple is not a common sign; it may be transient, intermittent, or persistent. Whether of serum, blood-stained serum, or blood its presence is indicative of some change in the mammary tissue, but is not *per se* diagnostic and can vary in the same woman.

A discharge of blood or blood-stained serum is associated essentially with an intraduct neoplasm, such as a papilloma or carcinoma, especially the former, or in the occasional case following injury to the breast sufficient to cause a hæmatoma and its subsequent drainage through the ducts. Bleeding from the nipple always calls for close observation and probably investigation, but is not closely associated with malignant or yet potentially malignant disease, unless a papilloma is included in the latter category.

With a clear distinction between the papilloma and cancer Geschickter gives the following interesting figures:—

"In 2393 cases of mammary cancer, a bloody discharge from the nipple was recorded in 4 per cent of the cases; in 35 cases of duct cancer, in 20 per cent.

"In 2917 cases of benign lesions of the breast, a bloody or blood-stained serous discharge was found in rather over 6 per cent, but, in 203 cases of intracystic papilloma—verified by operation—almost half had bleeding from the nipple."

Bleeding, or serous exudate, from the nipple can precede a lump, more often in the benign case; in malignant disease a mass generally precedes a discharge, but waiting for more definite signs is a risky procedure in a middle-aged woman.

Case.—Woman aged 58. Heavy build. One child, breast-fed for 6–7 months. First seen in June, 1936, for an occasional discharge from the nipple, mostly clear but sometimes reddish, which had been noticed for about six months. No complaint was made of any symptoms, no lump was found, no localizing signs. Transillumination was negative.

After a further six months' observation the patient herself discovered a lump about an inch and a half above the nipple and lateral to the midline. The discharge now was, if anything, less in amount than previously. The lump, about half an inch in diameter, rather hard and ill-defined—pressure over it caused no exudation—was excised for examination and reported to be a carcinoma.

In a number of cases pressure made over the central area of the breast enables the site of discharge or bleeding to be traced by expression from the nipple. This examination, though an essential one, should be limited owing to the risks of dissemination.

DERMATOLOGICAL LESIONS

The dermatological lesions of this region include: (1) Eczema; (2) Fissures of the nipple; (3) Microbic infections; (4) Scabies; (5) Syphilis; (6) The Fox-Fordyce disease; (7) Warts and allied conditions such as molluscum contagiosum; (8) Eruptive hydrc-adenoma; (9) Malignant disease including Paget's disease; (10) Tuberculosis (*see* Chapter VI, p. 151).

The female breast by reason of its specialized functions is far more vulnerable and prone to the above citations than the male. This is especially the case during pregnancy and lactation. With the exception of malignant disease, most of these cases are allocated to the third and fourth decades, but it should be appreciated that no less than 6 of the 10 conditions, Nos. 1–5 and 7, are due to, or at least associated with, lack of or defective hygiene and are therefore preventable.

1. Eczema.—Usually affects both sides, is of sudden onset, extremely irritable, and frequently acute with weeping or crusting. An exact causation is rarely demonstrable, but among the possibilities may be included the over-zealous application of antiseptic "hardening" agents in pre-natal clinics, and the well-intentioned but sometimes unskilful efforts to draw out a retracted nipple.

During actual lactation the aetiology is more obvious, for besides the effects of constant maceration the efforts of the suckling infant are a factor which, if too active, should be temporarily eliminated by the use of a breast-pump and feeding-bottle.

Treatment.—With adequate support of the breast and application of cold boracic or 1 per cent aluminium acetate compresses, frequently changed, and regular use of the breast-pump, resolution is usually only a matter of a few days, when feeding can be resumed. Scrupulous cleanliness and attention to the condition of the nipples, and bathing, after each feed, with a 20 per cent solution of spirit in water in order to harden them, will suffice to prevent relapses and the occasional complication of fissures. Unless infective complications ensue, antiseptics of all kinds are contra-indicated.

If there is no response to ordinary methods of treatment, superficial X-ray therapy is often valuable in assisting to heal this condition.

2. Fissures.—Under the more popular name of "cracked nipples", fissures can occur apart from the puerperium as a result of trauma or streptococcal infection.

Treatment.—Grease is not well tolerated, and ointments should be compounded with a lanette-wax base, e.g., Ung. H.E.B. A 5 per cent inclusion of tinct. benzoini co. will promote healing in early cases, or, if this fails, a twice daily application of 1–2 per cent solution of silver nitrate should be made by the nurse. In the indolent case, small localized doses of X rays, 75 r units, are valuable in inducing repair.

3. Microbic Infections.—A detailed description of the microbic infections of the breast which may be part of more generalized conditions is scarcely necessary. The sub-mammary region, however, is a favourite site for intertrigo (*Fig.* 97) particularly in the stout middle-aged woman with pendulous breasts, glycosuria, or a high blood-sugar content. Monilia or yeast infections may predominate in such a case—as frequently they do in the groins or perineum—or a seborrhœic diathesis or some other condition such as pityriasis versicolor (*Fig.* 98) may be underlying factors.

Treatment.—If inspection of the axillæ, scalp, and pubic region yields confirmatory evidence of seborrhœa, the correct approach to treatment will be indicated. Salicylic acid and sulphur in calamine lotion (āā 2 per cent) will usually afford prompt relief and should be combined with the correction of diet as indicated by the blood investigation. Meticulous cleanliness, the regular use of dusting powder, especially in hot weather, and a properly designed brassière to obviate the contact of opposing skin surfaces are essential prophylactic precautions.

4. Scabies.—In relation to the nipple and areolar areas scabies is a trap which has not infrequently caught even the most experienced practitioner. Whenever eczema of the breast fails to clear up the possibility of this underlying cause should be considered and search made for confirmatory signs on the wrists, between the fingers, and on the thighs and buttocks. The recovery of an acarus affords complete proof of the aetiology, though it is rarely found in the areolar area owing to the eczematization and secondary sepsis. The existence of contact cases, and increased itching during the night are sufficient indications for a therapeutic trial.

Treatment.—This consists in the application of sulphur or benzyl benzoate inunctions, which must of course include the whole body except the neck and face.

Scabies being a relatively common dermatosis, a good plan is to approach all cases of pruritus in this situation—whether eczematized or not—with that possibility in mind. Unless, however, an acarus is recovered the examiner would be wise to keep his suspicions to himself, and institute the specific treatment without explaining its necessity.

Fig. 97.—Intertrigo (streptococcal dermatitis following.)
(*Figs.* 97-99 *from Semon's 'Atlas of the Commoner Skin Diseases': Wright.*)

Fig. 98.—Pityriasis versicolor.

5. Syphilis.—The nipple is a relatively frequent site for the primary chancre, which, according to Fournier's statistics, occurred 19 times in 110 cases of extragenital infections. Most of the cases are venereal in origin, though in former days the wet-nurse was a frequent victim, with deplorable consequences to her own infant, her husband, and herself. The lesion is nearly always unilateral and single, involving the nipple in a relatively painless and infiltrating induration, which renders it much more prominent than its fellow. Ulceration soon ensues, which does not differ markedly from primary forms of syphilis elsewhere, associated with rapid, painless elastic enlargement of the corresponding chain of lymph-nodes. Confirmation by means of the dark-ground illumination ultra-microscope and the Wassermann reaction is of course obligatory before treatment is begun.

It is here unnecessary to delineate the two or three different types of chancre which have been emphasized in the past by French writers in particular. Unilaterality, painlessness, a fairly rapid development, and the invariable and characteristic glandular enlargement afford a clinical picture which can be mistaken for only one other—the malignant neoplasm—in which development is slow, painful, and often associated with bleeding and sepsis. In cases of doubt a biopsy, the ultra-microscope, and the Wassermann reaction will conclusively settle the diagnosis.

Like primary chancres elsewhere, healing promptly follows specific therapy, and scarring with deformity of the nipple is a very rare sequel.

The mucous plaques of the secondary stage are rarely seen on the nipple or surrounding areola, and seldom occur without simultaneous patches in the mouth, vulva, and perineal regions ; but the gumma is occasionally met with in breast tissue, and the surgeon would be wise to include a routine Wassermann test before proceeding to a radical mastectomy, however convinced he is of the accuracy of his diagnosis. A coexistence of the two diseases is by no means out of court and, if proved, indicates a brief but concentrated course of anti-syphilitic treatment before the operation.

6. Fox-Fordyce Disease.—This is a disorder of the apocrine glands. These glands are strongly developed in the deer, musk rat, etc., but in the human they rank as vestigial, and symptoms of their disorder are limited to women mainly during the menstrual period. Each gland is separately defined as a pin-head sized papule or " papulette ", sometimes of normal skin colour while others are slightly pink. The intervening skin is normal but may become lichenified as a result of rubbing, for the associated pruritus is often intense. The lesion develops round the nipple or on the areola, but a more common site is the axilla; the pubic area, in which apocrine glands survive, may also be affected.

Treatment.—There is no skin abnormality which responds better to œstrogen therapy; in fact its administration amounts to an acid test of the diagnosis.

7. Warts.—Warts of the flat type do not affect the nipple or areola to anything like the same extent as the pointed or filiform type known as condyloma acuminata. These are not syphilitic but are presumed to be due to a virus, which usually affects the genitals. Sepsis and superficial ulceration are frequently associated, and if a 1–4000 perchloride lotion frequently swabbed on does not cure the sepsis and condylomata within a few days, recourse must be made to a more specific treatment. This consists in careful application to the individual lesions of a 25 per cent suspension of podophyllin in liquid paraffin. The parts are then kept dry with dusting powder. One or two applications usually suffice.

Molluscum Contagiosum.—This is distinguished by the presence of isolated lentil- to pea-sized pearly oval or hemispherical papules (*Fig.* 99). Closely examined with a lens many of them will present a central dell or depression. If a fine curette be inserted into this, or if the lesion is squeezed with a small forceps, a cheesy substance is expressed. Examined in potash under a $\frac{1}{6}$ objective the characteristic "molluscum bodies" are easily identified and establish the diagnosis.

Cure can only be obtained by destruction of the individual lesions either by expression of each lesion or the application of the galvano-cautery. Several sessions may be required in a long-standing case.

It is contagious both by direct contact and by fomites—especially in Turkish baths.

8. Hydro-adenoma.—The eruptive hydro-adenoma is a rare and symptomless non-inflammatory lesion with a predilection for the thorax and particularly the breast. The small shotty lenticular papules of which the eruption is composed are covered by normal epidermis, and development appears to date from childhood and is exceedingly slow. The absence of itching serves to differentiate it from the papules of the Fox-Fordyce disease, and modern authorities tend to classify it among the sebaceous or sudoriparous nævi.

Fig. 99.—Molluscum contagiosum.

MALIGNANT DISEASE (PAGET'S DISEASE)

Pathology.—Microscopically, the epidermis is considerably thickened and sometimes appears to contain large rounded malignant cells resembling those found in intraduct carcinoma. The characteristic cell known as a "Paget cell", described as a large, clear vacuolated cell with small pyknotic nuclei, is found within the cell-layers of the epidermis. In addition evidence of chronic inflammation is always found in the superficial layers of the dermis as indicated by an extensive infiltration with small rounded and plasma cells. If the section includes neighbouring ducts, typical intraduct carcinoma will usually be found.

The histological picture of malignant disease of the nipple includes therefore: (1) Thickening of the epidermis with separation of the deeper layers and the presence of "Paget's cells"; (2) Chronic inflammation of the subepithelial tissue; (3) Intraduct carcinoma.

Paget's "eczema" is not necessarily confined to the nipple and areola; in one case eczematous areas covered much of the skin of the breast with, on examination of sections, the typical histological appearance. (*Figs.* 100, 103.)

Symptoms and Signs.—The true Paget's disease is a rare event; in a series of 508 cases of mammary cancer 3 only were classified as such. Paget's original communication in 1874 (*St. Bart's. Hosp. med. Rep.*, 1874, p. 83) was based on 15 cases in women between 40 and 60 years of age, all of whom subsequently developed scirrhous carcinoma of the breast. Difficulties and errors of diagnosis in these cases are still apt to occur and involve an unwarrantable delay in applying the correct therapeutic measures.

The following clinical points are outstanding and should be memorized:—

1. The patient has usually passed the menopause; the disease is rare before 55, more often 60–65.

2. The symptoms, which include discharge from the nipple and a well-defined infiltrated "eczematous" lesion of the areola and surrounding skin, are *always confined to one side*.

3. They never respond to the ordinary treatment for eczema. Once begun the process is irreversible.

4. Sooner or later the nipple is retracted or ulcerated and may ultimately disappear.

5. In the later stages nodules can be felt at varying levels in the breast tissue, and the homolateral axillary nodes become involved.

Amplifying this summary it should be noted that similar pathological processes with much the same histology have since been reported in and around the umbilicus, on the penis, and in the perineal region.

Fig. 100.—Intra-epidermic carcinoma of breast. The skin of the breast shows cystic spaces in the epidermis. Single cells and clumps of cells are present in these spaces. From a case of Paget's disease of the nipple with spread on to the surrounding skin surface. The mammary gland had both intraduct carcinoma and invasive carcinoma. (× 154.)

A discharge from the nipple as the primary symptom has led to the belief that malignant disease begins as a metaplasia of the lining cells of the mammary ducts ; if this is so proved, the so-called Paget's disease of other areas must have a different origin and should have a different name. The " eczematous " process on the areola and adjacent skin is a misnomer, since itching—inseparable from the term—is either absent or slight in most cases, and outcrops of the characteristic vesicles are the exception. The cutaneous manifestation (*Fig.* 101), the oozing, the florid or granular intensely red surface sometimes covered by crusts, is not an eczema but probably the result of lymphatic obstruction caused by cellular invasion of the dermal and epidermal layers of the skin. The sharply defined margin and the infiltration

Fig. 101.—Paget's disease in woman aged 76; 2–3 years' history. A coloured area of "eczema" about 4 in. in diameter was present. No definite tumour palpable in the breast tissue. Two enlarged, hard lymph-nodes were obvious in the axilla. (*Mr. H. Bailey's case.*)

produced "like a penny felt through cloth" is an almost invariable feature seldom or never seen in the ordinary eczematous reaction to irritants—chemical or microbic. If the condition is malignant the usual remedies applied for eczema have little or no effect beyond that of soothing, and the practitioner should not persist with them longer than a month, nor *for any unilateral affection* with the above characters in a woman at or past the menopause. A histological examination should be the next step, and in no case, in the authors' experience, has the essential malignant process been missed or mistaken by the pathologist.

Case.—A woman, aged 72, had had a lump in the right axilla removed 8 years previously. Section showed "spheroidal-celled carcinoma", but no primary was found.

June, 1947.—It was noticed that the right nipple was enlarged, weeping, and showed a number of raw areas. Wassermann reaction was negative. Biopsy of nipple gave an inconclusive picture.

November, 1947.—The nipple was twice normal size (*Fig.* 102). Areas of the nipple were raw and weeping. No mass in breast, no glands in axilla. Health good. A local mastectomy was performed.

August, 1949.—Reported well.

Fig. 102.—Paget's disease. Enlarged nipple showing raw and weeping areas.

Pathological report: The nipple feels somewhat thickened. The breast tissue underlying is somewhat nodular. No gross evidence of infiltrating carcinoma.

Microscopically it shows intraduct carcinoma of the large ducts of the nipple and the gradual replacement of normal epithelium by malignant epithelium whereby it has spread along the ducts to the surface of the nipple. The whole of the surface epithelium has not been replaced as Paget's cells can be recognized superficially: but there can be no doubt as to the malignant property of the basal cells—they are active. Intraduct carcinoma can be recognized in the deeper tissues but no infiltrative carcinoma. The superficial tissues show another feature of Paget's disease very well, the intense subepidermal round-cell infiltration (*Fig.* 103). This breast may be considered at the present time as showing low-grade malignancy.

To clarify the confusion apt to arise when the clinical picture does not conform either in character or degree to the above description,

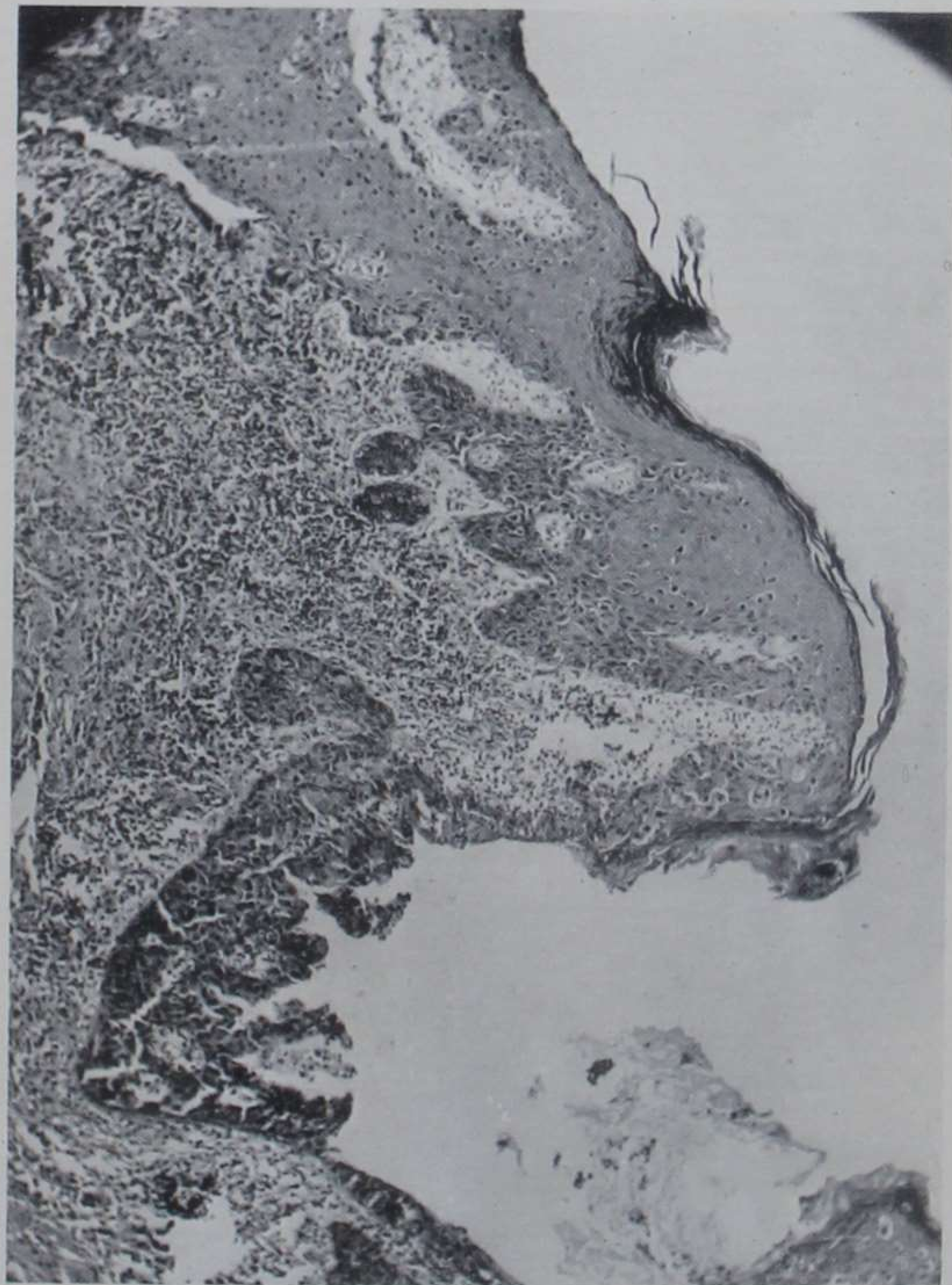

Fig. 103.—Microscopical section of the nipple in the case of Paget's disease shown in *Fig.* 102. Note the crust of dark exudate and especially the inflammatory reaction in the sub-epithelial tissue. The deeper cells of the epidermis have a malignant appearance, and small cystic spaces containing epithelial cells are present. (× 60.)

French writers have divided the clinical progress of malignant disease in this area into three stages :—

1. A serous discharge from the nipple with a surrounding zone of erythema, with or without crusting on the surface. This phase may last for months or even years.

2. The above signs persist, together with retraction of the nipple. A superficial ulceration takes the place of the erythema or

eczematous-like process, and isolated islets of epithelial re-growth may be seen in the denuded area, as if epidermal ulceration and repair were simultaneously contesting the field.

3. In the third phase the induration has penetrated into the breast, when nodules or masses of different consistency are palpable in its substance with the axillary lymph-nodes obviously sharing in the extension of the disease.

Perhaps such a classification is unnecessary. If the surface manifestations are accepted as secondary to a duct cancer it follows that the malignant process can extend in three directions, towards the nipple, into the skin or areola, or outside the ducts into the mammary gland. If a lateral extension to the skin predominates, the eczematous manifestation will be prominent ; but if into the mammary tissues, the condition loses its characteristic features and is practically indistinguishable, except on histological examination, from the ordinary carcinoma of the breast. On the other hand, if spread in each direction proceeds at about the same speed and the patient delays seeking advice, all three stages may be present, as indicated by a discharge from the nipple, with or without an oozing infiltrated patch, retraction of the nipple, and a lump in the breast.

The variable clinical features can thus be correlated with the underlying pathology, which affords a guide to the extent of the disease and the prognosis.*

Other surface types of malignant disease, including rodent ulcer, intra-epidermal and squamous carcinoma, may occur on the skin covering the breast, as well as pre-invasive forms and Bowen's precancerous dermatosis. A rodent ulcer has its typical history and appearance, and the squamous carcinoma may be distinguished by its elevation, gross ulceration, and rolled edge. Clinically there may be little if any difference between Bowen's disease and other surface cancers though histologically the conditions are distinguishable.

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* Differences of opinion on the site of origin of this form of malignant disease are sharp. An intra-epidermal origin is favoured by a number of histologists because of the " eczema ", a distinctive feature in the clinical picture. Others are of the opinion that the skin lesion is independent of what takes place elsewhere (Inglis), or that the condition is an example of two separate growths arising from one cancer-producing agent (Cheatle). Since, however, the malignant process is found mainly in the breast, an origin in mammary, or mammary duct (Muir), tissue is suggested which the author (H.C.S.) regards as conforming more accurately to the progress of the disease as described in the text.

The subject is complicated by the discovery that so-called Paget's disease can occur in other parts of the body where neither secretory glands nor ducts exist. Outside the breast Paget's cells appear to be of low malignancy ; they do not invade the dermis or underlying fascia nor give rise to secondary deposits.

Clinically these lesions somewhat resemble a rodent ulcer without its burrowing tendency or capacity.

Fig. 104.—Woman aged 72 with a pre-invasive lesion over the breast and a basi-squamous carcinoma in the axilla.

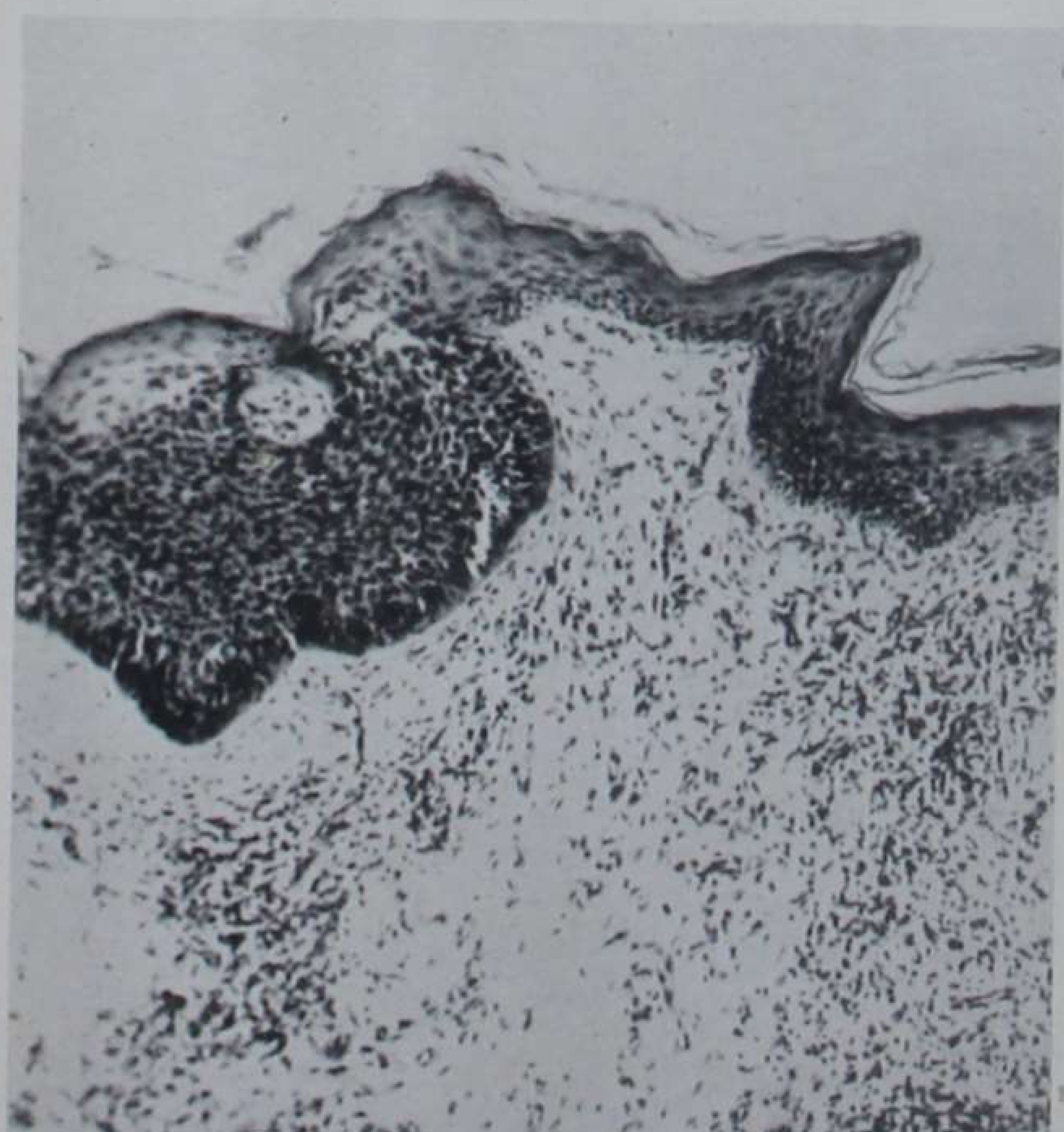

Fig. 105.—Photomicrograph in same case as *Fig.* 104, showing two foci of pre-invasive basal- and prickle-cell proliferation from skin lesion over lateral aspect of left breast adjacent to lesion figured in *Fig.* 104. (*Dr. P. M. Peters.*)

The multiple lesions of the following case suggest that these malignant processes are the same but seen in varying phases.

Case.—Woman aged 72. Multiple skin lesions (*Mr. A. Green's case*).
Besides lesions over the breast and in the axilla (*Figs.* 104–106) there were skin lesions over the 2nd right costal cartilage (Bowen's pre-cancerous

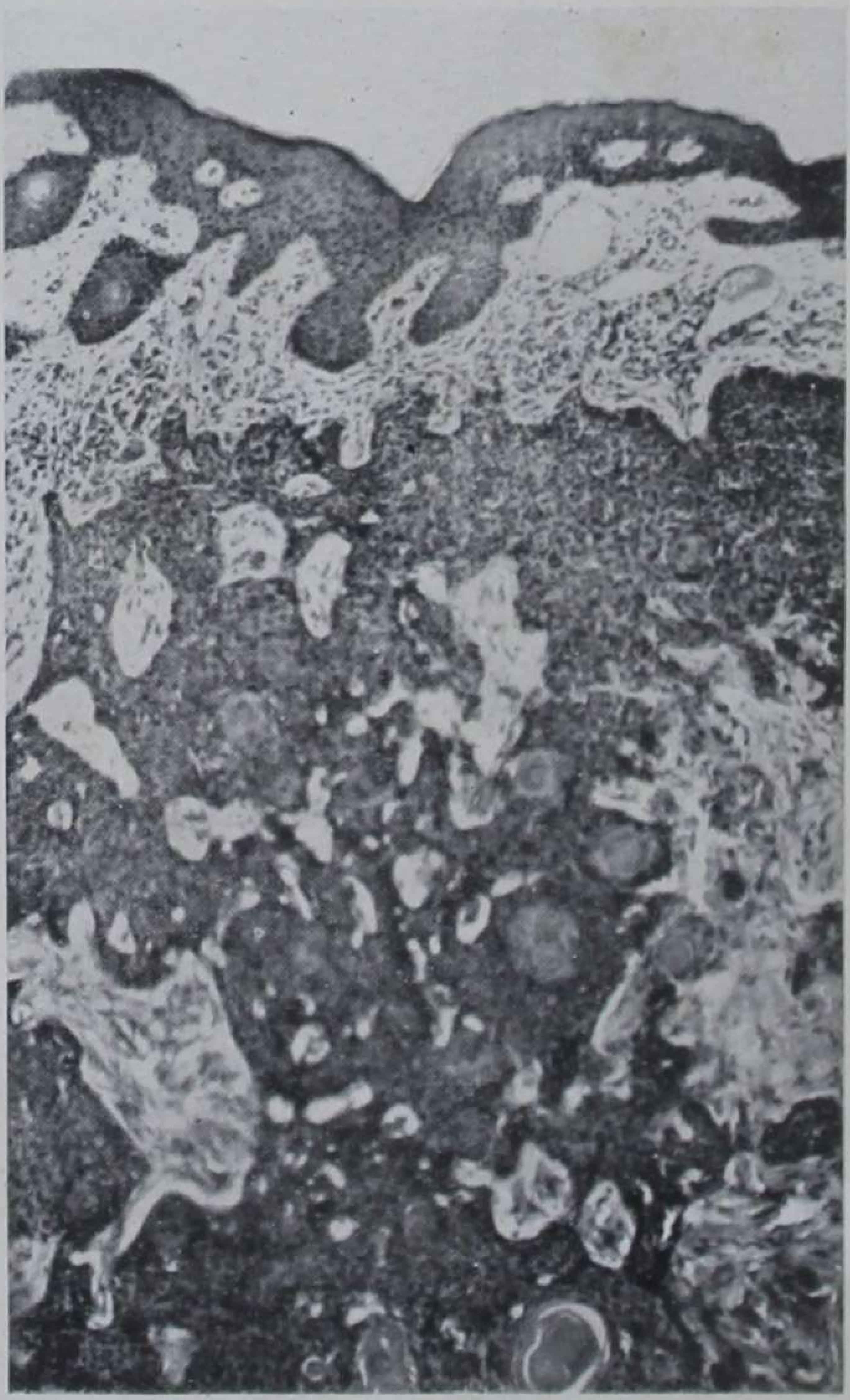

Fig. 106.—Photomicrograph in same case as *Fig.* 104, showing basi-squamous carcinoma of skin overlying axillary extension of breast. (*Dr. P. M. Peters.*)

dermatosis), over the left wrist (squamous carcinoma), and other scattered lesions showing pre-invasive hyperplasia, basal-celled carcinomata, cutaneous horns, etc.

Treatment.—The prognosis and treatment of the surface forms of malignant disease of the breast are guided by exactly the same considerations as for those originating in the substance of the gland.

A cancer of the nipple, or other apparently superficial type, should be dealt with by radiotherapy, but when doubt exists of its localization a radical mastectomy should be performed with the help of irradiation as required. A proved Paget's disease is an indication, in most cases, of an advanced mammary carcinoma.

Surface Conditions treated by Radiotherapy.—Often undiagnosed lesions of the breast, under the term "eczema", are sent for radiotherapy when routine dermatological treatment has failed.

The administration of small doses of X rays, 30–50 r, once or twice weekly, is used in acute conditions, but for the more chronic cases doses of 150 r weekly are required. *Keratosis* is effectively treated by a dose of 1500 r in a single exposure. Bowen's disease, or pre-cancerous dermatosis of the nipple, responds to slightly higher doses—2500 r. *Basal-celled carcinoma* also requires this dose—2500 r. *Squamous carcinoma* of the nipple is best treated by radium in the form of a surface applicator, giving a dose of 6000 r in 1 week.

CHAPTER VIII

CANCER: GENERAL CONSIDERATIONS

By P. O. Ellison and F. D. Saner

AETIOLOGY

Age.—Cancer of the breast contributes rather more than 30 per cent of the total number of cases of cancer in women and approximately 11 per cent of all cases of cancer. Rarely seen before 30 years of age, the incidence of the disease rises slowly until 40 and then more rapidly, varying, according to some statistics, in the single and the married woman. In the former the rise is sharp at 40 with a peak period spread over the next 15 years; in the latter the increase is more gradual and reaches a maximum between 50 and 55. But a liability continues into old age, and a woman between 75 and 79 is stated to be ten times more liable to develop a mammary carcinoma than one between 35 and 39 (Geschickter).

Age, then, is the predominating factor in malignant disease of the breast, especially the years round the menopause, the period of gradual cessation of a routine. An increased ageing of the population in general, therefore, will influence the number of cases proportionately.

A number of statistical investigations carried out in different countries and covering a fairly wide field have not revealed any outstanding factor, with the exception of age, to influence uniformly or strongly the development of cancer of the breast. Statistics and deductions differ, but certain conditions are thought to have an association with malignant disease and appear, in some degree, to increase individual liability.

Family History.—For the most part the investigations on the familial incidence of cancer have been limited to the families of women who have already developed malignant disease; from these some observers find a familial tendency, more especially to mammary cancer. In a wider investigation, including the families of non-cancerous women, Lane-Claypon says that her figures hardly support any theory of well-marked inherited tendencies. She points out that with no biological selection in mating the characteristics of the stock are almost unknown, while the lack of knowledge of the illnesses or cause of death of relatives, often even of the parents, limits the efforts to trace a presence or absence of the working of the laws of inheritance. The evidence, however, is probably sufficient for any woman with a near female relative known to be suffering from cancer of the breast to be on special guard.

The existence of the occasional cancer family is established and well known. The following woman is a member of such a family :—

Case.—Age 52. Single woman. In November, 1940, a radical mastectomy was performed for a carcinoma of the right breast. The axilla was extensively involved, both the basal and apical lymph-nodes being reported to contain malignant deposits (Stage 2*b*). Post-operative irradiation was given. (Reported well, June, 1948.)

This woman was one of a family of nine, of whom four, three brothers and a sister, had already developed malignant growths—two of the bowel, one of the larynx, and one in whom the site of growth was unknown. The cause of death of the parents and grandparents also was unknown.

Injury.—An impression prevails, perhaps a strong one, that an injury to the breast can be the initial factor in the formation of a malignant growth. A number of women will recall, maybe sometimes imagine, an injury when an abnormality in the breast is discovered.

A more definite criterion by which to judge the reality and degree of the injury is the presence of bruising (Lane-Claypon). On this basis cases are divided into three groups : those with a definite history of bruising, those with an injury without bruising, and others with repeated slight injury. (In the last group are included occupational injuries, pressure from ill-fitting corsets, repeated strains from lifting, etc.) An analysis of these shows the number of women who develop a mammary cancer after injury associated with bruising, as compared with those with no injury, to be in the ratio of about 7 : 2, a proportion significant enough to suggest a relationship.

On the other hand, in a review of 1061 cases of mammary cancer (British Empire Cancer Campaign) only 17 per cent were classed as related to injury ; in half of these the history was definite ; but in some 74 per cent of the cases questioned injury was not mentioned.

Possibly trauma can alter or arrest the function of an area of mammary tissue and promote changes in structure. It is probable, too, that injury may aggravate or accelerate the progress of an existing carcinoma, or, on the other hand, draw attention to a lump previously unnoticed. If, however, the percentage of injuries, slight and severe, to any part of the body is considered in relation to the number of those that have even a suggestion of being responsible for malignant changes, any general connexion between trauma and neoplasm appears to be very remote. Yet it is probably undeniable that a cancer occasionally follows a blow on the breast, though without knowledge of how long a malignant process takes to develop the association remains difficult to assess.

The following case is of interest :—

Case.—A woman, aged 58, was travelling, standing in a bus, in war-time London. Owing to a sudden swerve of the bus she received a hard blow over the breast bone and inner part of the right breast from the pointed elbow of a fellow passenger. The pain was described as sharp enough to make her feel sick and want to sit down. By the time she reached home, some 20 miles out of London, the pain had nearly gone. For 2 to 3 weeks, however, she was conscious of the area being tender, but observed no bruising. This occurred towards the end of July. In the following January she found a small lump on the edge of the right breast at the site of the injury. The lump persisted with some increase in size, and the patient sought medical advice about six weeks after the original discovery.

A small plaque of hard tissue $\frac{1}{2}$ to $\frac{3}{4}$ in. ($1\frac{1}{2}$ to 2 cm.) in diameter was palpable on the extreme margin of a large breast in the lower medial quadrant. No enlarged lymph-nodes were palpable. At the operation an immediate microscopical examination confirmed the presence of carcinoma (Stage 1*b*).

This woman had no doubt as to the association between the blow and growth, nor did any contradiction sound convincing. The absence of a previous lump and its unusual site were in favour of a relationship.

Marriage.—A difference of opinion is found in the relative frequency of carcinoma in the single and married women. The overlapping of these distinctions makes any comparison difficult, but some observers state that, age for age, the single woman is more liable, though others maintain equally that this point is not established ; it is generally admitted, however, that as a rule women of the cancer series are found to be less productive.

Lactation.—The influence of pregnancy and lactation on the development later in life of a mammary carcinoma, or of normal lactation acting as a safeguard against it, are controversial points with no convincing evidence one way or the other.

The occurrence of suppurative mastitis during lactation followed by abscess formation and drainage appears to exert little or no influence, but an acute infective process without pus formation which causes delayed or altered resolution and involution—sometimes referred to as a residual lactation mastitis—is regarded as a potential danger.

A point made by Lane-Claypon is that the habit of suckling for a very long period, or the complete failure to suckle, are far more common in the cancer than in the control series.

Abnormalities of function and of structure, such as the infantile and adolescent hypertrophies of the breast, gross deformities or absence

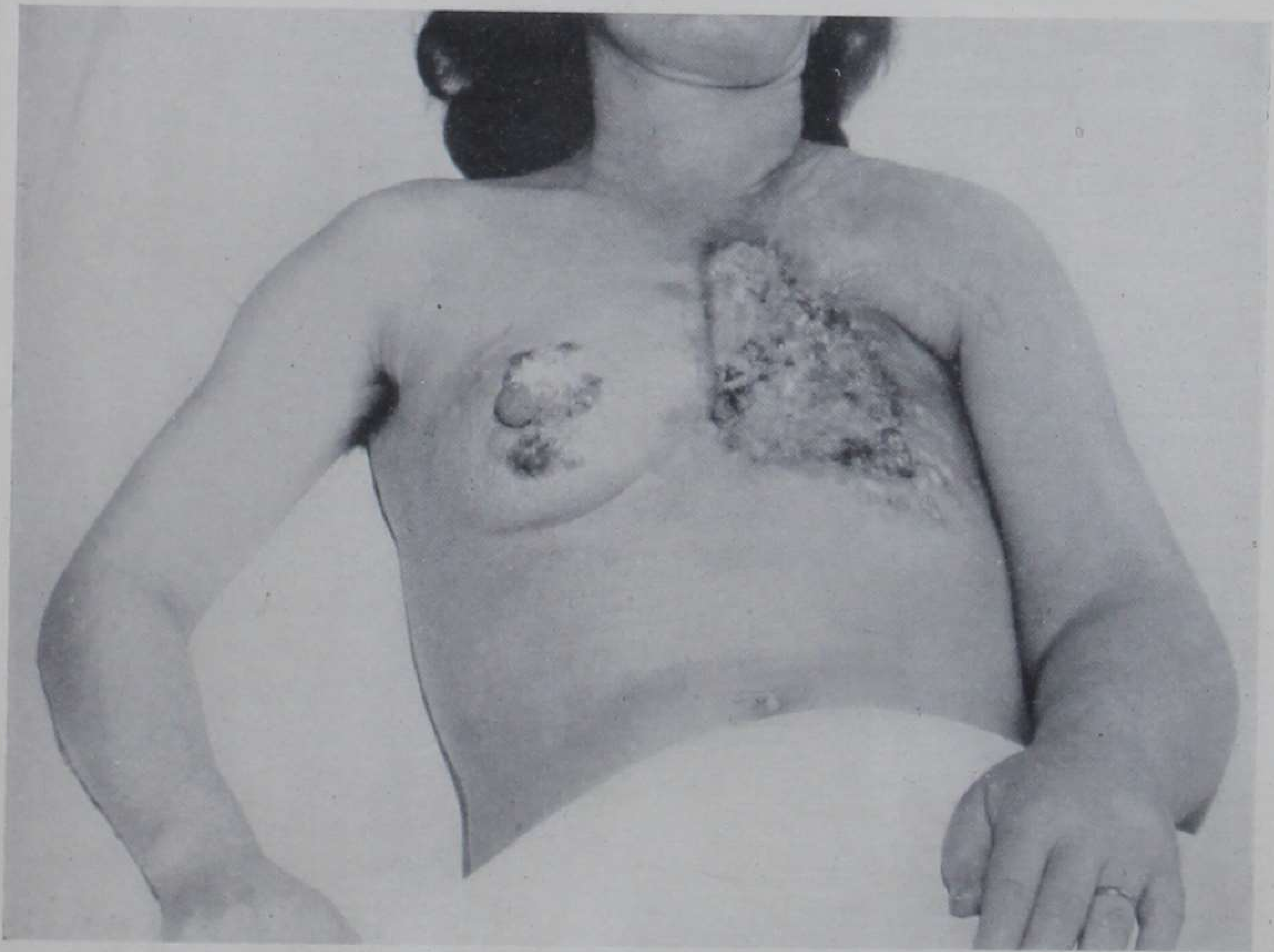

Fig. 107.—Advanced carcinoma of the breast in a woman aged 43. Previous left radical mastectomy. Bilateral mammary carcinoma. Involvement of axillary and left supra-clavicular lymph-nodes. Horner's syndrome. Œdema of left arm. (*Mr. McNeill Love's case.*)

of the nipple, though uncommon, are also regarded as having an association with the development of malignant disease. The cracked or fissured nipple is not included in this category, nor is unilateral lactation regarded as harmful.

GROWTH AND SPREAD

If it is true that carcinomata originate as intraduct or intra-acinar neoplasms, the first stage of their spread is a break through into the surrounding connective tissue. Malignant cells then spread along the fascial planes, infiltrate the fat, and enter the lymphatics. The direct spread may be associated with a reactive fibrosis which is usually most marked in the centre of the neoplasm ; here the fibrous tissue may be very dense and the cells very scanty. Frequently the fibrosis seems to precede the malignant penetration, but not uncommonly, on the other hand, the edge of a growth is found to be cellular with little fibrous tissue.

According to Sampson Handley, the malignant cells grow along the lymphatics in an ever widening circle with the living cancer cells at the periphery and a destructive fibrosis behind, which fails, however, to hold the growing edges. If permeation of the lymphatics takes place towards the skin, the result may be an œdema of a varying area of the surface, when, as the result of fixation of the hair follicles, a pitted appearance is given, described as *peau d'orange*. If, with continuous spread, nodules of growth are formed in the superficial layers of the dermis—*cancer en cuirasse*—a solid leather-like mass with multiple nodules eventually covers much of the chest and abdominal walls.

While, however, permeation appears to be the main method of spread in certain types of case, in others emboli of cancer cells are carried, separately or in addition, in the lymph- and blood-streams to near or distant parts of the body.* As soon, then, as the disease is established the possibility or the probability of an embolus being transmitted outside the breast area steadily increases without immediate clinical appreciation of such spread. (*Fig.* 107.)

GRADING OF CARCINOMA

A method of grading mammary carcinoma and the likelihood of its dissemination has been suggested on the histological appearance

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* In the description of the lymphatic drainage of the breast (Chapter I, p. 17) mention has been made of how an invading neoplasm, by obstructing the lymphatics, leads to the opening of new channels and ramifications. Consequently, dissemination travels beyond the normal drainage.

For blood-borne deposits of growth the conventional end-station is in the lungs. Attention has also been called to a peripheral venous anastomosis at each segment between the thoracico-abdominal veins and the corresponding azygos, vertebral, and epidural veins (Batson). This system is stated to have no valves and very low pressure gradients, so that normal flow can be readily reversed by any form of Valsalva effort (coughing, straining, etc.). Communications have also been demonstrated between the veins of the breast and those of the clavicle, humerus, vertebræ, and brain (Batson). Statistics of the results of a series of some 200 fatal cases of mammary cancer subjected to autopsy confirm that intrathoracic deposits are the most common (89 per cent), then intra-abdominal, skeletal, and central nervous system, in that order. This distribution of deposits tends to confirm the conclusions drawn from a study of the anatomical pathways. There seems little doubt, however, in the majority of cases, that regional lymph-node deposits precede others and probably represent the first station in the general centrifugal migration of the tumour.

of the growth. Broders' work on this subject may be roughly summarized as follows :—

In normal tissue a cell is differentiated according to its special purpose, such as cells of the Malpighian layer in the surface epithelium which ultimately form keratinized material. The more highly a cell is differentiated the less is its malignant capacity, until, if differentiated beyond a certain stage, the power of reproduction is lost. Conversely, the less differentiated a cell the greater its production capacity and potential malignancy.

Expressed in another way, a malignant cell may be regarded as the result of de-differentiation of a normal cell, and one totally undifferentiated or de-differentiated possesses the highest degree of malignancy. If composed wholly of such cells, a tumour is possessed of highly malignant characteristics, and the presence of numerous mitotic figures would seem to confirm this. The so-called encephaloid carcinoma is of this type, while, on the other hand, the rare columnar carcinoma has relatively a low-grade malignancy.

Again, when a carcinoma tends to form acini, its grade of malignancy is assumed to be less than if solid alveoli are formed ; yet in the scirrhous carcinoma, a tumour of high malignancy, malignant acini are not uncommonly found. But an intraduct carcinoma, which is regarded as relatively benign in spite of its cellularity, usually shows the formation of acini in an otherwise solid column of cells. When associated with a lobular hyperplasia only, the intraduct carcinoma is probably not more than a potential danger ; when the break-through occurs, the characteristics are altered to that of a highly malignant scirrhous carcinoma.

The latter point suggests the possibility of a more surgical or clinical method of grading malignant tumours, based not so much on cellular types—which is, however, deemed important by the radiotherapist—and their potentialities, which are speculative, but rather on what a tumour has already done. On this basis a carcinoma confined to the ducts—if indeed at this stage carcinoma is a correct label—is the least malignant. The next grade is the infiltrating carcinoma of 10 mm. or less in diameter, of 20 mm., and so on, with increasing potential or actual dissemination.

Inevitably, then, a carcinoma of the breast grows, infiltrates, and disseminates, and the speed of its progress and behaviour to the surrounding tissues gives some measure of its malignancy. Also the actual site of growth—if, for instance, it is near the medial border of the breast—may influence, unfavourably, the direction and depth of the initial dissemination.

From the breast carcinoma spreads to the regional lymph-nodes. This move precedes a more widespread dissemination probably in most cases, and represents the first step in a general centrifugal migration of these immature cells, whose inception and primary momentum is almost certainly influenced by the conditions existing in the breast at the time.

A mammary carcinoma may start during the menstrual cycle, in a pregnancy–lactation period, at the menopause, or in old age. When it is associated with highly activated vascular tissue the situation promotes rapid growth and spread. In a less active and less vascular medium the soil is not so suitable and progress is accordingly slower until, in some instances, it seems to be brought nearly to a standstill. The minute structure of a carcinoma depends on the site of its inception in the mammary tissue ; its nature may well be a product of the soil in which it grows. Once general dissemination has started, however, the speed probably varies but little in any case.

CLASSIFICATION AND PATHOLOGY

For purposes of record and clinical description the following classification, which is meant only to cover most of the routine cases,

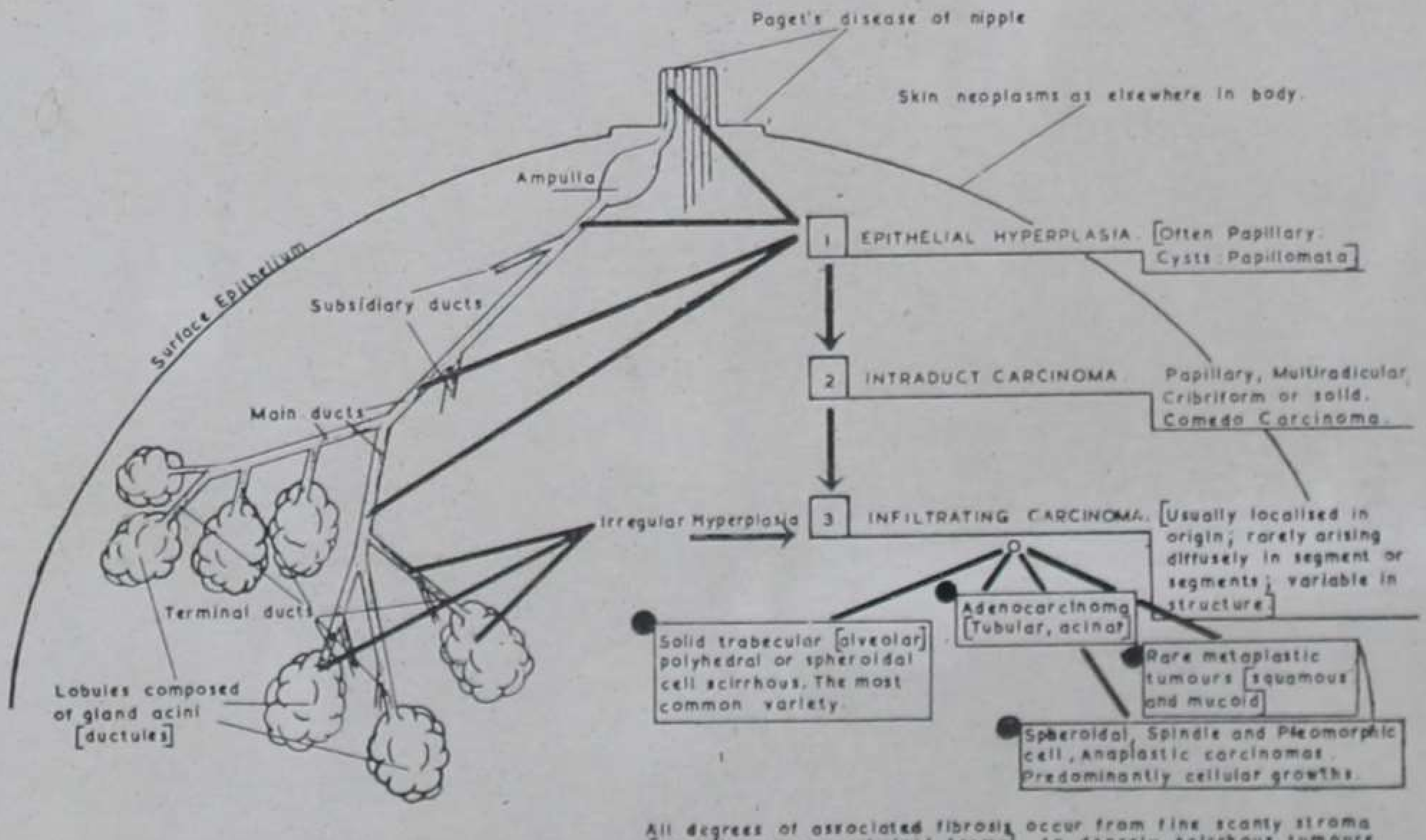


Fig. 108.—Simplified topographical scheme of breast carcinoma. Histogenic classifications of this group are tentative at present ; most terms employed have descriptive value only. Questions of precursor states and fundamental pathology have largely been omitted. Mixed types of growth are common—e.g., intraduct carcinoma plus infiltrating carcinoma ; trabecular and tubular structures, etc. For clarity the drawing is not to scale. (*Dr. P. M. Peters.*)

is suggested. It should be emphasized, however, that the difference between these types is essentially biological and that every gradation exists (*Fig.* 108). For example, a scirrhous carcinoma is the result of fibrous reaction in the host, and so-called encephaloid carcinoma demonstrates the absence of this reaction.

1. Spheroidal-celled carcinoma { Scirrhous / Encephaloid
2. Adenocarcinoma
3. Colloid carcinoma
4. Duct carcinoma
5. Neoplastic disease of the nipple region
6. Sarcoma.

Of these the scirrhous carcinoma is the most common and probably easily outnumbers all other breast lesions.

1. Spheroidal-celled Carcinoma.—

Scirrhous Carcinoma.—On section with the knife this growth is hard, feels gritty on scraping—giving the well-known "cut pear"

Fig. 109.—Scirrhous carcinoma of the breast.

feel—and the cut surface becomes concave, due to the retraction of fibrous tissue, especially in the centre of the growth. The hard area merges almost imperceptibly into the surrounding fat, with a defined radial striated appearance due to degenerating cells forming small yellow streaks. (*Fig.* 109.)

Microscopically, the cells, usually described as spheroidal, form small solid islands of growth extending along the fascial planes, accompanied by a considerable amount of fibrous tissue. In the variety called carcinoma simplex (*Fig.* 110) little columns of round

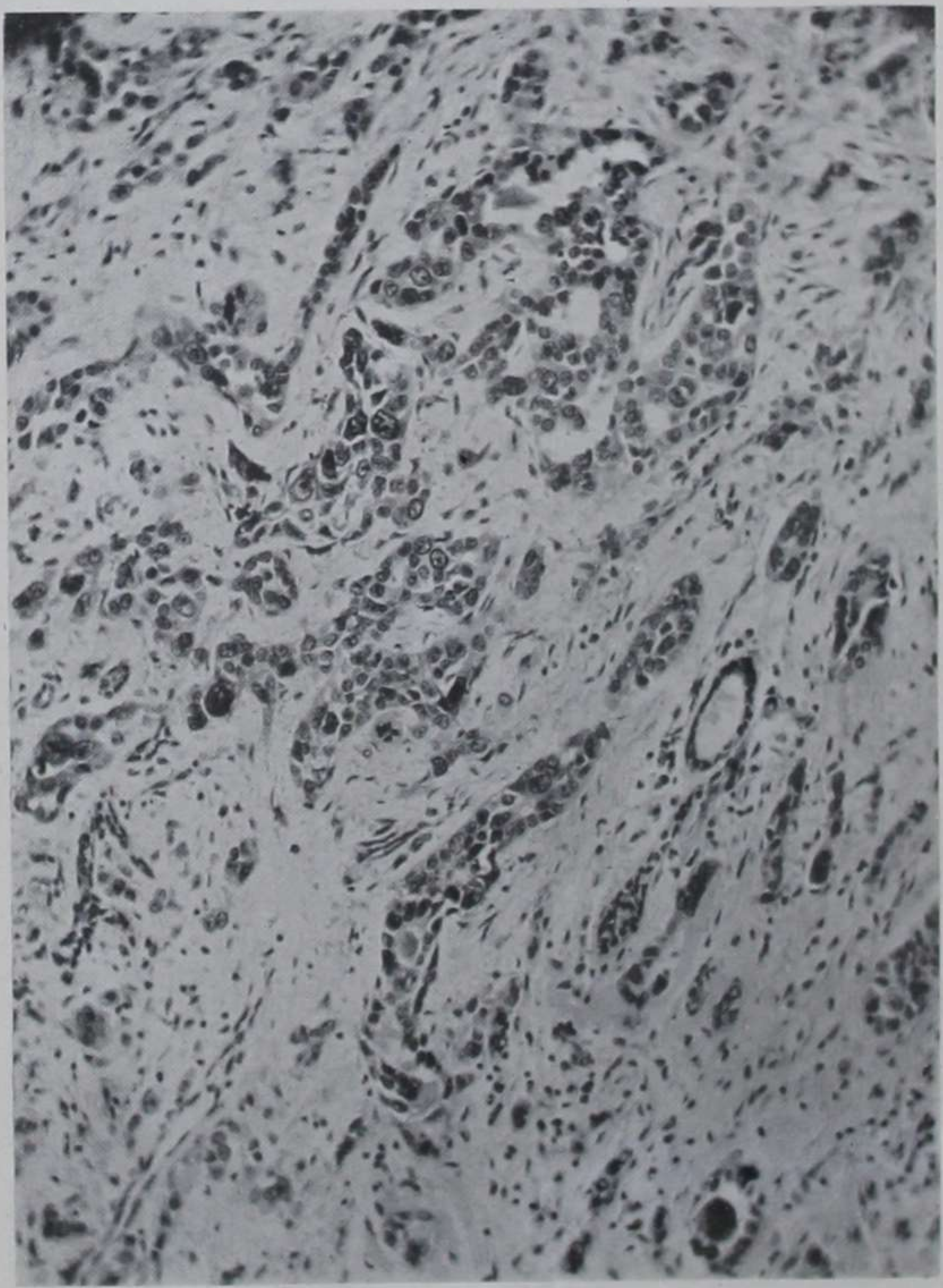


Fig. 110.—Invasive carcinoma of breast. This section of a typical scirrhous carcinoma of the breast shows the malignant cells singly, in small groups, and in tubules. (× 130.)

cells are scattered throughout a dense fibrous-tissue stroma, but the amount of this varies considerably in different growths or even in the same growth. The atrophic scirrhus consists of dense fibrous tissue with but few recognizable carcinoma cells. Such a growth is limited to old people and presumably might—probably never quite—destroy itself.

Again, a long-standing case may show a large and almost acellular area of fibrous tissue in the centre of the mass, with columns of cells extending into the fat and fibrous tissue at the periphery of the breast. Or cancerous alveoli and fibrous tissue may be almost equal in one

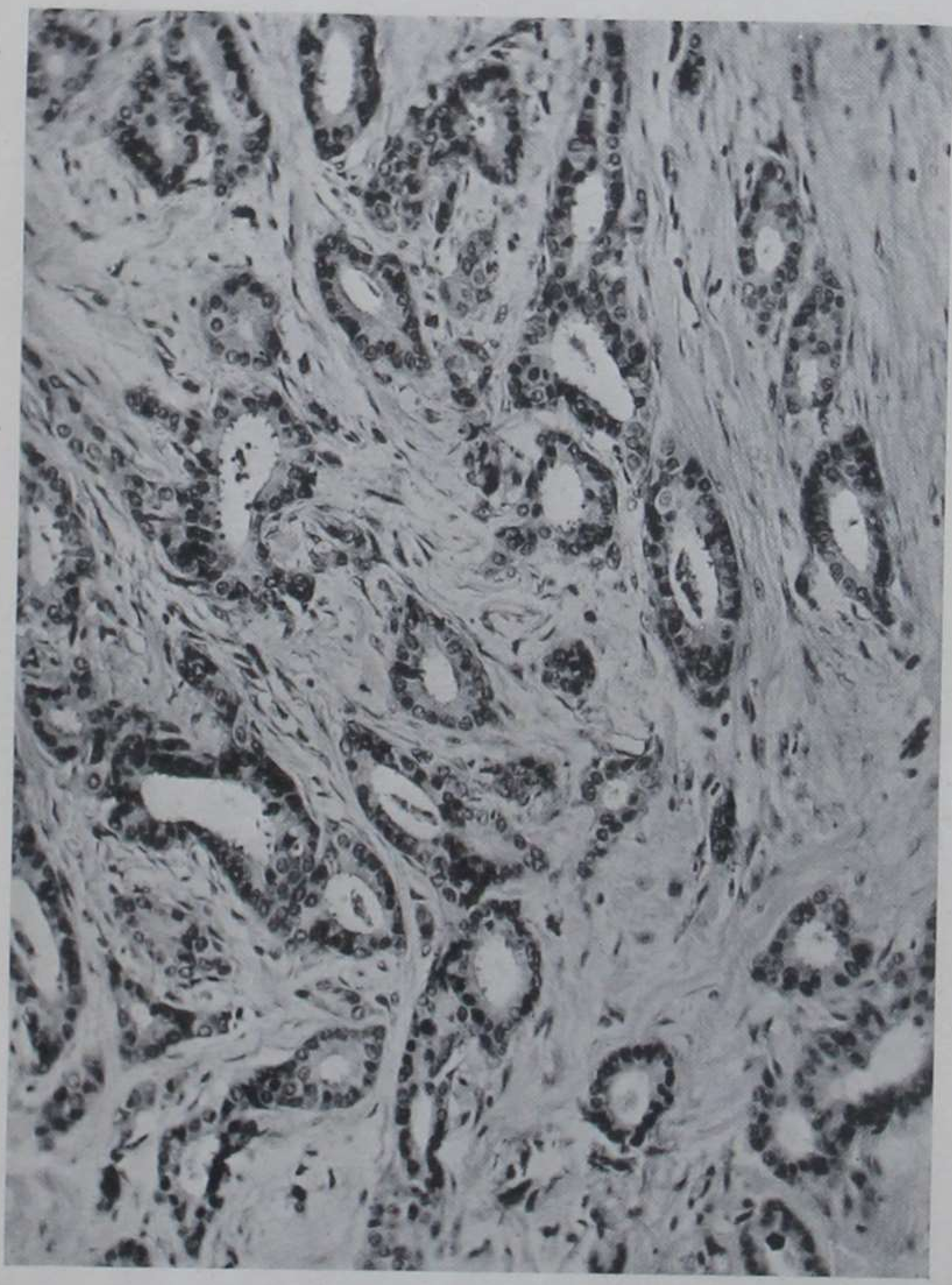


Fig. 111.—Secondary deposit of carcinoma in an axillary lymph-node. Note the tubular arrangement of the malignant epithelial cells. From a case of typical scirrhous carcinoma of the breast. (× 110.)

area, while in others large masses of cancer cells are present with little or no fibrous tissue.

Whereas a scirrhous carcinoma of the breast is described as being composed normally of small solid columns or larger solid alveoli of spheroidal cells, a considerable variation of this can exist in the same growth. Thus, although the main mass consists of solid bundles of cells, not only may there be some irregularity in the shape of the cell but actual tubule formation—not unlike acini though without collection into lobules—with, however, a deeper staining reaction and rather different colour from normal glandular tissue. An otherwise

Fig. 112.—Secondary deposit of carcinoma in an axillary lymph-node. Note the solid clumps of malignant epithelial cells—from the same section as *Fig.* 111. These sections illustrate the varied appearance that one disease may produce. (× 110.)

typical scirrhus may be composed almost wholly of such tubules. (*Figs.* 111, 112.)

As the growth advances the normal tissue may be undergoing atrophy or disappearing, but on occasion cancer cells can be recognized mingling with normal cells of the acini. Does, then, a malignant cell travel along the ductule and crowd out the normal cell or does the latter undergo a malignant metamorphosis?

Encephaloid or Medullary Carcinoma.—This form of carcinoma was thought, at one time, to be most common in the woman under 40. Not infrequently, however, it is found in a large fatty

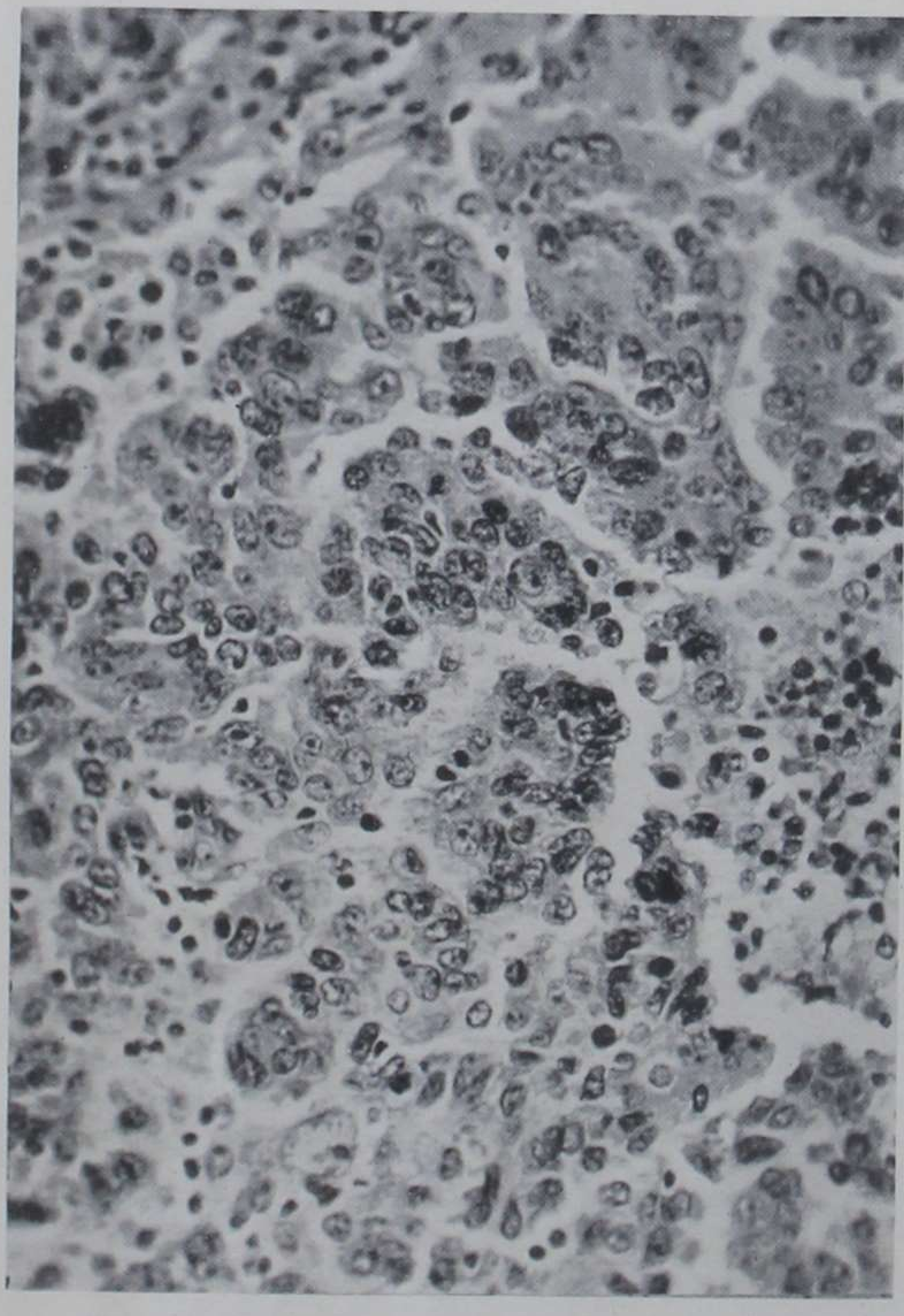


Fig. 113.—Encephaloid carcinoma of breast. High-power view of a very cellular carcinoma of breast with little fibrous-tissue reaction. Clinically thought to be a cyst, it was excised three days after its discovery. (× 300.)

breast of the middle-aged woman when—if seen early—the circumscribed softish lump is very apt to be mistaken for a cyst. In a woman aged 75 a small rounded lump in the right breast was diagnosed as a cyst on clinical examination, but on local removal examination proved it to be an encephaloid carcinoma. At the subsequent operation no obvious secondary deposits were found (*Fig.* 113).

Microscopically, these encephaloid growths consist of large sheets of cells separated into islands by scanty fibrous-tissue bands. The cells are large, round, and frequently show considerable mitosis, in

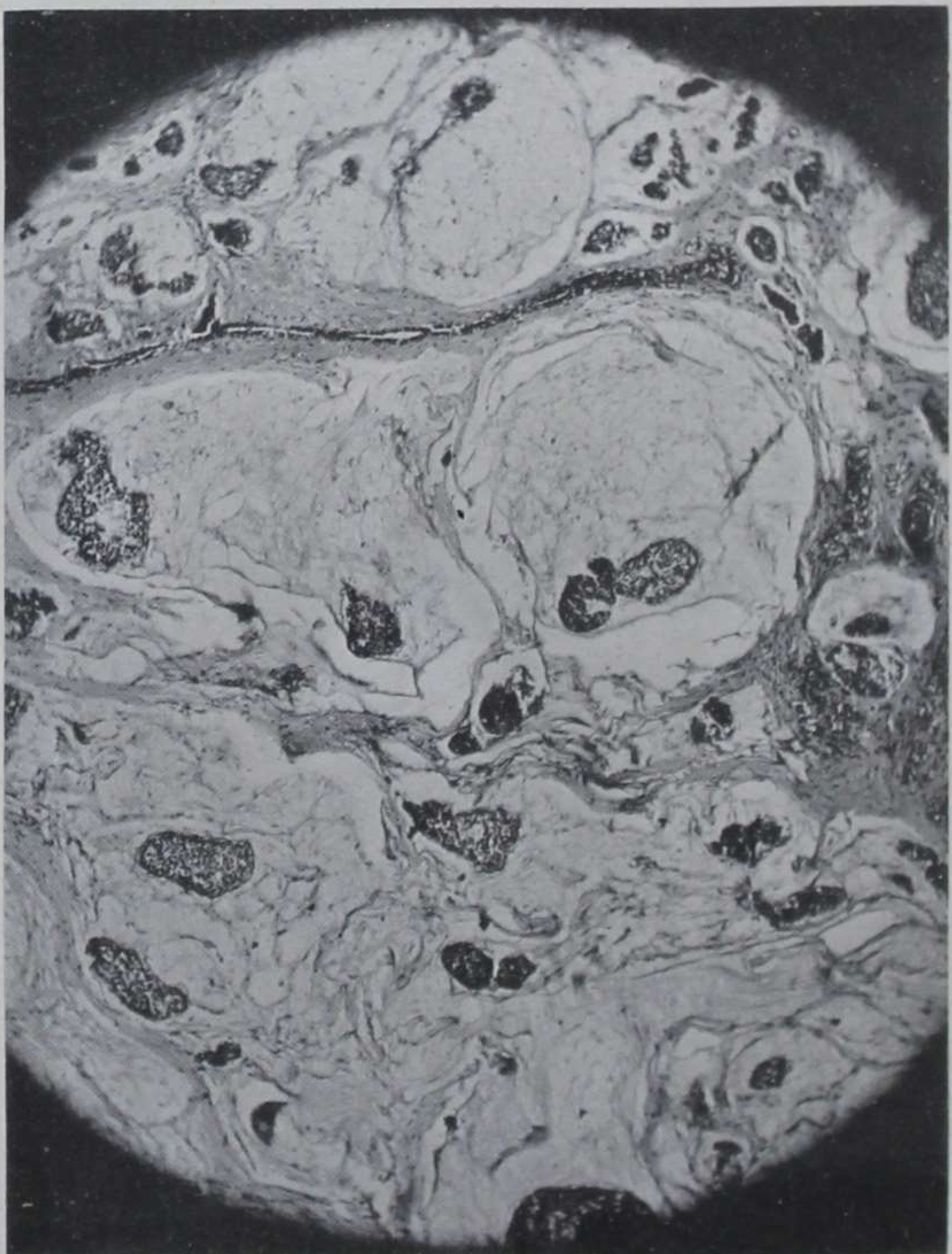


Fig. 114.—Colloid carcinoma of breast. Note the clumps of epithelial cells in the midst of masses of mucoid material. Occasionally the epithelial elements may be almost completely absent, and a large cyst may be formed—in one of our cases the cyst was over 6 in. in diameter. (× 48.)

contradistinction to the scirrhous type in which mitosis is inconspicuous. In some instances the cells are distorted and elongated, resembling a sarcoma.

2. Adenocarcinoma.—This type is rare unless carcinomata are included with a tendency to tubule formation, as in some scirrhous and many intraduct carcinomata. Of low-grade malignancy and slow growing, an adenocarcinoma tends to form a soft bulky mass which in time ulcerates through the skin and fungates. In some instances secondary deposits in the axillary lymph-nodes are not found even at this stage.

3. Colloid Carcinoma (*Fig.* 114).—Colloid degeneration, an uncommon though not rare condition, may be limited to a small proportion of the cells of a fairly cellular growth or involve the whole tumour mass. Not infrequently small clusters of cells are seen to be

Fig. 115.—Cystic degeneration of carcinoma of the breast in a woman of 45. Posterior aspect of the breast. There was advanced axillary involvement (Stage 2*b*).

losing their shape in scattered areas of the growth. Or a cyst may be found containing gelatinous material in which, except for a few scattered clumps, it is difficult to distinguish any cells at all. A cyst up to 2 in. or more in size and involving most of the breast tissue is sometimes seen. A woman, over 70 years of age, had an enormous cyst in the right breast. The gelatinous nature of the contents provided a clue, and a small patch of carcinoma cells was found in a fibrous wall. Such a condition can well be described as a cancer cyst. (*Fig.* 115.)

If the main mass of a carcinoma is thus involved in colloidal degeneration, its malignancy is of low grade, but for a small area this statement does not apply. If, on the other hand, the degeneration is of the stroma and not the cancer cell, the process is highly malignant, a rare condition known as carcinoma-myxomatodes.

Fig. 116.—Papillary carcinoma of breast. The section shows a number of papillary processes covered by layers of deeply staining epithelial cells, many of which are columnar. The condition suggested malignancy. (× 120.)

4. **Duct Carcinoma.**—The term duct carcinoma should probably be restricted to duct papillomata showing malignant changes—for example, the presence of bundles of epithelial cells in the fibrous pedicle. Such growths are uncommon, and the diagnosis may remain in doubt unless a secondary deposit in an axillary lymph-node confirms it. (*Figs.* 116, 117.)

The term duct carcinoma implies a malignant growth of epithelial cells of the ducts. Cheatle and others maintain that most carcinomas arise in the ducts, and Muir (1941) has described the genesis of

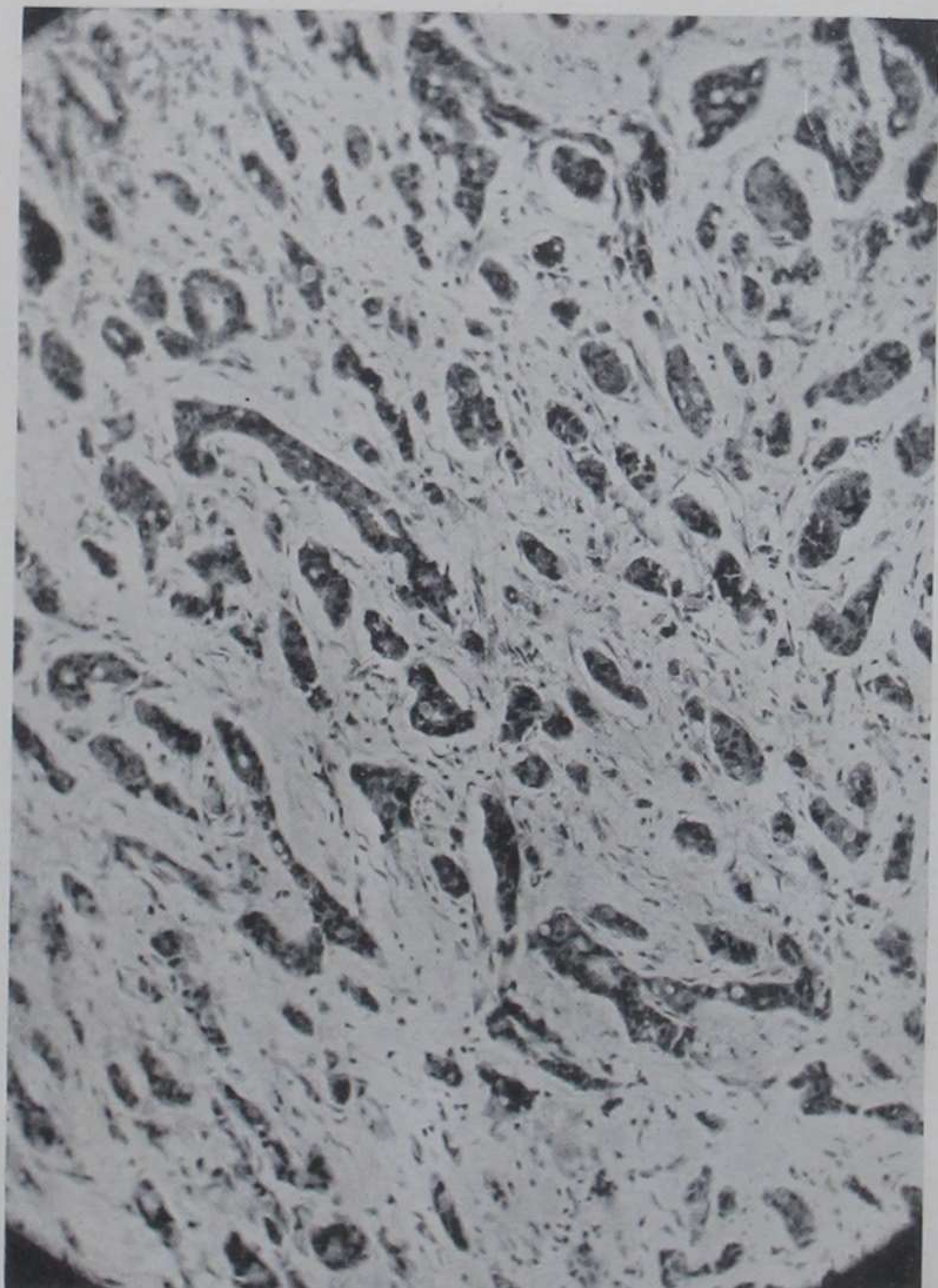


Fig. 117.—Invasive carcinoma from the same breast as that shown in *Fig.* 116. Two small areas immediately adjacent to the papillary processes showed a typical carcinoma of the scirrhous type. (× 120.)

carcinoma from ducts and acini. Undoubtedly the vast majority of carcinomas of the breast must arise from the ducts or their termination in acini, although sweat-gland cancers are also described. The existence of the latter is regarded by some authorities (Ewing, Geschickter) as definite, while equally definite opinions are held to the contrary (E. K. Dawson, 1932). Whichever view is held, in histological evidence, however, there is no clinical distinction to be made.

The circumscribed carcinoma that clinically resembles a cyst is in all probability primarily a duct carcinoma.

Fig. 118.—Intraduct carcinoma. Note the cribriform appearance. 'Cribriform' carcinoma is produced by the formation of small tubules in the solid masses of cells. This breast had an invasive carcinoma as well. (× 140.)

Intraduct Carcinoma (*Fig.* 118).—This carcinoma, when confined to the ducts, presents none of the solidity associated with the usual type of growth. When incised, yellowish areas are seen, and casts of thick yellowish material can be squeezed out. On microscopical examination small cystic areas are seen containing deeply staining epithelial cells resembling carcinoma cells. The term 'comedo-carcinoma' has been applied by Bloodgood to this condition (*American Journal of Cancer*, 1934). In some cases no evidence of an infiltrative carcinoma is found, and this type has probably the best prognosis of all the mammary carcinomata (Geschickter, *Diseases of the Breast*, p. 506). The condition is almost certain to recur with local excision only, e.g., in one case a recurrence appeared 12 months after local excision, but no infiltrating carcinoma was found.

When, however, infiltration of the surrounding breast tissue does take place, this carcinoma assumes the ordinary characteristics.

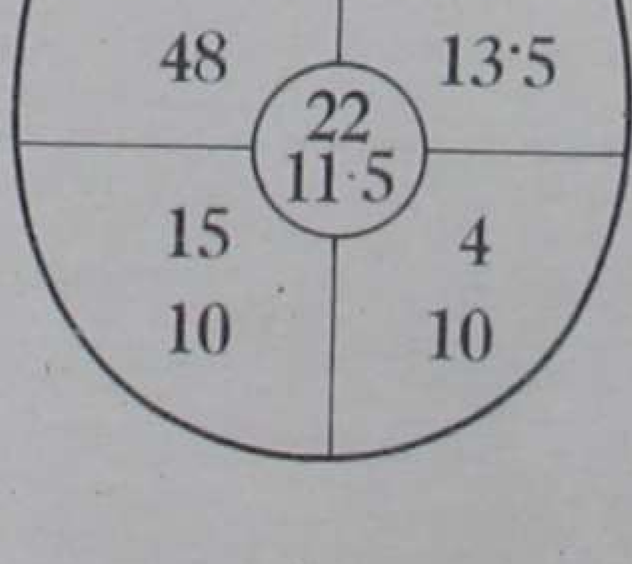
5. Neoplastic Disease of the Nipple Region.—(*See* Chapter VII.)

6. Sarcoma.—Sarcoma of the breast is rare, and probably forms considerably less than one per cent of malignant mammary neoplasms. A sarcoma may arise in the fibrous tissue of the breast, or in the fibrous tissue of a fibro-adenoma. In one case a small spindle-celled sarcoma was found growing in the wall of a cyst from the breast of a woman aged 70. A small area in adjacent breast tissue showed evidence of an obsolete lobular hyperplasia (hyperplastic cystic disease).

In another case a woman of under 40 had a typical intracanalicular fibro-adenoma removed from the left breast. Following the operation the breast became indurated and rapidly grew into a massive neoplasm of finally over $6\frac{1}{2}$ in. in diameter. Death occurred some six weeks later, when, on examination, no secondary deposits were found and the primary growth showed histologically a mixed-celled sarcoma of high malignancy. Sarcomas of the breast grow with great rapidity and fungate early. Their mode of dissemination is by the blood-stream.

DISTRIBUTION

The greater number, some 60 per cent, of malignant neoplasms occur in the lateral half of the breast and mainly the upper quadrant. Some 20 per cent are found in the central and medial areas. So far as can be ascertained there is no explanation of this distribution on anatomical grounds.



Schematic representation of a breast, showing the percentages of malignant neoplasms in different regions. The upper figures are given by Geschickter, the lower—diffuse growths not included—by the British Empire Cancer Campaign.

SYMPTOMS AND SIGNS

(*See also* Chapter IV, Examination and Diagnosis)

In the British Empire Cancer Campaign analysis of a pre-war investigation only 25 per cent of women were reported as seeking advice within 2 months of finding something wrong in the breast ; in about 16 per cent it was 18 months or over. Some, especially the old, are apt to wait until ulceration and bleeding drive them to take action, but also far too many younger women are seen for the first time in an already hopeless condition. (*Figs.* 119–121.) A number of factors,

Fig. 119.—Advanced carcinoma of right breast. Massive ulceration in a woman aged 53. Condition when disclosed for the first time. Widespread secondary deposits already present (Stage 4).

no doubt including fear, influence the timing of a decision to ask medical advice, but a reason for procrastination, given again and again, is the absence of pain. This fact, that the disease is unlikely to produce symptoms or depreciation of general health until advanced, requires emphasis and a reasonable publicity, as already stated. A transient pain in the breast, described as stabbing or shooting, is sometimes mentioned, but in most cases pain and tenderness, if present at all, are indicative of an advanced growth.

In the majority of cases the only indication of a carcinoma of the breast is a lump in its substance, and the physical signs are, for the most part, in direct proportion to the progress of the disease. In an analysis of 1061 cases (British Empire Cancer Campaign) a lump was the first indication in 852 and pain in 107. Geschickter gives a nearly similar proportion for 1452 cases, and states that pain or tenderness rarely precedes the discovery of a lump, though these symptoms are noted, at some stage of the disease, in rather under half the cases.

Other primary signs are discharge from, ulceration, retraction, or elevation of the nipple, 3 per cent; eczema or ulcer, 3 per cent;

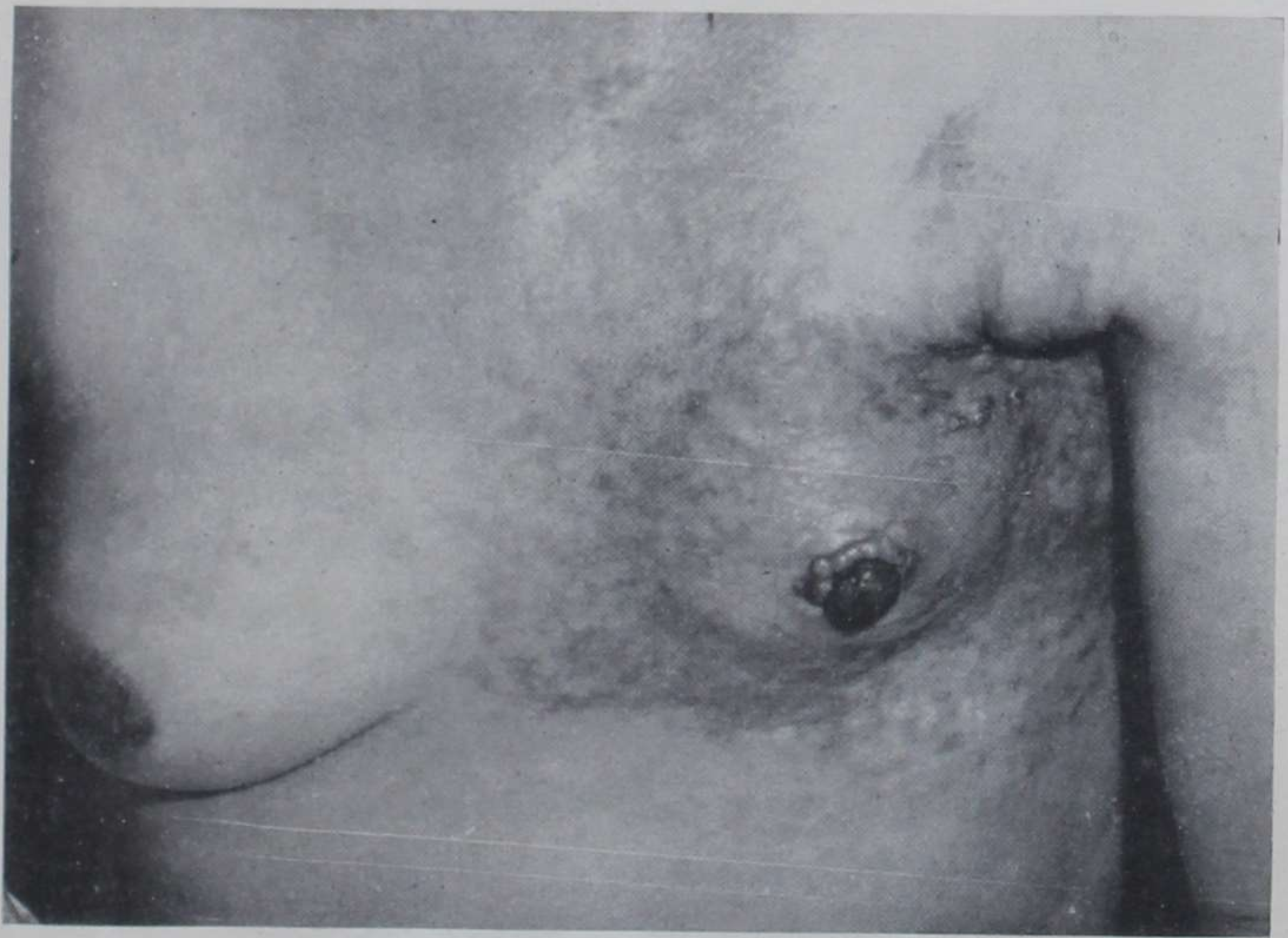


Fig. 120.—Advanced carcinoma of left breast in a woman aged 56. Condition on first attendance. Infiltration *en cuirasse* of the skin, involvement of axillary and supraclavicular lymph-nodes, and radiographic evidence of pulmonary deposits. Patient noted "stiffness" of the left breast while swimming 3 months previously but took no notice till the skin covering the breast became discoloured and the left arm swollen (Stage 4).

symptoms due to secondary deposits, 2 per cent; and accidental discovery during routine examination, 1 per cent.

Case.—Single woman aged 63. Consulted her doctor for the first time for over 25 years, because of a few raised, slightly red, and pea-like nodules in the skin over the centre of her back. These, noticed in the mirror, were symptomless but seemed to be increasing in numbers. On examination a small mass was found in the left breast and an enlarged lymph-node in the axilla. A biopsy of a skin nodule confirmed the association. This case is an example, possibly, of lymph-borne deposits rather than continuous permeation.

As a definable clinical entity a mammary carcinoma may be presented as an area of raised discoloured skin, a small, thin plaque of hard tissue of little depth, isolated or superimposed in more nodular form on an area of mastitic tissue, as a small circumscribed discrete tumour, or as an unmistakable mass. When still small, a carcinoma may be palpable in a thin breast or on the margin of a full one; if deep in the substance of the latter, detection can be wellnigh impossible.

As a carcinoma grows its outline is diffused into the surrounding tissues and lost, and its surface becomes harder and rougher, aptly

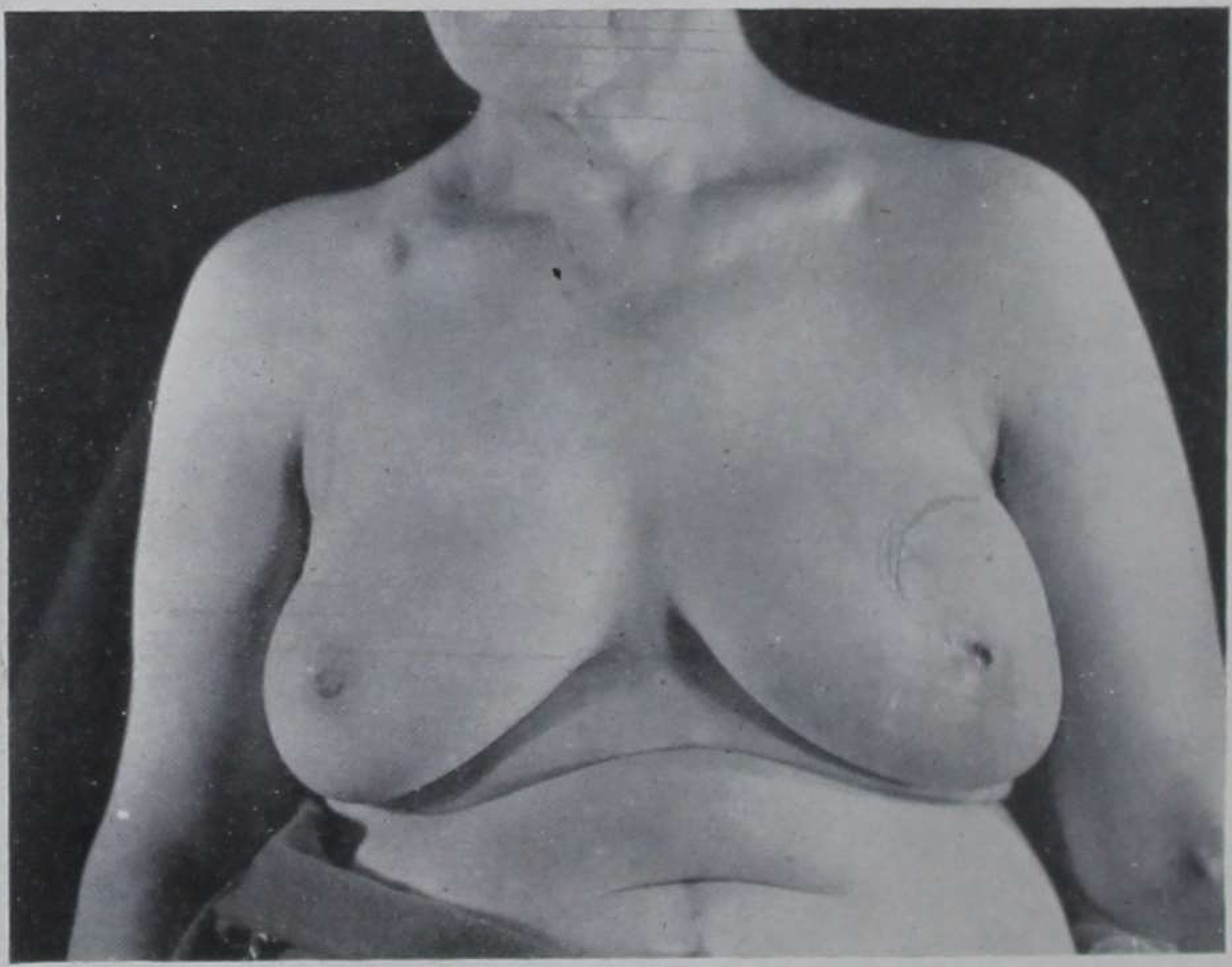


Fig. 121.—A large mass of growth in the upper half of the left breast causing marked retraction of the nipple in a woman aged 63. There was massive involvement of the axillary nodes (Stage 2*b*).

described as "craggy". If superficial, a bulge in the outline of the breast may be obvious, while if deep in the mammary tissue a carcinoma usually feels near the surface owing to the disappearance of fat over it. Attachment to, or pressure on, the framework of the mammary tissue causes deformities of the surface of the breast such as dimpling, wrinkling, or inversion of the skin and elevation or retraction of the nipple, though all these signs are indicative of a well-established growth. Eventually the skin may become reddish and shiny, and finally ulcerated.

Many of the signs associated with a malignant state in the breast are presented by the accompanying fibrosis, but the more rapidly growing carcinomata, on examination, convey a sense rather of inflammatory or indurated tissue without a hard definable tumour mass. Such growths may occur in the pregnancy-lactation period and also in the young or older woman apart from this.

Case.—Woman aged 32. Two children, younger aged $4\frac{1}{2}$. Both breast-fed for about 3 months. A big woman with good health; menses regular and normal. Advice was sought because of a raised and discoloured patch in the skin of the right breast, noticed for a few weeks and thought to be growing.

On examination, a rounded area of skin, half an inch in diameter, reddish in appearance, slightly raised, not unduly hard, and well defined, was found situated in the midline of the upper half of a large breast. No tumour could be said to exist, but there was a feeling of depth and infiltration.

An operative investigation was advised, but owing to the outbreak of war, evacuation, and other domestic trials, some six months elapsed before this woman reported again, when much of the breast was solid with growth and widespread dissemination obvious.

A malignant state already existent in the breast at the onset of a pregnancy receives in full measure the general stimulation and grows rapidly. Or it may arise at any point of the pregnancy-lactation period, and develop on occasion into one of the most malignant of all cancers.

Carcinoma of the Male Breast (*Fig.* 122).—Although, of course, a comparative rarity, carcinoma of the male breast does not otherwise differ in structure, mode of growth, or spread from that of the female. It appears about the same time of life, with the occasional extreme variation, and in any type of breast, but, in general, owing to the scarcity of mammary tissue the nipple and skin are more quickly involved. In most cases when first seen the skin over the growth is discoloured and shiny, if not actually ulcerated, with enlargement of the axillary lymph-nodes. Before, however, this clinical picture is presented the condition will have been in existence for a considerable time. The average duration of symptoms in men (Geschickter) is estimated at some $2\frac{1}{2}$ years, as compared to a year, or rather under, in women, with consequently a markedly worse prognosis.

The principles guiding diagnosis and treatment are exactly the same as for women.

CLINICAL GROUPS

Generally speaking a clinician can recognize only one mammary carcinoma, which is imperceptible in its early stages and is only found later in varying circumstances, different sites, and many stages of its cycle of growth and dissemination. Any classification is necessarily an arbitrary one, based on the obvious spread of the growth as indicated by gross physical signs and radiographic examination. Concealed dissemination is unrecognizable by either, though

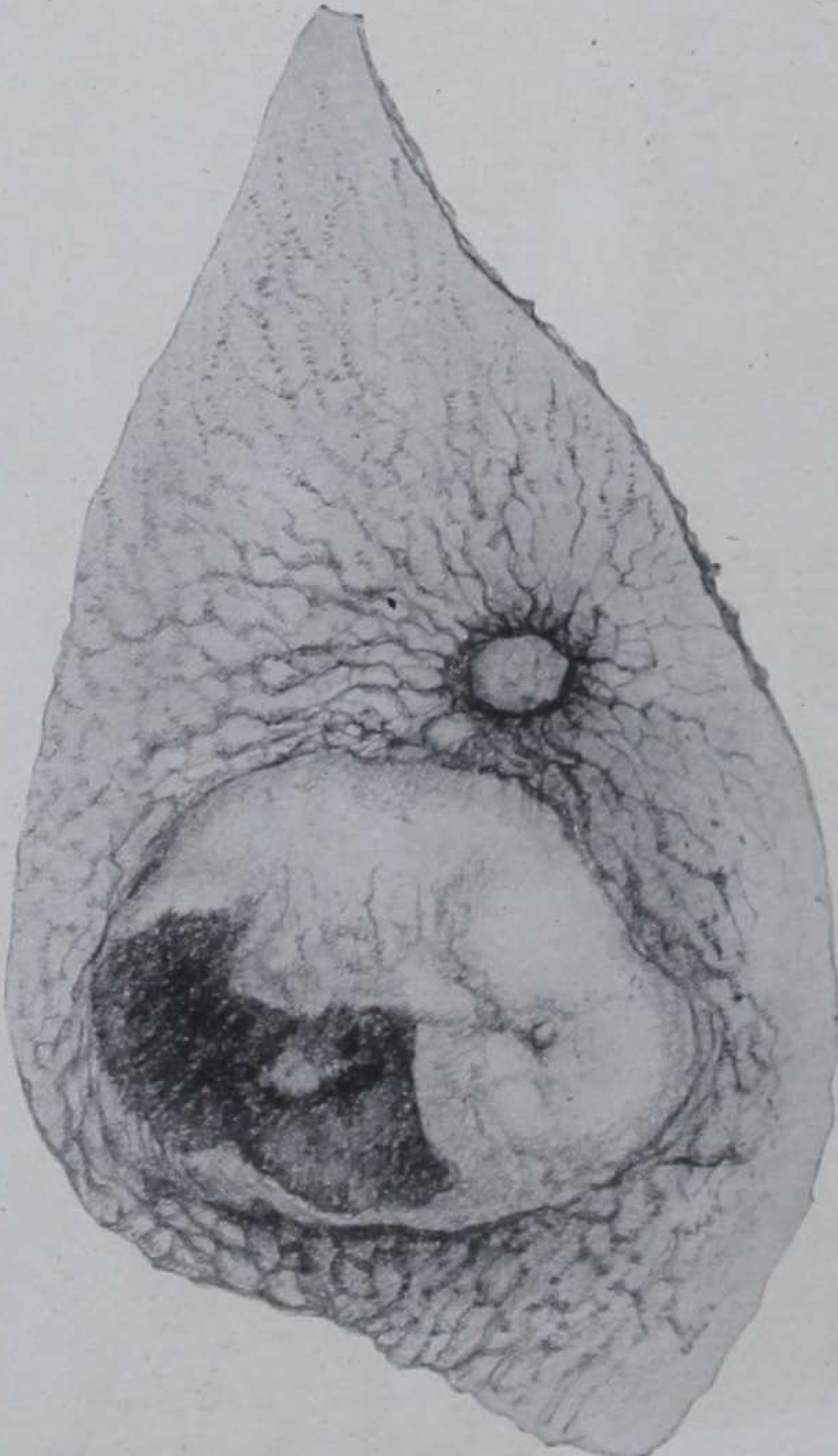


Fig. 122.—Ulcerating carcinoma of the left breast below the nipple, involving the muscle in a man aged 47. The axillary nodes contained malignant deposits. A lump had been noticed for some twelve months. (*Mr. McNeill Love's case.*)

the measure of this is to some extent, certainly not altogether, concurrent with the obvious. But as a rough guide and a basis for treatment and prognosis the progress of the ordinary case can be divided into four main stages, with a sub-division of the first three.*

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* The arrangement suggested here is based on Steinthal's original classification in which he divides cases of mammary carcinoma into three groups (" Zur Danerheilung des Brustkrebses ", *Beitr. klin. Chir.*, 1905, **47**, 226–239). The word stage is used instead of group, as more indicative, perhaps, of the inevitable progress of growth.

STAGE 1.—Within the area of the mammary tissue :—

a. 2 cm. and under in diameter. A suggested measurement to indicate an early stage.

b. Over 2 cm. in diameter : (i) Situated on the margin of the breast (axillary tail excluded) ; (ii) Situated near the medial border of the breast ; (iii) Puckering of the skin ; (iv) A high degree of malignancy reported on histological examination. (Broders 3 or 4.)

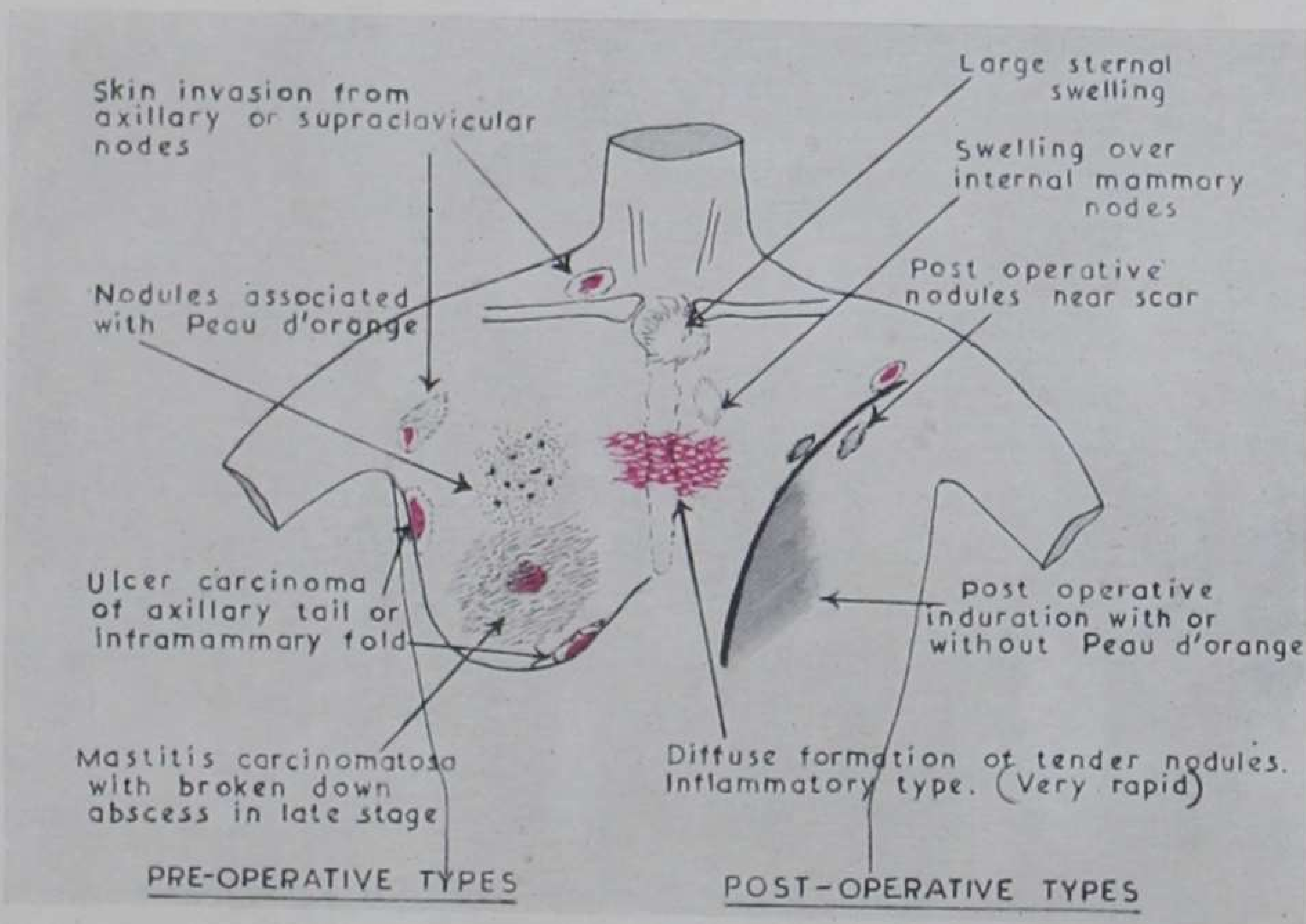

Fig. 123.—Skin invasion from breast cancer. (*Mr. Anthony Green.*)

STAGE 2.—Dissemination to the axilla.

a. Basal nodes only.

b. Basal and apical nodes or the latter only.

STAGE 3.—Further dissemination to :—

a. Internal mammary nodes (*see* Chapter IX).*

b. Supraclavicular and perhaps other groups of cervical nodes.†

c. As regards treatment, but not necessarily prognosis, most cases with extensive skin infiltration or ulceration are included in this stage. (*Fig.* 123.)

STAGE 4.—Dissemination to distant areas of the body.

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* The terms internal mammary, intercostal, and sternal refer to the same chain of lymph-nodes and are used interchangeably in all chapters.

† Healed tuberculosis may be mistaken for malignant nodes. Radiographs of the neck will show calcareous deposits, or a biopsy may be required.

The progress of a malignant growth in the breast appears to follow the routine of these stages fairly closely, with definite intervals between Stages 1 and 2 and 3 although the later stages are often indistinguishable. The longest interval by far is probably between the first and second, which has been reckoned to average about ten months, but as a carcinoma is only found when forming a discoverable lump and not at its inception, this appears to be a considerable under-estimate.

In an interesting analysis of over a thousand cases, Geschickter reports that in 10 per cent of cases of an estimated three months' duration the diameter of the growth was under 2 cm., in 45 per cent of over eight months' duration the diameter was 2–3 cm., and that a diameter of 5 cm. was reached in the tenth to eleventh month. The incidence of obvious secondary deposits was noted to rise sharply after this.

The length of history, however, and the size of a carcinoma, although reckoned as proportionate, are not always true measures of its permeation. Infiltrating carcinomata when, say, 10 mm. or less in diameter are probably localized, but of those of 20 mm.—as a recognizable clinical entity they can scarcely be less—a proportion will have disseminated. A carcinoma of even 4–5 cm. may yet have failed to do so. Some element of chance in the surrounding situation and method of growth seems to play a part in the timing of the primary dissemination, but, in the absence of signs of this, size is important when estimating the likelihood of spread.

Case.—A simple mastectomy was performed on a woman of 60. On examination afterwards a minute area of suspected malignant tissue in the lower lateral quadrant was estimated, on measurement, to be under $\frac{1}{2}$ cm. in diameter and about $1\frac{1}{2}$ cm. from the surface. Later, an intraduct carcinoma was reported.

Because of a strong family history of mammary carcinoma this patient made a careful examination of herself once a month and had done so for nearly three years. Consequently, in a large breast, this minute area of hardness was discovered, which—unless pointed out—might well have escaped detection.

The axillary lymph-nodes can be accepted as the initial site for secondary deposits in the majority of cases of mammary cancer. A malignant deposit, however small, in one axillary node indicates that growth has left the breast, with a corresponding depreciation in the outlook. Negative findings in the axilla, on the other hand, although promising, cannot be taken altogether to exclude dissemination elsewhere. Still, as a guide for the management of a case, the interval between Stages 1 and 2 may be regarded as the border between a localized and disseminated, or, in effect, between an established and advanced, state of the malignant process.

In order, then, to assess a case of carcinoma of the breast a knowledge of the state of the axilla is of primary importance. The presence of malignant lymph-nodes, unless grossly enlarged, can easily be missed when examining a thickly built or an obese woman, nor can the possibility of their existence be excluded. A number of cases, then, although reckoned by examination to be in Stage 1, may actually have reached Stage 2, or on occasion Stages 3 and 4.

Case.—Woman aged 53. One child. Found a small lump in the right breast and sought advice immediately. No previous history.

A thin woman with scanty breast tissue. Near the lateral margin of the right breast, a little above nipple level, was a thin plaque of hard tissue with defined edges and under half an inch (1 to $1\frac{1}{2}$ cm.) in diameter. When, however, the arm was raised above the head slight puckering of the skin over the site of the lump could be seen. No evidence of dissemination was found. Assessed as Stage 1*b*.

At the operation an immediate microscopical examination of the suspected tissue confirmed its malignancy and a radical mastectomy was performed. A further detailed microscopical examination of the mammary and axillary tissue failed to produce any evidence of dissemination. Because of this and the prevailing conditions (November, 1940) irradiation was omitted.

For over $5\frac{1}{2}$ years this woman continued apparently well, when, after some minor injury, pain was complained of in the lower back. This persisted and, later, radiographs showed evidence of malignant deposits in the lumbar spine.

This case is fairly typical of a number in whom a carcinoma is apparently localized when first seen. Presumably an embolus of cancer cells has left the breast area before treatment is undertaken which, whatever its situation, is in effect a concealed deposit.

A more accurate measure of the absence or extent of axillary deposits—also of the internal mammary nodes—can only be made by operative exposure with direct and finally histological, examination of both basal and apical lymph-nodes. For the grading, management, and eventual assessment of the results of treatment of the apparently Stage 1 cases this investigation seems to be an essential step. In Stage 2 cases the extent of the axillary invasion may be taken as a rough measure of the chances of dissemination outside the breast area.

In the exceptional case an enlarged axillary lymph-node may be discovered and later be proved malignant without an obvious primary source in the breast or elsewhere. The histology generally confirms a mammary origin.

Case.—Woman, aged 56. A large softish lymph-node was removed from the left axilla in October, 1945, and found on histological examination to contain a deposit of spheroidal-celled carcinoma. At no time before or for six months or more after removal of the gland, in spite of repeated and careful examination of a moderately large breast, could a primary lesion be detected.

The woman failed to report again until some eighteen months later when a mass in the upper and outer quadrant was obvious with further axillary deposits.

The finding of a malignant axillary lymph-node which is suggestive, histologically, of a primary source in the breast, though without signs, is an indication for radical treatment. (*See* case of Paget's disease on p. 166.)

In the various forms of chronic mastitis a few slightly enlarged soft pectoral nodes may be present, which, though perhaps associated with the condition, are of no clinical significance. Again, a tuberculous mastitis or residual mammary abscess, both very uncommon conditions, are manifested as a mass in the breast substance with enlarged axillary lymph-nodes.

PROGNOSIS

From the development of a mammary carcinoma to the fatal issue, the expectation of life in an untreated case has been reckoned to be approximately $3\frac{1}{2}$ to 4 years. As a result of treatment—grouping all cases together without grading—the expectation is raised some 10–15 per cent of this estimate. Broadly speaking, though influenced, of course, by existing circumstances, each month lost without treatment lessens the chance of relief by something like 10 per cent.

Prognosis depends directly on the extent of the disease at the time when treatment is undertaken. If still within the scope of treatment a carcinoma of the breast and its satellite growths can be eradicated. Against this are such formidable obstacles as its insidious onset and dissemination, the impossibility of recognition without gross manifestations, as well as the apathy of a number of women in seeking advice, and often enough inadequate treatment.

The term generally used to describe a failure of treatment is a recurrence. This implies eradication in the first instance and then fresh growth, rather than a sequel to a deposit of malignant cells undetected and undamaged during treatment. Such a deposit provides a basis for a continuation of a carcinoma and the formation of metastases in the skeleton, viscera, or elsewhere. The terms 'recurrence' and 'metastases', then, are interchangeable, and although they are not misleading descriptions, the term secondary deposit gives a rather more appropriate and accurate picture.

Secondary deposits make their appearance mainly in the first three years after treatment—only some 17 per cent afterwards—and prognosis accordingly becomes more clearly defined at this time. On this basis a five-year period is suitable for reckoning statistical relief-rates. At the same time deposits are reported ten and even up to twenty years after treatment of the primary growth, a tribute to the power of some tissues to hold malignant cells in check, perhaps even to destroy them. In this respect the resistance of the body, an immeasurable factor, appears to be influenced by the state of the general health. The following case illustrates some of the points mentioned :—

Case.—Woman aged 60. Stage 2*a* case. A radical mastectomy was performed in March, 1937, and post-operative irradiation given. Histological examination showed a spheroidal-celled carcinoma undergoing colloid degeneration and one basal lymph-node to contain a large deposit of growth.

In February, 1945, a severe attack of "influenza" left her weak and depressed for several weeks. In the June she noticed a small hard "spot" on her side which, as it persisted, she reported. The nodule, which was in the posterior axillary line about nipple level, was removed and found to contain malignant cells. Further clinical and radiographic examinations were negative. (Reported well, June, 1948.)

Some 40 per cent of secondary deposits are of the nodular type in the breast area, 30 per cent in the supraclavicular nodes, and in about the same proportion in viscera. (Lane-Claypon, 1926.) More recent figures (Freid and Goldberg, 1943) show 25 per cent of secondary skin deposits in 641 cases. The peripheral ramifications of the lactiferous ducts in the subcutaneous tissue (Hicken, 1940) probably account for the high incidence of surface deposits. With a wide removal of subcutaneous tissue at operation and irradiation these figures should not remain so high, and already there is evidence of improvement. (*See* APPENDIX, p. 303.)

Cessation of the 'follow-up' schemes during the war period has delayed publication of recent statistics, though such as are available tend to show an improvement in the five-year relief rate. For Stage 1 and 2 cases—not subdivided—this is accepted as about 70 per cent and 35 per cent respectively ; some figures are rather higher. With an allowance for deaths from other causes, these statistics may be taken as a measure of the adequacy or of the failure of treatment ; also in a number of cases, of wrong grading in the first instance.

With the exception of some of the skin cases placed in Stage 3 to indicate treatment rather than prognosis, the outlook for the case in this group is unfavourable. For Stage 4 cases the chance of permanent relief has passed, though help can be given to relieve symptoms and extend life. (*See also* Chapter XI, SECONDARY DEPOSITS, p. 266.)

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CHAPTER IX

CANCER: INVASION OF THE INTERNAL MAMMARY LYMPHATIC CHAIN

By R. S. Handley

Though anatomists have long taught that lymph from the medial side of the breast drains into the internal mammary lymphatic chain, surgeons have paid little attention to the implications of this knowledge. In 1938 an investigation by R. W. Scarff and R. S. Handley of a series of 172 cases of carcinoma of the breast with a ten-year follow-up showed a considerable and continuing mortality among patients with Stage 1 growths—those in whom one might theoretically expect 100 per cent cure after radical mastectomy: and attention was drawn to the fact that the state of the internal mammary lymph-nodes might be responsible, at least in part, for the continuing mortality though no quantitative microscopical evidence was available on the subject. To check this point and to investigate W. Sampson Handley's (1927) belief that the internal mammary chain was invaded at about the same time as the axillary nodes, the author started, in collaboration with A. C. Thackray of the Bland Sutton Institute of Pathology, to remove the second intercostal space node of the internal mammary chain in cases of carcinoma of the breast. The second intercostal space was chosen because it contains the largest and most constant node in the chain. This work is still in its early stages and has been a pathological investigation. Removal of the second space node has been practised not as a method of treatment but as a reconnaissance designed to yield information on which an intelligent plan of treatment can be based. On the basis of the 65 cases which comprise the material to date, it may legitimately be concluded that the internal mammary chain is often invaded at the same time as the axilla, and sometimes before it, especially if the growth is in the medial half of the breast.

RESULTS OF SECOND INTERCOSTAL SPACE BIOPSIES

The series of 65 cases subjected to intercostal biopsy is almost continuous. The patients were operated on between 1947 and 1949 without operative mortality and are consecutive except for patients whose growths were so advanced that any operative interference was thought unjustifiable.

Table I sets out the results. In 18 patients both the axillary and the internal mammary nodes had been invaded. In 5 the internal mammary nodes alone had been involved and the axilla was clear. In 22 the axillary nodes alone had been involved. Only in 20 patients was there no evidence of carcinoma cells outside the breast, and their progress will be watched with keen interest in the hope that cure has been achieved. *Table II* shows the cases divided into two groups, according as to whether the primary growth was in the inner or outer half of the breast. The figures are too small for final conclusions, but it is interesting that 14 of the 22 carcinomata occurring in the medial half of the breast had already metastasized to the internal mammary chain.

The effect of these findings on the staging of the growths is interesting. Of the 25 patients who without intercostal biopsy would have been placed in Stage 1, 5 were found to show invasion of the internal mammary chain and to be therefore in Stage 3. The intercostal biopsy has moreover moved no less than 15 of the 36 clinical Stage 2 growths into Stage 3. It seems that distinction between Stages 2 and 3 is of no great value, a point which is borne out by the small difference in mortality between Stage 2 and 3 growths in the large reported series (e.g., Truscott, 1947).

Table I.—All Cases

Axillary and intercostal nodes both invaded	18
Intercostal nodes only invaded	5
Axillary nodes only invaded	22
No lymph-node invasion	20
Total	65

Table II.—Cases Divided According to Position of Primary Growth

	Primary growth in: Inner half of breast	Outer half of breast	
Axillary and intercostal nodes both invaded	11	7	
Intercostal nodes only invaded	3	2	
Axillary nodes only invaded	3	19	
No lymph-node invasion	5	15	
Total	22 +	43 =	65

ANATOMY OF THE INTERNAL MAMMARY LYMPHATIC CHAIN

Fig. 124, redrawn from Stibbe's (1918) paper, shows the salient anatomical points. The internal mammary lymphatic chain lies both medial and lateral to the internal mammary artery, and in a plane immediately anterior to it. The position of the nodes in the intercostal space is variable, as is the number of nodes. Stibbe found the second intercostal space to contain one or more nodes in 96 per cent of the 60 subjects he examined, but the other intercostal spaces contained nodes much less often. The chain empties itself above either into the great veins at the root of the neck or into a node behind the medial end of the clavicle. It collects lymph from the chest

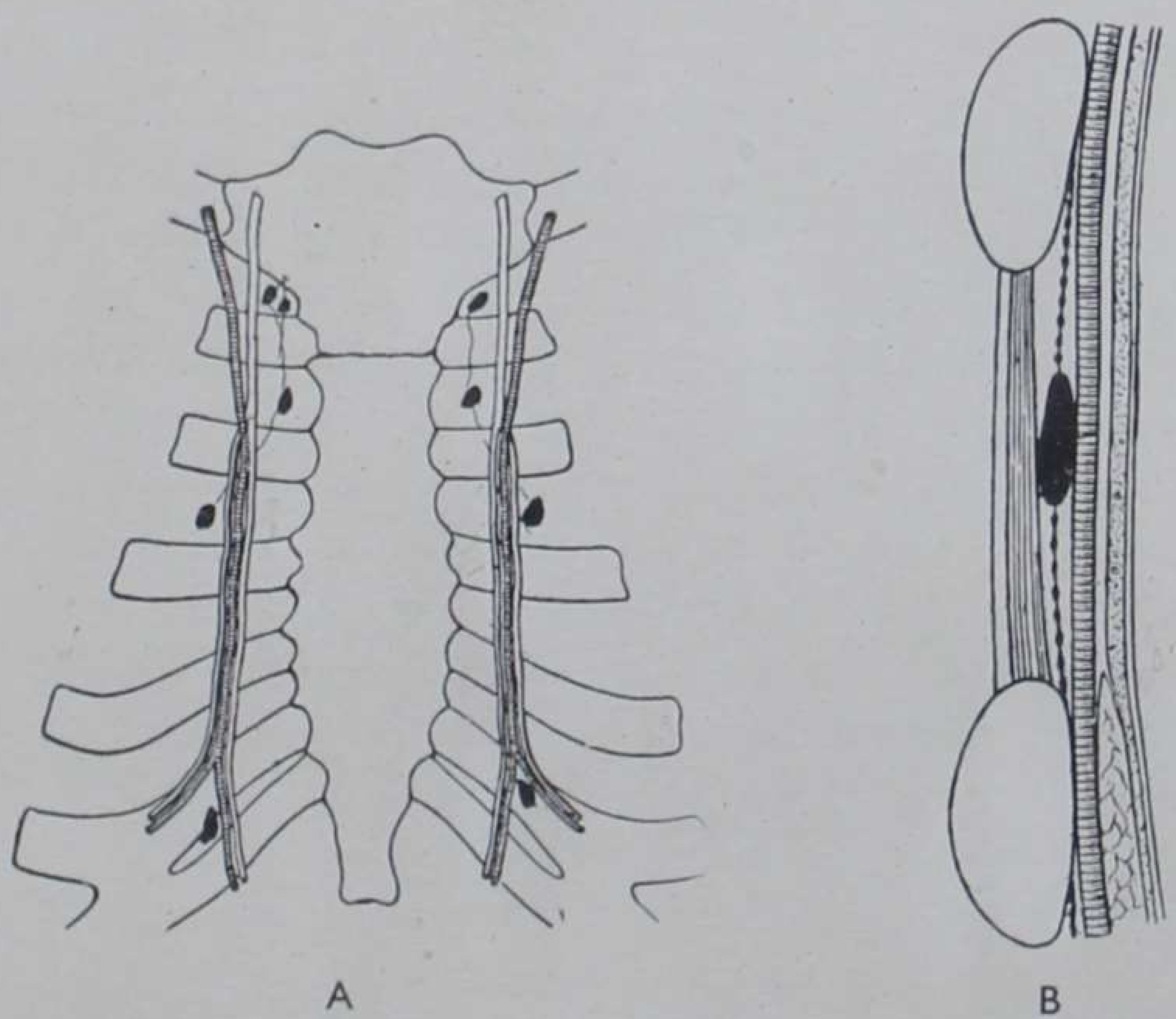

Fig. 124.—Diagrams to illustrate the anatomy of the internal mammary glands. A, Seen from behind; B, Sagittal section through the anteromedial end of the second intercostal space. (*After E. P. Stibbe.*) (*Figs.* 124, 125 *by kind permission of the 'Journal of Cancer.'*)

wall via intercostal lymphatics, from that part of the great subfascial plexus draining the skin on the anteromedial aspect of the thorax, and from the periphery of the diaphragm. (*See also* Chapter I, p. 12.) The surgical importance of these arrangements needs no emphasis.

SURGICAL REMOVAL OF THE SECOND INTERCOSTAL SPACE GLAND

If the intercostal musculature has not already been exposed in the course of a radical mastectomy, a skin incision from two to three inches long, depending on the obesity of the patient, is made over the anterior end of the second intercostal space midway between the second and third costal cartilages and parallel with the long axis of the cartilages. The medial end of this incision should lie over the sternum, about half an inch from its edge. The incision is deepened to the surface of the external intercostal membrane by splitting the fibres of the pectoralis major, and, if necessary, detaching some of its fibres at their origin from the sternum. The intercostal musculature is then incised with a knife, again midway between the costal cartilages and parallel with them. This incision should be about one and a half inches long, and extend to the lateral border of the sternum. A large perforating branch of the internal mammary artery emerges in close contact with the lower border of the second rib, and a smaller branch may emerge in contact with the upper border of the third rib; the incision described avoids injuring both. The somewhat ragged edges of the intercostal musculature are retracted, as soon as all its fibres have been divided, with two small retractors and dissection proceeds with two fine non-toothed dissecting forceps and gauze. The internal mammary artery is readily identified, usually about half an inch lateral to the sternal edge, and the lung surface can be seen moving beneath the pleura in spare subjects. If the intercostal space has not been invaded by carcinoma, it may be very difficult to identify lymphatic glandular tissue, but all the fat removed from around the internal mammary artery should be sectioned. It is often possible to tell when invasion of the space has taken place by the matting of the tissues in it, but it is still frequently difficult to find a node. The largest encountered has been the size of an orange pip; the smallest (*Fig.* 125), the size of an ordinary pin-head, was not recognized as a gland at all until it had been histologically examined. In one case it was difficult to find a node even though the intercostal muscles themselves were obviously full of carcinoma, a fact later substantiated by the microscope. For any surgeon proposing for the first time to enter an intercostal space in the living, a preliminary dissection on the sternum as removed at a routine post-mortem examination is very helpful, since both the internal and external aspects of the medial end of the intercostal space can be inspected.

Closure of the intercostal space is not possible. The cut edges of its muscles will not hold sutures. It is usually possible to leave a tag of pectoralis major, even in a radical mastectomy, to close the space but this does not seem to be essential unless the line of the skin incision crosses the open space.

Serious trouble in intercostal space biopsy has been met once. The pleura was injured without the accident being recognized, and it was not until the patient's colour had greatly deteriorated that a needle was introduced into the pleura and much air aspirated. A subsequent X-ray showed the pneumothorax to be inexplicably bilateral, and, after aspiration of the contralateral side, the patient made an uninterrupted recovery. An obvious tear in the pleura has occurred once and is easier to cope with, for, once recognized, it can be met without difficulty by modern anæsthetic apparatus. Bleeding from the perforating arteries and veins, especially the veins, is sometimes a nuisance, but has readily yielded to a fine curved

Fig. 125.—Section of internal mammary lymph-node, showing invasion by carcinoma. This was the smallest invaded node recovered in the series described. (× 40.)

hæmostat or pressure. With ordinary care the main internal mammary trunks should not be in jeopardy. If they were wounded and were difficult to secure, packing of the second space would probably control the bleeding while they were being tied in the first and third spaces.

APPLICATIONS OF AND INDICATIONS FOR SECOND INTERCOSTAL SPACE BIOPSY

The applications of and indications for exploration of the intercostal spaces in cases of carcinoma of the breast are still tentative. It may be necessary to change any of the opinions which follow in the light of subsequent experience.

If the internal mammary chain has been invaded by carcinoma, the patient cannot be cured by surgery alone. An invaded lymphatic node is the red signal which shows the surgeon that the train has already passed through the station, and removal of one or two nodes through an intercostal space is not a radical measure. An excision of the chain *in toto* after removal of all the costal cartilages is surgically feasible, but would undoubtedly add very greatly to the operative mortality without a guarantee of compensating benefits. A positive

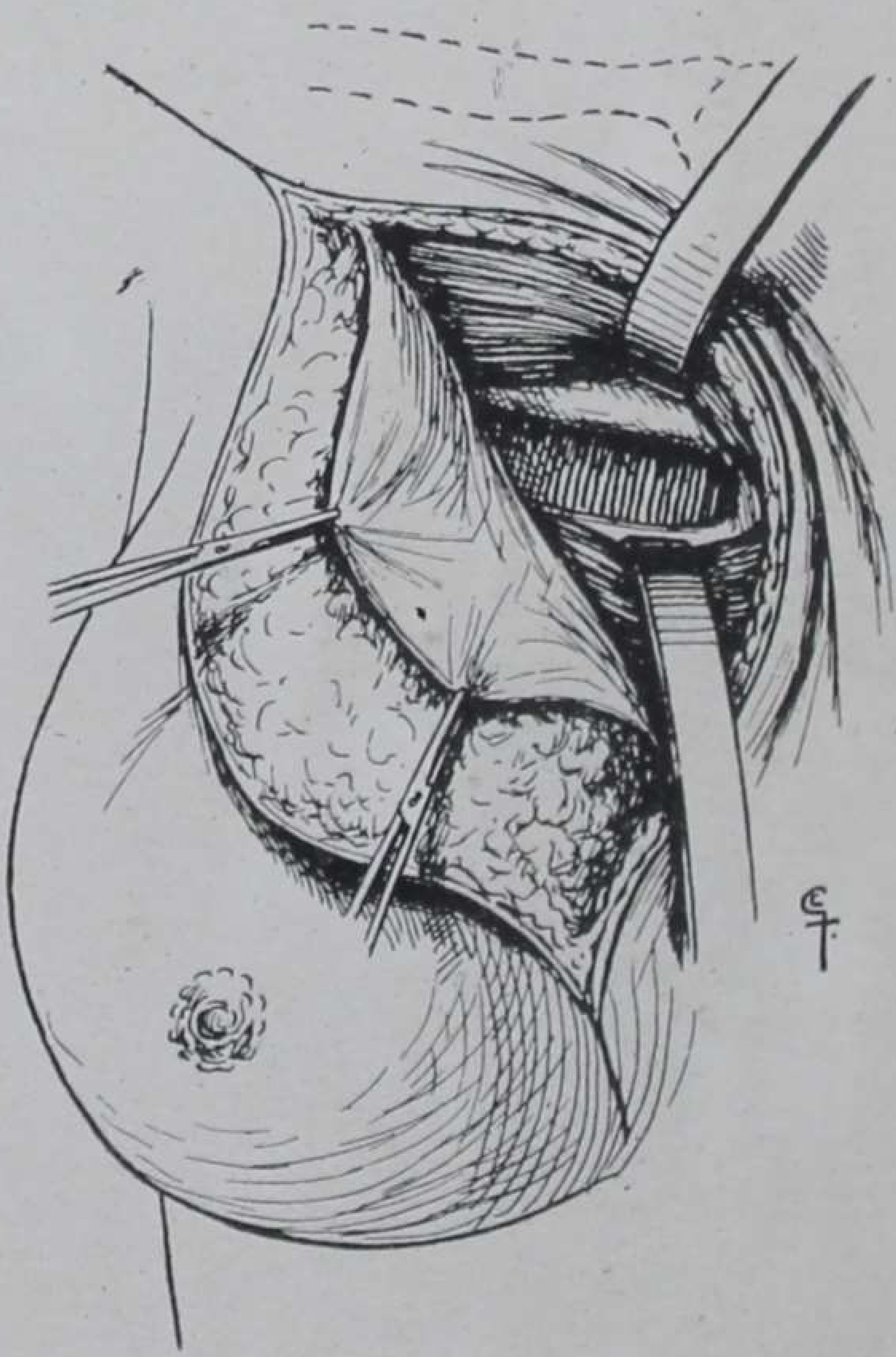

Fig. 126.—Second intercostal space biopsy as a preliminary to mastectomy. The medial skin-flap has been partly raised, the fascia dissected from the surface of the pectoralis major, and the latter split to expose the 2nd and 3rd ribs and the intervening external intercostal membrane.

intercostal biopsy is, therefore, not an end in itself but a measure of spread and an indication for the radiotherapist.

If the above opinions are accepted, it follows that early cases of carcinoma of the breast, where the axilla is clinically free or contains only one or two small hard mobile glands, should be subjected to an intercostal biopsy early in the operation. In such cases it will already have been decided that the breast and its primary growth is to be removed and the medial skin-flap can therefore be raised as the first step in the operation (*Fig.* 126). In the region of the second intercostal space, the breast and fascia can then be dissected off the pectoralis major, the latter muscle split, and the internal mammary chain reached as already described (*Fig.* 127). Tissue removed is then examined by frozen section to yield a pathological report in five to eight minutes. Barker and Clayden (1934) have published a technique which yields sections almost the equal of good paraffin sections in a few minutes, and their interpretation (after a little practice) is no more difficult than with paraffin sections. If this examination proves negative a radical mastectomy is performed. If positive, an extended simple mastectomy, leaving the treatment of all secondary deposits to radiotherapy, offers an alternative procedure.

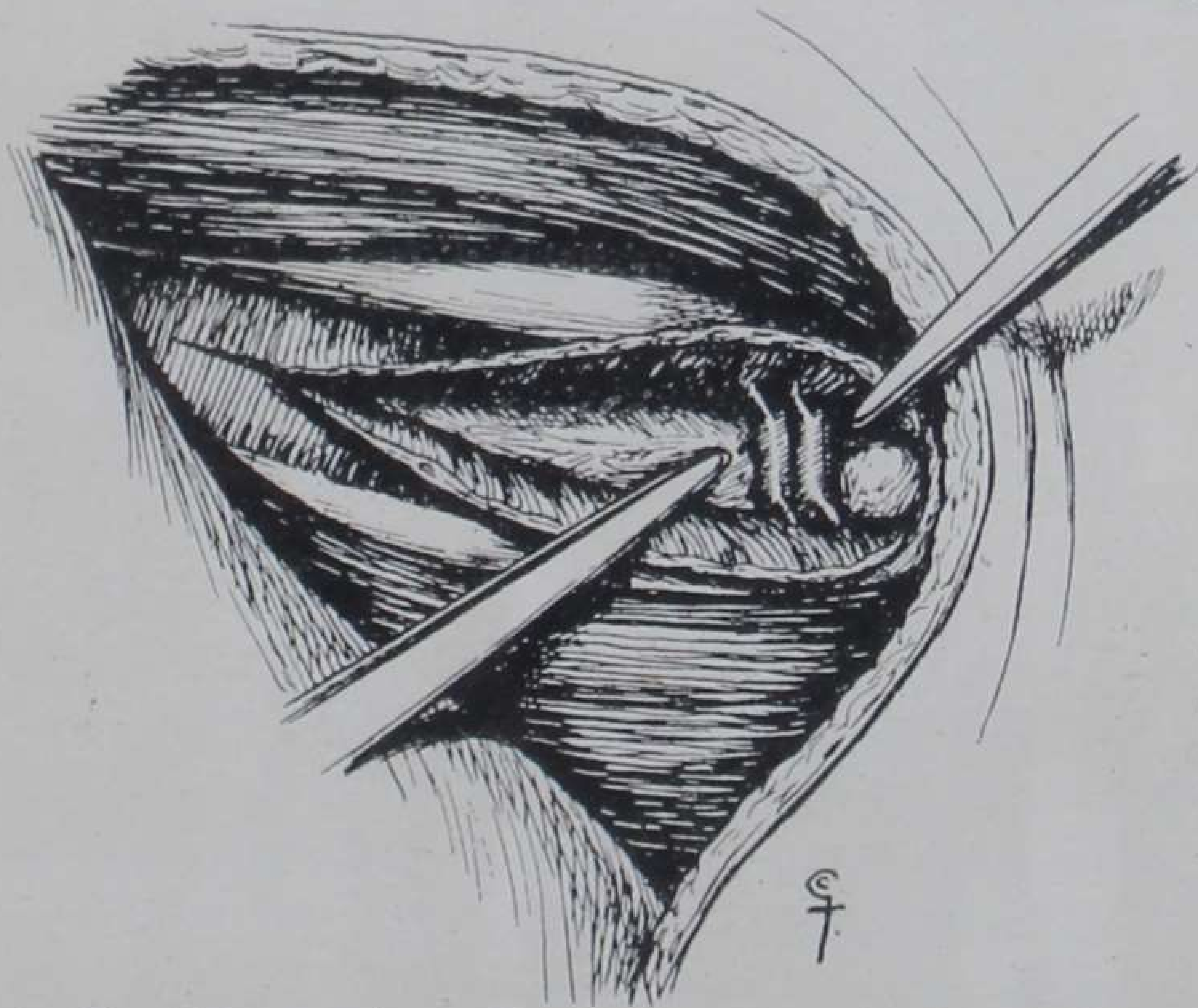

Fig. 127.—Second intercostal space biopsy as a preliminary to mastectomy. The intercostal musculature has been incised to expose the internal mammary vessels. The lymph-node (shown in the drawing at least twice as large as it is commonly seen), lies medial to the vessels, just clear of the edge of the sternum.

When internal mammary deposits are present, there would appear to be at least a case for the trial of a less mutilating operation than radical mastectomy.

Cases with extensive axillary invasion (Stage 2*b*) and those frankly in Stage 3 will not derive any practical benefit from intercostal biopsy. It can be presumed with considerable confidence that the internal mammary nodes are already invaded, and treatment is based on this presumption.

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CHAPTER X

CANCER: TREATMENT

By Agnes Kennedy, Raymond Greene, and F. D. Saner

GENERAL CONSIDERATIONS

Radical therapy implies a complete removal or destruction of the primary focus of malignant disease, together with any tissue in which dissemination is obvious or there is a significant possibility of its existence. Consequently when assessing the value of a therapeutic procedure a comparison has to be made between the extent of the pathological process so far as it can be judged, but which of course is uncertain, and the volume of tissue capable of being excised or irradiated. So far, surgery, by the actual removal of malignant tissue, and radiotherapy, by causing disintegration, provide the only reliable means of eradicating a cancer and are effective provided the malignant state is within the area of treatment. A slowing of its progress or even temporary arrest would appear, in some instances, to be achieved by certain forms of chemotherapy.

Surgery aims at the excision *en bloc* of the primary growth together with adjacent extensions to lymph-nodes and a margin of uninvaded tissues, and is still the most effective form of treatment. But it is hampered by a lack of definition of the extent of the disease and by the actual limitations to an operative procedure. The performance of a radical mastectomy, in spite of its name, does not materially alter in efficiency, nor is it easy to conceive of a technique by which its limits could be usefully extended. In primary breast cancer with a small growth and lymph-nodes uninvaded surgery alone gives a 70–75 per cent relief rate. If the axillary lymph-nodes are invaded the failures following surgery alone approach the same figures.

Radiotherapy has its limitations in the varying resistance of malignant tissue and in the matter of its application in sufficient dosage to destroy a carcinoma within the tolerance of normal tissue. Irradiation, however, is unlimited in its range and a maximum effect is exerted in highly malignant tumours and secondary deposits. If then the main cause of the failures of surgery is extension of the disease beyond the field of operation, in order to improve results the aim should be to irradiate all areas likely to be the site of secondary deposits.

The employment, therefore, of radiotherapy is of prime importance in any case in which malignant tissue is near the boundary of a radical mastectomy. The extent and timing of the respective use of surgery and radiotherapy is dependent on the state of the disease and will be subject to adjustment as experience increases, but the merit of a combination of the two methods is undoubted. The management of many cases of mammary carcinoma should be planned on a long-term basis.

Irradiation can transform a tumour full of active mitotic figures, indicating a high degree of malignancy, into a relatively inert tumour. Broders proved that the surgical results in the lip were poor with a high degree of malignancy and good with a low degree of malignancy. In the breast, where the majority of neoplasms are on the more highly malignant side of Broders' divisions, the importance of such a transformation to a quiescent tumour state is clearly of considerable importance.

The development of X-ray therapy within the last decade has enabled many primary growths, of borderline operability because of their extent, ulceration, or fixation, to be rendered suitable for a radical mastectomy. It is a mistake, however, to attempt operative measures unless there is reasonable prospect of removal of all evident tumour tissue. Useful fibrotic barriers may be interfered with and malignant tissue, which has been controlled, disturbed.

Stockholm statistics show that if a radical mastectomy is done as a primary measure when the axillary nodes have invaded their capsules, the survival rate is only 6 per cent. This applies to nearly all large axillary-node masses. With pre-operative irradiation the survival rate is 20 per cent—a striking, but not unexpected, difference.

Forsell showed how the routine administration of pre- and post-operative irradiation substantially increased the survival rate as compared with post-operative irradiation alone.

Irradiation should be the primary treatment in all cases when a carcinoma is not limited in size and clear of the edge of the breast, or if axillary invasion is suspected to have extended beyond the basal group. In many cases the initial dosage may be limited and followed almost immediately by a radical mastectomy. When, however, the skin is infiltrated and the margin consequently doubtful, or the axillary mass is substantial or fixed, a full course of radiotherapy is indicated before any operation is undertaken.

Treatment of a carcinoma of the breast by radium alone has provided results comparable with surgery, as has been shown by Keynes, Cade, and others. A decision to employ this method of treatment may depend on :—

1. *The age and general health of the patient.* A limited radium implantation of the breast area and lower axilla can be performed under local anæsthesia.

2. *The size of the breast.* Implantation of radium is simple and effective for a small tumour, especially in a thin breast. A massive tumour should be treated primarily by X rays, but a residual mass may be suitable for radium implantation.

3. *Æsthetic considerations.* This is placed last on the list, but a few women, though otherwise fit, refuse to have a radical amputation if any alternative treatment is possible.

(For a full account of Radiotherapy, *see* Chapter XI.)

GENERAL SUGGESTIONS FOR TREATMENT

The following suggestions for treatment, which are applicable with modifications to the majority of cases, are submitted. The necessity for pre-operative irradiation should be judged for each case individually.

Stage 1*a*.—Radical mastectomy.

Stage 1*b*.—Radical mastectomy followed by post-operative irradiation ; pre-operative irradiation should be given when any marginal skin is involved.

Stage 2*a*.—The same as for 1*b*.

Omitting patients with unrecognized dissemination, the prospect of permanent relief after treatment is mainly favourable at all these stages. If Stage 3 has been reached, whatever the treatment the final outlook is unfavourable. At the intermediate stage—2*b*—the door to permanent relief is not entirely closed, but opinions differ considerably on how to take the best advantage of this.

A prima facie case certainly exists in favour of employing surgery and radiotherapy in fullest measure. If the disease is still confined to the breast and axilla, albeit the apex, the chance of a complete clearance is offered by a meticulous radical mastectomy with radiotherapy to precede and follow the operation as an additional powerful attack.

To the contrary it is urged that secondary deposits are probably beyond the reach of any effective operative procedure, which must tend therefore to aggravate dissemination, and that an ineffective radical mastectomy is a useless mutilation. For these reasons it is advocated, especially by the Edinburgh school, that surgery should be limited to removal of the primary growth by a simple mastectomy with radiotherapy as the main treatment.

In actual practice, in many cases—more especially in the thickly built or obese woman—an accurate assessment of the extent of axillary invasion is only made at operation, when, with the axilla fully exposed, a direct examination can be made of the whole area. An obvious or suspected involvement of the group of nodes on the first rib interspace, deep to the pectoralis minor muscle, is not, in itself, a contra-indication to a radical mastectomy. Also a routine microscopical examination of basal and apical axillary lymph-nodes separately proves not only the clinical but also the operative assessment to be faulty in a number of instances. The finding of a positive sternal node as described in Chapter IX may be taken as an indication to curtail further operative procedure. Yet, since the element of chance is present in the treatment of all these cases, it seems justifiable to remove all the malignant tissue possible—provided it is not obviously cut across—and to rely on the radiotherapist to deal, so far as he can, with the periphery.

A suggested procedure for the doubtful 2*a* case on clinical examination is as follows :—

1. Pre-operative irradiation of single dose, giving approximately 1000 r (D.X.R.) to the primary growth and all regional nodes.

2. Radical mastectomy. This is performed between the 3rd and 7th day after irradiation, which allows the general effects of the exposure to pass but precedes the skin reaction.

3. Post-operative irradiation.

The treatment of Stage 3 and 4 cases is discussed in the chapter on RADIOTHERAPY. For the majority, radiotherapy is the primary and, in many, the only helpful treatment ; surgery is limited to the removal of residual masses in selected cases.

CONTRA-INDICATIONS TO OPERATIVE TREATMENT

The main contra-indications to operative treatment as a primary measure may be summarized as follows :—

1. **General.**—Advanced pulmonary, cardiovascular, or renal failure.

2. **Age.**—Age, *per se*, is not a contra-indication to an operation. The object, though, may be to relieve symptoms rather than to extend life, and in the absence of pain, ulceration, or abnormal size, radical

treatment need not be urged. A woman of 80 or more with a scirrhous carcinoma beginning to ulcerate through the skin may, if the general condition permits, be submitted to a modified radical mastectomy, and usually the operation is well tolerated.

3. Secondary Deposits (*see also* Chapter XI).—Radiographic or other evidence of visceral or skeletal deposits is a contra-indication to surgery. Skeletal deposits of carcinoma are well advanced before giving radiographic evidence, but where there is complaint of suggestive symptoms, e.g., backache, sacro-iliac or sciatic pain, an operation should be postponed and investigation repeated.

4. Skin.—Ulceration of the skin does not necessarily imply a carcinoma of long standing or high degree of malignancy. In an early stage ulceration is not itself a contra-indication to a radical mastectomy, especially in the large fat breast which permits a wide margin of normal tissue to be removed round the growth. (Penicillin is used to deal with the infective element.) If, however, this is not practicable, pre-operative radiotherapy should be given. Radiotherapy includes some of its most dramatic benefits in this type of case and should be the primary treatment for the majority.

Cases of skin infiltration of the *peau d'orange* and *en cuirasse* types, as regards treatment, should be classed as Stage 3. Such cases are indicative of inestimable lymphatic spread.

5. Pregnancy and Lactation.—A number of cases, probably the majority, of carcinomata occurring in the pregnancy-lactation period are inoperable when first seen because of the extent of the skin invasion or widespread dissemination. This does not exclude all from operative treatment if seen in the Stage 1 or 2 categories or after confinement (*see* p. 224).

6. Massive Invasion of the Axilla, with fixation of the mass to the skin. Also invasion of the supraclavicular lymph-nodes, or contralateral nodes in any position.

7. Invasion of the Chest Wall by Growth.

OPERATIVE TREATMENT

Every case of malignant or suspected malignant disease of the breast should be regarded as urgent.

PRE-OPERATIVE CONSIDERATIONS AND PREPARATION

Apart from the dread of malignant disease itself, the trials of treatment are formidable, and encouragement as to the issue, with an avoidance of the words " cancer " and " malignant ", may help in some measure to relieve anxiety of mind and to restore a confidence that has been badly shaken. An estimate of the position should be given to a responsible relative rather than to the patient herself.

Preparation

a. **Breathing Exercises.**—Instruction in a few suitable exercises before the operation, preferably by a physiotherapist, is of use afterwards, when the large area of the operation field and the tightness of the wound and bandage tend to limit respiratory exercises.

b. **Blood-count. Clotting Time. Grouping.**—These should be routine examinations, and any undue depreciation of the first two dealt with by appropriate measures. Very occasionally a pre-operative blood transfusion—or vitamin K—is required.

c. **Sedation.**—This should be assured on the night before the operation, for which one of the long-acting barbiturates, e.g., sodium soneryl gr. 3, is usually sufficient. A full hour or more before the operation, a hypodermic injection of omnopon gr. $\frac{1}{3}$ and scopolamine gr. $\frac{1}{150}$ is given, which in most cases assures a pleasant state of drowsiness and forgetfulness.

d. **General and Local Preparation.**—The general and skin preparation does not differ from that of other operations and, for the most part, is a matter of personal choice or hospital routine. A spirit or ether preparation is mostly used, followed by iodine, cetavlon (I.C.I.), or other non-irritating antiseptic on the operating table.

e. **Anæsthesia.**—General anæsthesia by any of the usual agents which gives a satisfactory light anæsthesia is the method of choice. Ether and cyclopropane are avoided if the diathermy current is likely to be used, though the latter may be regarded as generally unsuitable because of its tendency to cause capillary oozing.

A useful routine is to induce anæsthesia with thiopentone 0·3 g., administered intravenously, followed by nitrous oxide–oxygen and trilene to maintain an early third-stage level throughout the operation. Tachypnœa can usually be controlled by the addition of a small amount of ether.

f. **Position of the Patient.**—On the operating table the patient is placed on her back with the arm of the affected side abducted to about a right angle with the elbow flexed to the same degree ; a nurse, sitting next to the anæsthetist, holds the arm in this position throughout the operation. Undue stretching of the neck by separation of the head and shoulder, and over-abduction of the arm, must be guarded against, especially in the thin and older woman, as a brachial palsy can result from this which, though transient, adds considerably to the already existing trials.

RADICAL MASTECTOMY*

Surgeons, accepting for the most part the principle that the removal of tissue must be extensive, tend to evolve their own method of performing a radical mastectomy, based on Halsted's conception and Handley's modifications, with probably only minor differences in details of technique. The extent, though, to which skin should be removed is still a contested point, but however wide this may be, no guarantee can be given that it will be sufficient if the skin is infiltrated with growth. In most cases the skin covering the whole breast is removed, with wide undermining of the skin-flaps each way and excision of subcutaneous tissue to this extent. The wound can then usually be closed with reasonable ease to the general benefit of the patient, and access to post-operative irradiation is permitted at an early stage.

Incision and Closure (*see also* PLASTIC SURGERY, Chapter XII). —The incision (*Fig.* 128) is started at a point just above the insertion of the pectoralis major, curving upwards over the axilla at the level of the upper margin of the muscle and then downwards over the coracoid process. This part of the incision should be kept high to avoid an axillary scar.

The incision is continued downwards with a slight curve medially along the inner margin of the breast, then laterally towards the point of the lower ribs. An incision extended on to the abdominal wall contributes nothing to the eradication of growth and renders post-operative irradiation more difficult. This medial flap is undermined, leaving a margin of subcutaneous tissue, say $\frac{1}{8}$ to $\frac{1}{4}$ in., upwards to the clavicle, medially to nearly the midline of the sternum, and downwards exposing the upper part of the fascia covering the rectus abdominis muscle. Scrupulous attention should be paid throughout the operation to arresting bleeding, which varies much in amount in different patients but can be sufficient to demand an immediate plasma or blood transfusion. The whole operation area not being immediately worked on must be kept covered with warm packs.

The lateral incision starts from the first at a point below the coracoid process, varying quite considerably with the size of the breast,

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* For the different methods and more detailed description of performing this operation, and its complications, the reader is referred to books on operative surgery. The object here is to give a broad description only of the requirements of the operation.

and is continued downwards following the outer margin of the breast until it is curved medially to join the original incision some two to

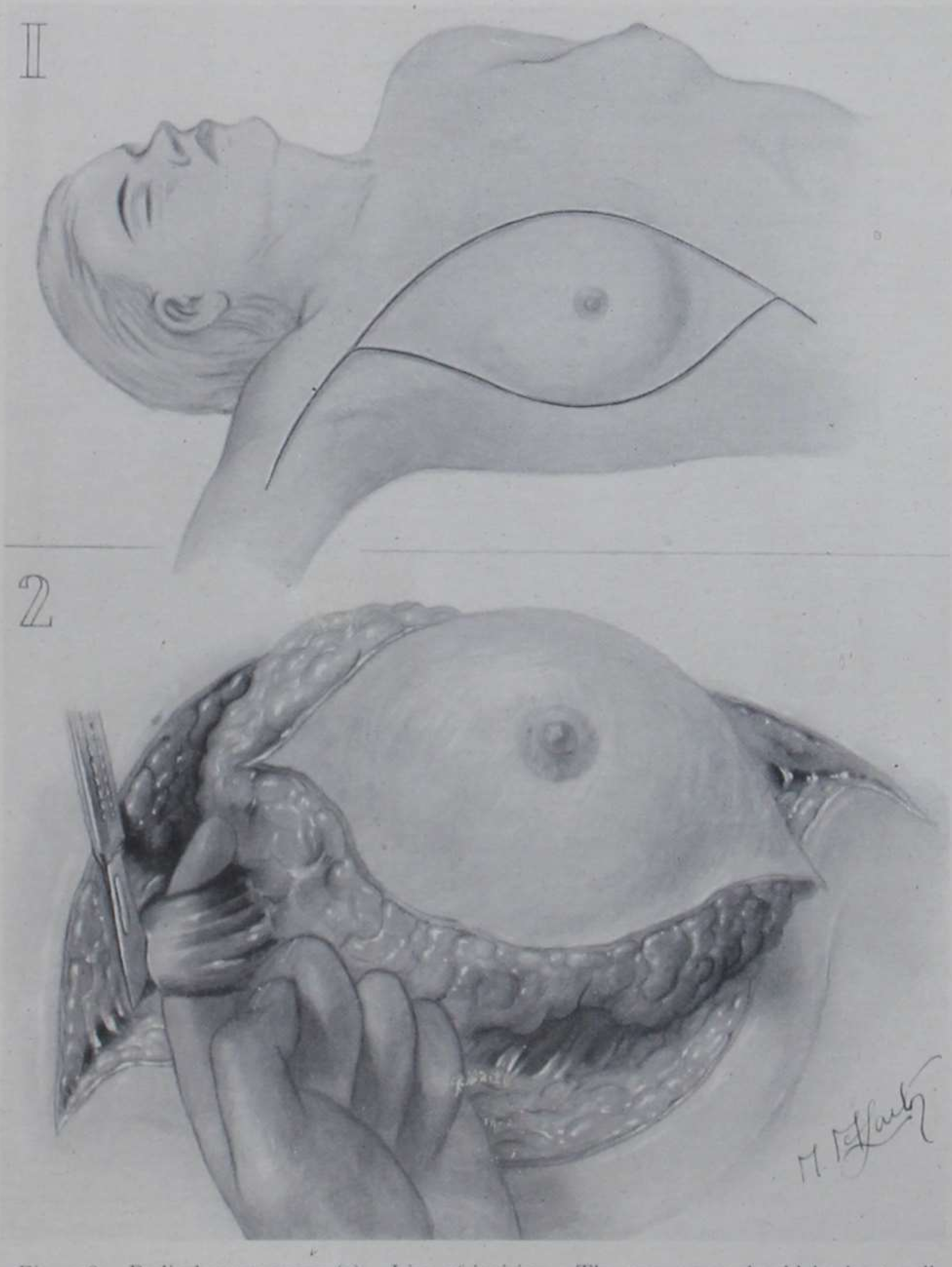

Fig. 128.—Radical mastectomy (1). Line of incision. The upper part should be kept well above the axilla.

Fig. 129.—Radical mastectomy (2). After undermining the medial flap to nearly the midline and the lateral flap to the lateral margin of the latissimus dorsi muscle, the insertion of the pectoralis major muscle is exposed and divided.

three inches below the lower margin. This flap is then reflected and undermined to expose the lateral chest wall and the axilla to the lateral border of the latissimus dorsi and above to the line of the insertion of the pectoralis major muscle.

The pectoralis major muscle is divided near its insertion into the humerus (*Fig.* 129), separated from the deltoid and, together with the sub-pectoral fascia and fat, reflected medially until the pectoralis minor muscle is exposed. Dissection is now begun along

Fig. 130.—Radical mastectomy (3). The pectoralis major muscle, clavipectoral fascia, and axillary contents are cleared towards the midline until the lateral border of the pectoralis minor muscle is exposed. This muscle is then divided and the apex of the axilla cleared.

the lateral border of the axilla from the level of the brachial vessels above down to the lower point of the axilla. The fat, cellular tissue, and lymph-nodes, the fascia covering the subscapularis muscle together with the small vessels leaving or returning to the main ones—the subscapular vessels can usually be preserved—and the fascia covering the lateral chest wall, are all reflected up to the main mass of the breast and pectorals. The nerves of the axilla are left unless the clearance of malignant tissue is thereby hampered, nor is it necessary to strip the sheath of the main vessels if growth is not actually adherent. If the wall of the vein has been invaded a section of vein can be excised, but this procedure is of doubtful value as, at this stage, the chances of operative clearance are remote.

When the penetrating thoracic vessels have been isolated and ligated, the pectoralis minor muscle is divided near its origin and reflected downwards and the lymph-nodes and tissue cleared from the first rib interspace. The axillary contents, the pectoralis minor

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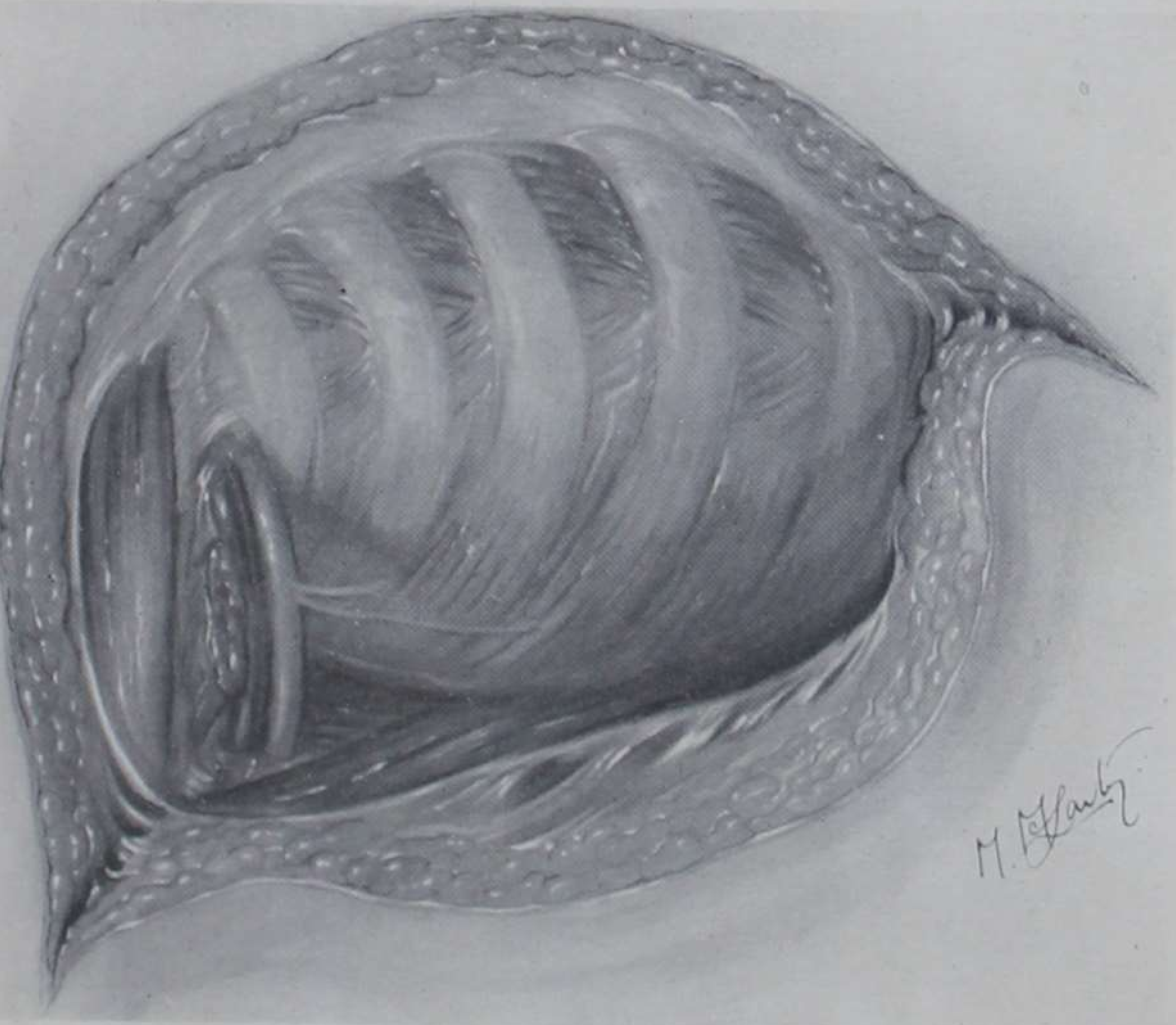

Fig. 131.—Radical mastectomy (4). Appearance of wound after removal of the breast, muscles, and axillary contents.

muscle, the pectoralis major so far as it is divided, together with the breast, are held retracted medially by the two hands of the assistant (*Fig.* 130), while the whole mass is gradually removed by separation of the muscles from the ribs together with the subcutaneous fat and tissue of the remainder of the area (*Fig.* 131). The clavicular portion of the pectoralis major muscle can be separated near the clavicle, or, preferably, a breadth of an inch or more of the muscle is left in situ to afford a protective cover to the main vessels and finally removed by division near its origin from the sternum. Previous to this the perforating branches of the internal mammary artery are picked up as far as possible before being divided.

Hæmostasis must be complete before the skin wound is closed by nylon or silkworm sutures. A narrow tube (3–4 in.) is inserted

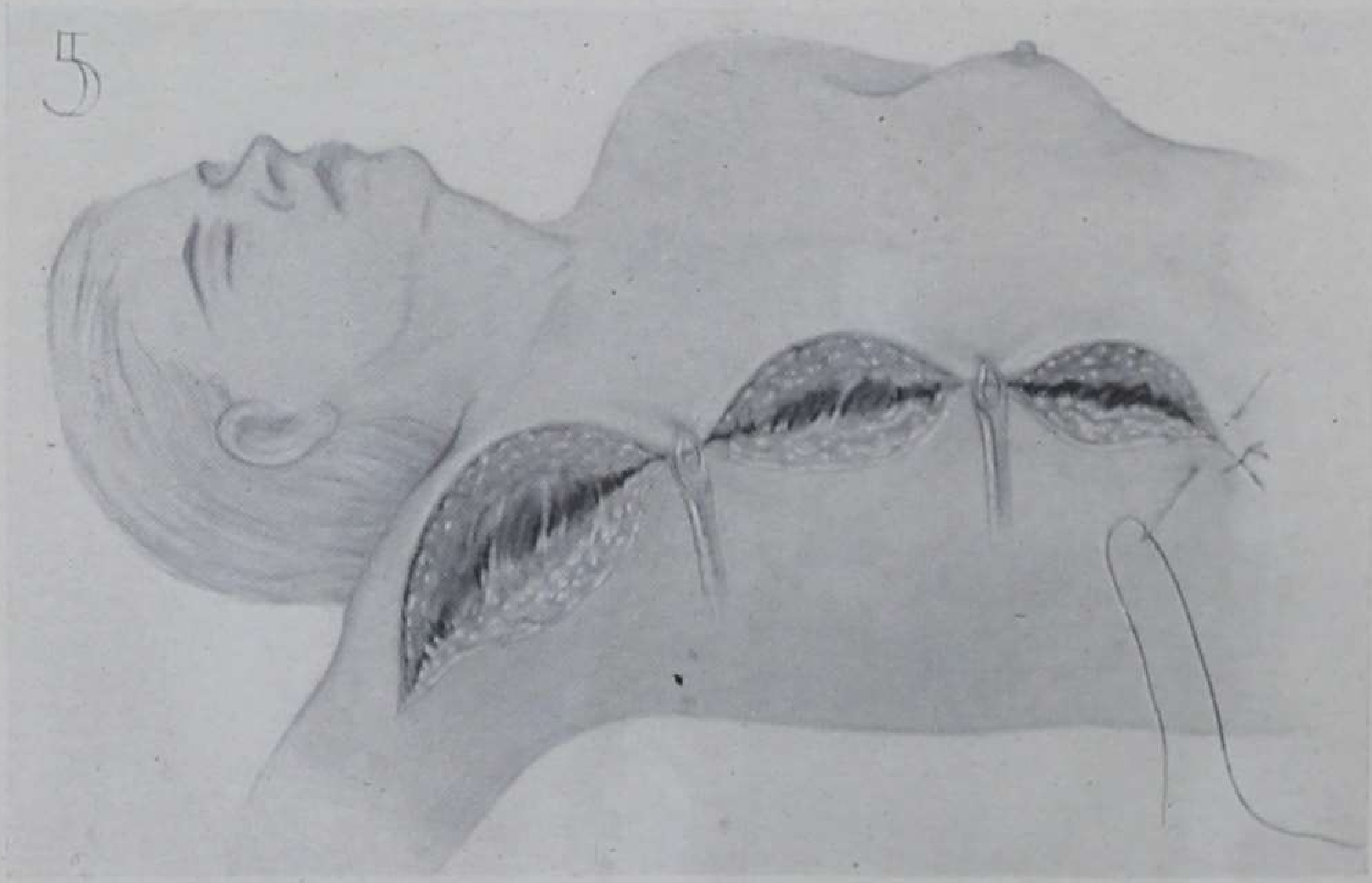

Fig. 132.—Radical mastectomy (5). Preparation for closure.

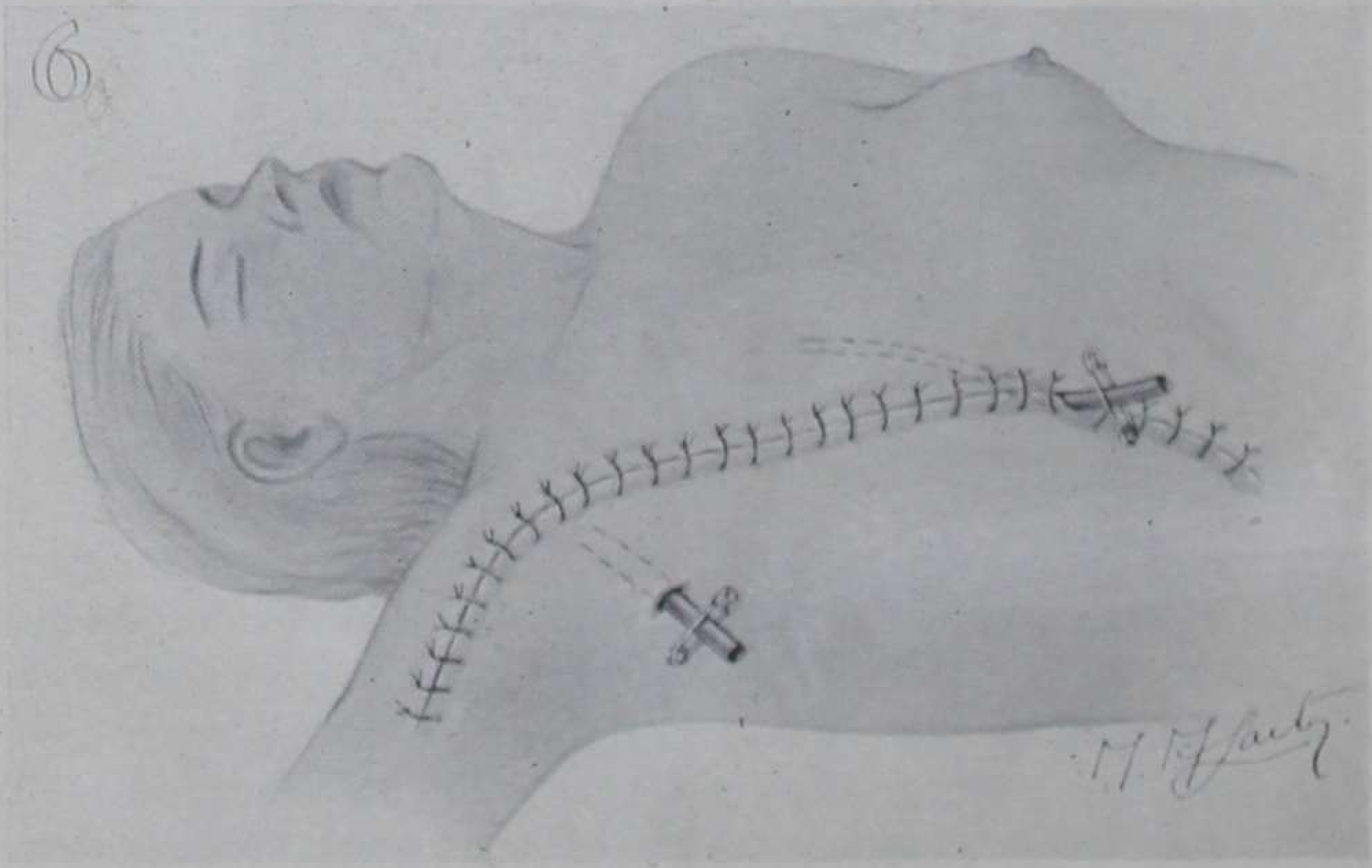

Fig. 133.—Radical mastectomy (6). Closure of wound.

at the lower end of the wound and directed upwards, while a short second tube is inserted through a stab wound in the lower axillary skin and directed towards the apex of the axilla. (*Figs.* 132, 133.)

Vaseline petroleum jelly is applied to the skin surrounding the wound in its whole length; sterile gauze dressings are applied first to each side of the wound and then to cover it. With some such arrangement the skin is kept soft and the dressings do not stick to the wound. After a generous allowance of gauze dressings, wool is applied to cover the whole of the affected side, half the back, the upper arm, the shoulder, the lower neck, and the opposite axilla. A shoulder spica bandage is applied with sufficient firmness to maintain the dressings in position but with enough play to permit of limited movements at the shoulder-joint. After this the dressing is completed by a many-tailed bandage with shoulder-straps, avoiding tightness over the lower thorax. On return to bed the arm is abducted to about 45° from the side and rested on a pillow.

Rectal salines—or other treatment suitable to the degree of dehydration—can be usefully given in most cases.

Post-operative Treatment.—The immediate post-operative routine includes the removal of the drainage tubes and care of the wound, the details varying with individual choice. The principle of non-interference with a wound after an operation is especially important after a radical mastectomy with its length of incision and dead space. A general routine of leaving the dressing untouched for 5 or 6 days, provided the patient is comfortable, then removing the tubes, and a second dressing on the 11th or 12th day for removal of the stitches, is usually all that is required. When pre-operative irradiation has been employed sutures should be left, if possible, for 2–3 weeks. A penicillin-cream dressing is helpful in preventing the sepsis to which irradiated tissue is prone.

Attention to the use of the arm should be given on the day after the operation when the use of the fingers and hand, wrist, and elbow is encouraged by sewing, knitting, etc. Shoulder movements, limited to start with, are begun on the third day, and, provided the wound is placed well above the axilla no difficulties should be encountered in restoring movements of the arm to their full range within 3 to 4 weeks after the operation.

One of the many advantages of a post-operative follow-up system—apart from the observation of these patients for record purposes—is a supervision of the general health. An attendance of every three months should be encouraged for the first year, every six months during the second and third years, and once a year after this.

Œdema of the Arm.—A varying degree of œdema of the arm and hand may follow a radical mastectomy, from the pressure of a too tight axillary scar, while it is an occasional sequel to post-operative irradiation.

In many cases the œdema is not incapacitating nor painful nor sufficient to prove more than a nuisance, but should it be so, light massage and periodic support of the arm in a sling are helpful.

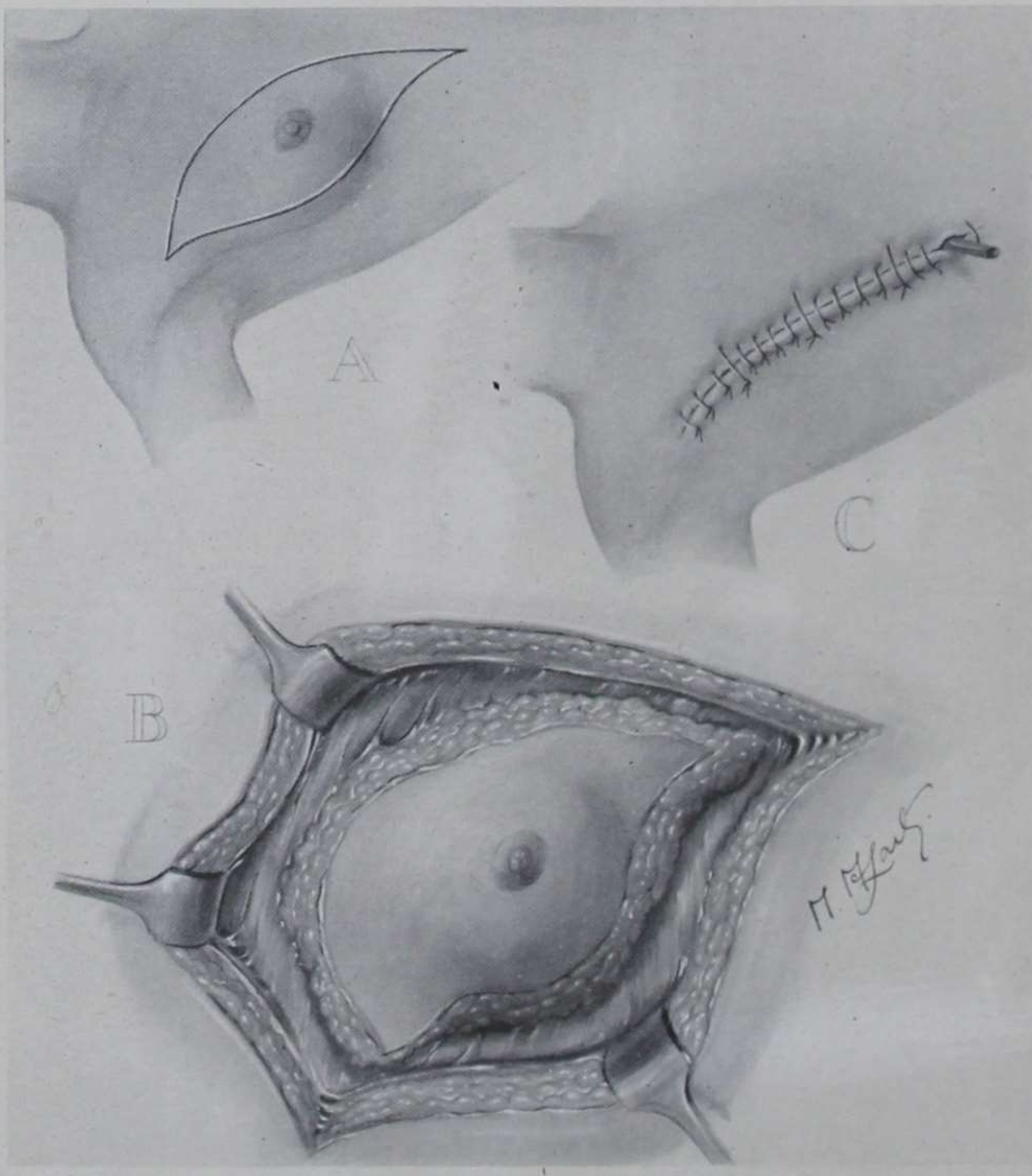

Fig. 134.—Simple mastectomy. A, Incision ; B, The breast ready for removal from the pectoral fascia ; C, Closure.

The more gross cases of œdema appearing at a later stage with pain of great intensity are the result of malignant growth causing pressure at the apex of the axilla. Radiotherapy, unless contra-indicated, should be given. But if this fails treatment has little to offer except to attempt to relieve the pain by means of sedatives.

In the severe cases the injection of alcohol into the trunks of the brachial plexus or division of the sensory areas in the spinal cord has been performed, but the results are far from encouraging.

SIMPLE MASTECTOMY

A simple mastectomy may be employed for benign or, on occasion, for malignant conditions. There are no fixed indications for its use.

The incision (*Figs.* 134, 135) starts at a point over the pectoral muscle just before it crosses the axilla, and is directed downwards with

Fig. 135.—Transverse incision for simple mastectomy. The axilla can be exposed by the further incision A. Useful for a modified radical mastectomy.

a slight curve medially over the medial half of the breast. It passes about an inch, or just over, from the areolar margin and then curves slightly laterally to finish some two inches below the centre of the lower margin of the breast (*Fig.* 134, A).

The lateral incision, starting at the same point, passes down over the lateral half of the breast at the same distance from the centre and joins the medial incision at its termination.

The skin-flaps are undermined and reflected so as to expose the whole of the breast tissue with its pectoral tail (*Fig.* 134, B) and the breast is then removed by separating it from the fascia covering the pectoralis major and perhaps the lateral chest wall.

Hæmostasis complete, the wound is closed, and a small tube inserted at its lower end only (*Fig.* 134, C).

ENDOCRINE TREATMENT

The remarkable (and rational) success of the treatment of cancer of the prostate by means of *œstrogens* led quickly to attempts to treat other forms of cancer by similar means, attempts which at first sight appeared to many endocrinologists to be completely irrational. Of these attempts, the one which on theoretical grounds appeared least likely to succeed was the attack on cancer of the breast by means of stilbœstrol, since, as already pointed out, in certain experimental animals œstrogens may actually provoke cancer of the breast. In 1916 Loeb discovered that oöphorectomy, and a consequent diminution of œstrogen, prevented the appearance of mammary cancer in a strain of mice in which the spontaneous development of the disease was common. The work of Bittner led to the discovery of the transmission of a cancerous tendency by the mother's milk and also of a hereditary tendency, without diminishing the importance of the carcinogenic influence of œstrogens. In mice three factors operate, an inherited susceptibility, a substance which passes from mother or foster-mother in the milk, and the action of œstrogens. A combination of the three produces the highest incidence, but œstrogens are capable of producing cancer of the breast even in males and in mice of a strain in which the spontaneous incidence is low. In 1939 Geschickter, by means of ketohydroxyœstrin, succeeded in inducing mammary cancer in 25 out of 86 rats of a strain in which spontaneous cancer has never been observed. Lacassagne (1938) produced similar results with stilbœstrol. In further experiments Lindford and Dmochowski (1947) investigated the action of diethylstilbœstrol on ten different transplantable mouse tumours in mice of four inbred strains. There was no specific inhibition of the growths. It was demonstrated by the same workers that stilbœstrol has no action comparable with that of colchicine, which brings all cell division to an end by preventing the formation of the mitotic spindle and also induces hæmorrhage in rapidly growing tumours.

A number of reports were presented at a meeting of the Radiology Section of the Royal Society of Medicine in 1944 on the treatment of advanced mammary carcinoma in women with stilbœstrol. Of 68 women over 60 years of age, 32 (some 50 per cent) were improved, 5 of them "spectacularly". Of 100 women under 60 years of age, an improvement was reported in 15 per cent, and a "spectacular" one in 1 per cent, though other workers had gained no success in this younger age group. The series was criticized as lacking rigid controls.

A report of the treatment of a further 22 advanced cases was made later by Haddow and Paterson (1944), who observed an initial but only temporary improvement in 10 of these. In one case, although the primary breast lesion was regressing, secondary deposits developed in the lung during treatment. No evidence was obtained to suggest that the drug prevents dissemination. On the contrary, the impression was gained that malignant tissue becomes progressively more resistant to the earlier inhibitory effects produced by the drug. In one case only was there prolonged arrest of the disease; in others its progress was unaltered. The degree of retardation obtained was probably much less than could be expected from local palliative irradiation. The conclusions of Haddow and Paterson will probably stand the test of time, and it seems unlikely that the œstrogenic treatment of mammary cancer will gain ground. (Dosage: Stilbœstrol up to 15 mg. a day is given.)

On theoretical grounds treatment by means of *androgens* should be more effective. Although in some respects androgens and œstrogens have similar activity, in others their action is directly antagonistic. Administration of testosterone propionate greatly reduces the incidence of mammary cancer in susceptible strains of mice. According to Lacassagne (1939) testosterone suppresses the pituitary and secondarily induces a diminution in ovarian secretion. On the other hand, testosterone has no effect on mouse tumours already in existence. Its effect, therefore, is prophylactic rather than curative, and may be compared with the clinical observation of the effects of oöphorectomy on human breast cancer, which appears to be without influence in the established disease.

Adair and Herrmann (1946) treated 11 patients with advanced breast cancer with massive doses of testosterone propionate. In 4 a remarkable improvement occurred. These cases received total dosages of 3·9, 2·4, 4·1, and 2·1 g. In one the primary growth and secondary deposits in the breast, skin, axilla, and right subclavicular space disappeared. In the second an effect was exerted on deposits in bone and the patient lost her pain. A report by A. Prudente (1945) of the effects of the post-operative treatment of mammary carcinoma by testosterone suggests that it may exert influence on the development of secondary deposits, but the series, though adequately controlled, was too small for sound conclusions to be drawn.*

THE PREGNANCY-LACTATION PERIOD

A malignant state already in existence at the start of a pregnancy or developing in the breast during a pregnancy-lactation period is considerably accelerated both in growth and dissemination by the prevailing stimulation and activity. As the result of rapid growth the absence of fibrosis is a feature of these cases and the classical signs of cragginess, fixation, retraction, etc., are consequently missing. The feel of a rapidly growing carcinoma may suggest inflammatory much more than malignant tissue. Such an abnormality, too, unless noticed by the woman before the pregnancy, is apt to be regarded as a change compatible with the condition, until discoloration or alteration of texture of the skin or massive induration of the breast causes advice to be sought.

An inflammatory or erysipeloid carcinoma, so called from the manner in which it affects the skin, although seen occasionally in ordinary cases, when associated with the lactating breast ranks among the most malignant of all cancers. In addition to the dusky appearance of the skin, a rise of temperature, a mild leucocytosis, and sometimes pain, increase the resemblance to an inflammatory process sufficiently perhaps to influence the diagnosis and management of a case. Any such condition which fails to respond to treatment in say 8 to 10 days should be suspect and a biopsy straightway made.

During the latter part of lactation a carcinoma is of more average type and comes within the range of effective treatment.

Treatment.—As regards treatment, cases fall roughly into three groups :—

1. Advanced carcinomata, or secondary deposits, already in existence before pregnancy and seen about the third or fourth month.

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* The dosage of testosterone now being tried (W. E. Tindall) varies between 30 mg. daily by mouth, 100–300 mg. of the propionate given daily by injection, or up to 1000 mg. total of methyl testosterone by implantation. The optimum dosage for individual cases is judged by results after a 6–8 weeks trial.

Clinical experience now shows that hormone therapy exerts its most beneficial effects in elderly women. A temporary regression or disappearance of skin, skeletal, and visceral deposits from breast cancer is brought about in a certain number of cases with corresponding relief. In younger women results are uncertain and may be adverse.

Œstrogen or androgen therapy should, as yet, be reserved for palliation in otherwise hopeless cases and not used to replace, or to amplify, radical therapy.

2. Seen in the latter months of pregnancy.

3. Seen during lactation.

In the first and second groups the cases may be so advanced with skin infiltration and dissemination that radical treatment is out of the question. Any attempt to eradicate malignant disease during a pregnancy involves its termination, preceded or followed by surgery and radiotherapy.

Alternatively, in the advanced case or in the latter months of pregnancy, a viable child may be the first consideration. Each case presents its own particular problems, but in view of the fact that it is difficult to find any record of survivals beyond about 20 to 24 months, a pregnancy may justifiably be allowed to continue if desired and treatment be limited to a course of radiotherapy with careful abdominal screenage. The chance of helpful operative treatment is assessed after the confinement.

In the third group, omitting the very acute types, lactation is stopped and treatment follows the usual lines.

Illustrative Cases.—

Case 1.—Woman aged 25. Immediately before her confinement in May, 1940, (stillbirth after forceps delivery) a lump was noticed in the upper and outer quadrant of the right breast. After recovery from the confinement the lump itself appeared unaltered, but an enlarged, though somewhat soft, lymph-node was palpable in the axilla. A radical mastectomy was performed.

Pathological Report.—" Spheroidal-celled carcinoma in breast and node. Broders' classification Group 4, showing approximately 80 per cent undifferentiated cells with very numerous mitotic figures."

In 1942 this woman again became pregnant. When, in the mid months of this pregnancy, she reported again, secondary carcinomatous deposits were obvious in the right breast area and in radiographs of the lumbar spine. Although her general health was obviously failing—and her husband overseas—this woman never wavered in her determination to go through with the pregnancy.

In mid-September a live baby was delivered by a Cæsarean section followed by a hysterectomy (Mr. H. M. Rees). Post-operative convalescence was uneventful. Death occurred some 4 to 5 months later.

Case 2.—Woman aged 38. Had been feeding her first child for six months when an area of " thickening " was noted in the upper part of the right breast—no pain—and she reported some three weeks later. At an operative investigation and microscopical examination in the theatre malignant cells were found. A radical mastectomy was followed by radiotherapy. (Reported well, now over 3 years.)

Histological Report.—Carcinoma of breast consisting of large, pale-staining rounded cells showing active cell division, forming a solid tumour mass. Infiltration not marked. A lactating breast. No secondary deposits found in the axillary nodes. Active but not extreme malignancy.

Case 3.—Malignant galactocele. (*Professor R. Milnes Walker's case.*)
Woman aged 43 years. Four children, last 18 months ago. Twelve months ago while lactating she noticed a lump in the right breast but did not consult her doctor as she did not want to leave her children.

Fig. 136.—Malignant galactocele of right breast. (*Professor R. Milnes Walker's case.*)

It has steadily increased in size since. No pain. Slight blood-stained discharge from the nipple on a few occasions, mixed with milk.

Present Condition.—A spherical, fluctuant tumour, 10 cm. in diameter, occupying the whole of the right breast (*Fig.* 136). Skin stretched firmly over it and rather darker in colour than normal. Two enlarged lymph-nodes felt in right axilla. Left breast and axilla normal.

Dec. 15, 1947.—Pre-operative radiation commenced.

Jan. 1, 1948.—Radical mastectomy.

Specimen.—The breast is replaced by a spherical cystic mass containing thick turbid fluid with a solid wall varying from ½ to 1 cm. in thickness (*Fig.* 137). Milk found present in the surrounding breast tissue. The enlarged lymph-nodes do not contain growth on naked-eye examination.

Histological Report.—The breast tumour consists of masses of neoplastic cells in a fibrous stroma.

Case 4.—Woman aged 42. Spare build. $6\frac{1}{2}$–7 months pregnant. One child aged 8. No previous medical history until just at the beginning of the immediate pregnancy, when she attended out-patients' department for a pain in the left side of her chest. Radiographs of the chest were negative except for evidence of small areas of healed tubercle at the apex of each lung. Nothing else was found.

A lump was first noticed in the left breast when she was about five months pregnant. No complaint of pain was made and the previous pain

Fig. 137.—Section of the breast shown in *Fig.* 136, which is seen to consist of a spherical cystic mass. (*Professor R. Milnes Walker's case.*)

in the chest was stated to have lasted only a short time and had not recurred. In a small breast a hard mass with irregular surface and vague in outline (5 × $2\frac{1}{2}$ cm.) was obvious in the central medial area of the lower half and was firmly fixed to the chest wall. The breast was deformed by the mass, but the skin, which was slightly œdematous, and also the subcutaneous tissue, appeared to be movable over it. One enlarged basal lymph-node was palpable in the axilla. A provisional diagnosis of carcinoma was made.

A wish was expressed and maintained by the patient that nothing should be done which might in any way prejudice the pregnancy. A course of deep therapy was advised and given and caused considerable shrinkage of the mass. The general health was maintained at a satisfactory level throughout. Further radiographs of the chest showed no material change. The confinement, though somewhat premature, was otherwise uneventful. Twins were born, one of whom died. About a fortnight after this a radical mastectomy was performed. On the deep surface of the lower medial aspect of the breast yellowish-looking necrotic tissue was attached to the aponeurosis of the fifth rib interspace and periosteum covering the sixth rib. This was excised by the diathermy knife. No involvement of the rib itself was noted.

The pathologist reported the condition to be a tuberculous mastitis in a breast showing limited activities of early lactation. This histological diagnosis was supported by the finding of a typical follicle in the axillary lymph-nodes. No evidence of malignancy was found. A zone of dense fibrous tissue surrounding the tuberculous area accounted for the consistence of the original mass on examination.

Case 5.—Woman aged 38. No previous confinements. Twins born June, 1948. In November, 1948, when breast feeding was being continued though supplemented, a small lump was found in the left breast and reported straightway.

On examination a soft-to-firm, rounded, discrete, and freely movable nodule, about 1–1½ cm. in diameter, was easily palpable in the central area of the breast close to its upper margin. On account of the clinical findings and certain domestic issues that were raised, temporary observation was regarded as justifiable. After two attendances this patient watched the lump herself and noticed no change until mid-October, 1949, when it started to grow. Four weeks later, although bigger (4–5 cm.) and harder, it had otherwise just the same characteristics described above. The skin was normal and no enlarged lymph-nodes were found.

At an operative investigation an immediate histological examination revealed the tissue to be carcinomatous and of high malignancy. A radical mastectomy was performed. No evidence was then found of dissemination to basal or apical axillary nodes nor to the internal mammary chain (second interspace). These negative findings were later supported after full pathological examination. Post-operative irradiation was given.

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CHAPTER XI

RADIOTHERAPY

By Anthony Green and R. F. Hendtlass

I. INTRODUCTION

Radiotherapy comprises the use of penetrating rays in the treatment of disease such as those emitted by X-ray tubes, radium, and various other radio-active substances both natural and artificially produced. Since the measurement of radiation is essential to dosage, physics is of fundamental importance in radiotherapy. The amount and penetrating power of the radiations, two important factors on which dosage depends, are measured by the physicist.

The effects of absorption of radiant energy are both general and local. Locally these effects vary in different tissues, some being sensitive and others resistant to the rays. A measure of the absorption can be estimated on a physical basis, but the physical dose is but one factor in assessing the biological response. The rate at which the radiation is given must also be taken into account; for example, some tissues show rapid recovery when radiation is spread over a period of time and others are destroyed even if the rate of delivery is very slow.

These complex and varying actions of radiation on living matter form part of the science of radio-biology, which incorporates the study of cell metabolism in general. This subject is of increasing importance due to the production of radio-active elements which in their normal state make up a cell. An example is radio-active phosphorus, which when introduced into the body emits radiation from within the cells of which it forms a part.

From the large number of cases of cancer of the breast seen in a radiotherapy department particular opportunities are afforded for its study. The section on secondary deposits has been composed from the authors' own experience, and the methods of irradiation described for the treatment of the disease have been evolved and tested over a number of years with encouraging results.

This chapter is primarily concerned with radiotherapy in the treatment of malignant disease of the breast, but includes brief descriptions of the principles guiding its use in general. With a view to interesting the clinician as well as the radiotherapist some sections, such as the physics, have been simplified and details which do not apply to the breast have been omitted.

II. PHYSICS

Light, a familiar form of radiant energy, is similar to the radiant energy used in radiotherapy. There are in Nature a whole range of radiant energies of which visible light forms only a fraction. This small range is readily divided into its component parts, as seen in a rainbow. If this section of the whole is followed from violet to red and beyond, the range of wireless waves is reached, whereas if followed from red to violet and beyond, X rays and gamma rays are reached.

When radiating from their source of origin X rays and gamma rays may ' collide ' with any substance in their path such as air, metal, human tissue, etc. To appreciate what occurs it is necessary to refer briefly to the structure of such material. The body cells, in the main, are composed of water and protein molecules. The protein molecules are built up of a large number of atoms. Each atom is made up of a central nucleus around which electrons revolve as the planets revolve in space around the sun. When X rays or gamma rays pass among these atoms, a few of the planetary electrons are struck and some are ejected from their parent atoms. These electrons then collide with other atoms in their path, knocking out further electrons, until they have lost all their energy. This process represents the main way in which the energy of the original X rays or gamma rays is transferred to the medium in the path of the beam. The damaged atoms generally recapture their lost electrons, but in tissue, following such atomic disruption, the cells are permanently changed due to molecular alteration or chromosome injury.

Atoms of one element differ in their structure from those of another element. They range from those with small nuclei with few planetary electrons to those with large and complex nuclei with many electrons. In some of the most complicated atoms, the arrangement is unstable, and these atoms break down spontaneously, giving rise to radiations. This process, termed radio-activity, can result in the emission of three types of rays : (1) Alpha rays, which are small parts of the nucleus ; (2) Beta rays, which are electrons ; and (3) Gamma rays, which are radiations of the same nature as X rays and light. Radium is such a radio-active substance, and is one of the most powerful natural sources of the above radiations. It is now possible to alter the structure of certain atoms artificially so that they too become unstable, i.e., radio-active, and so can be utilized as a source of radiation (atomic energy).

X RAYS

In metals, the atoms are arranged in a regular pattern, or lattice, and many of the planetary electrons are shared between the atoms, travelling around amongst the lattice structure. When the metal is heated, they travel more rapidly and those near the surface may escape away from the structure altogether. This effect has been

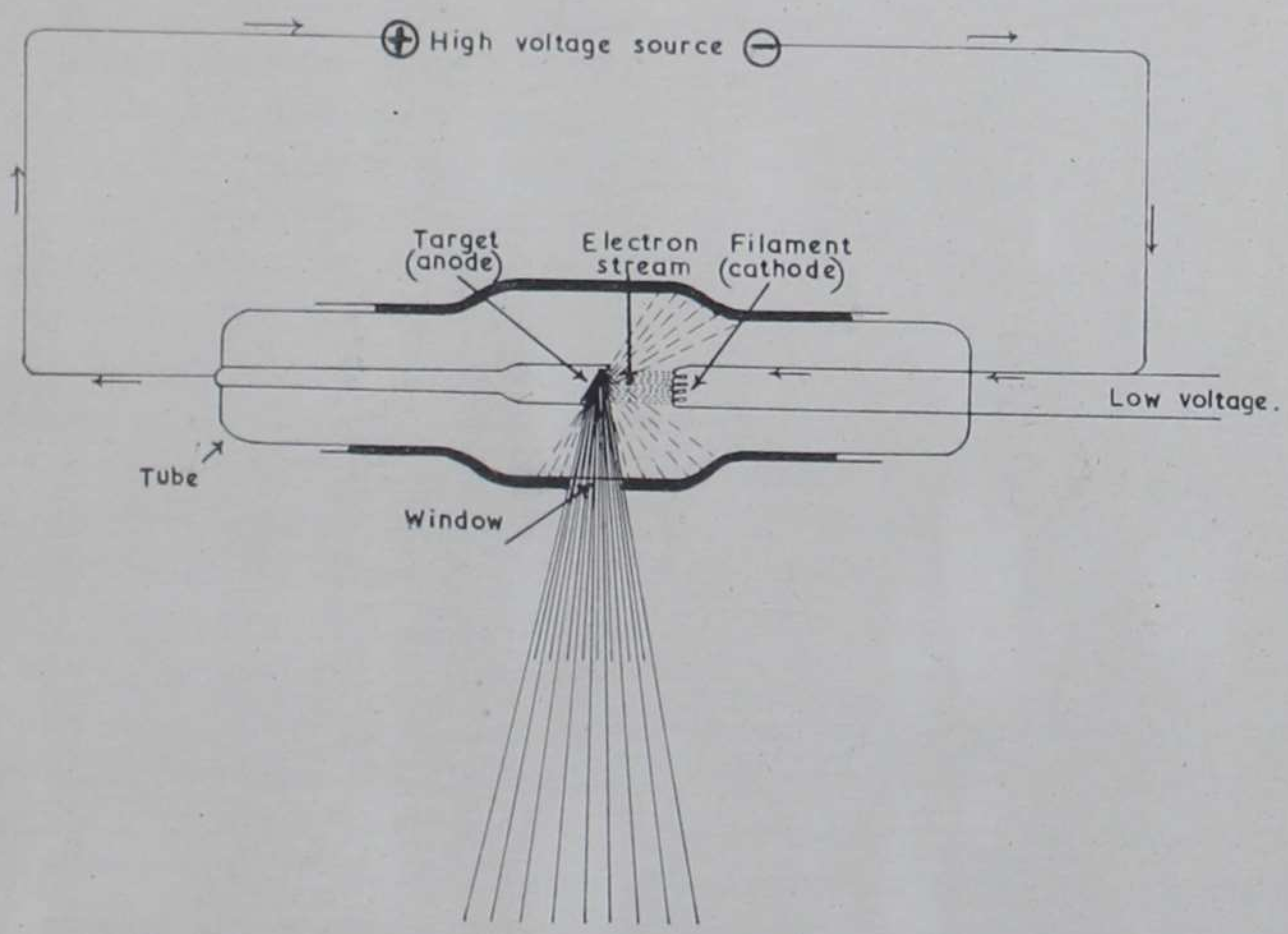


Fig. 138.—Essential features of an X-ray tube, showing the broadening beam of useful X rays.

used in the design of X-ray tubes, for the filament in such a tube is a heated metal coil, thus providing a source of electrons. If now a high voltage is applied (measured in thousands of volts, i.e., kilovolts) this powerful electrical force attracts these electrons towards the opposite end of the tube where they complete the circuit on the positive side (anode). When these very fast moving electrons strike the anode, known as the target, the disruption of the atoms of that target under such a bombardment leads to the production of X rays.

Those X rays produced by electrons attracted by small kilo-voltages have little penetrating power and are known as 'soft' or superficial X rays, whereas those produced with high kilovoltages have a high penetrating power and are known as 'hard' or deep X rays.

In *Fig.* 138 the essential details of an X-ray tube are depicted. It will be seen that the X rays issue as a beam of radiation. The strength or intensity of the X rays in air diminishes with distance from the target because the beam is spreading wider and wider. This effect can be expressed by the inverse-square law, e.g., at double the distance from the target the intensity of radiation falls to one quarter, and at three times the distance, to one-ninth. When the X rays pass through human tissue (or other matter) collisions as previously described result in the loss of energy from the beam which is absorbed in the tissue. The denser the material the greater the absorption.

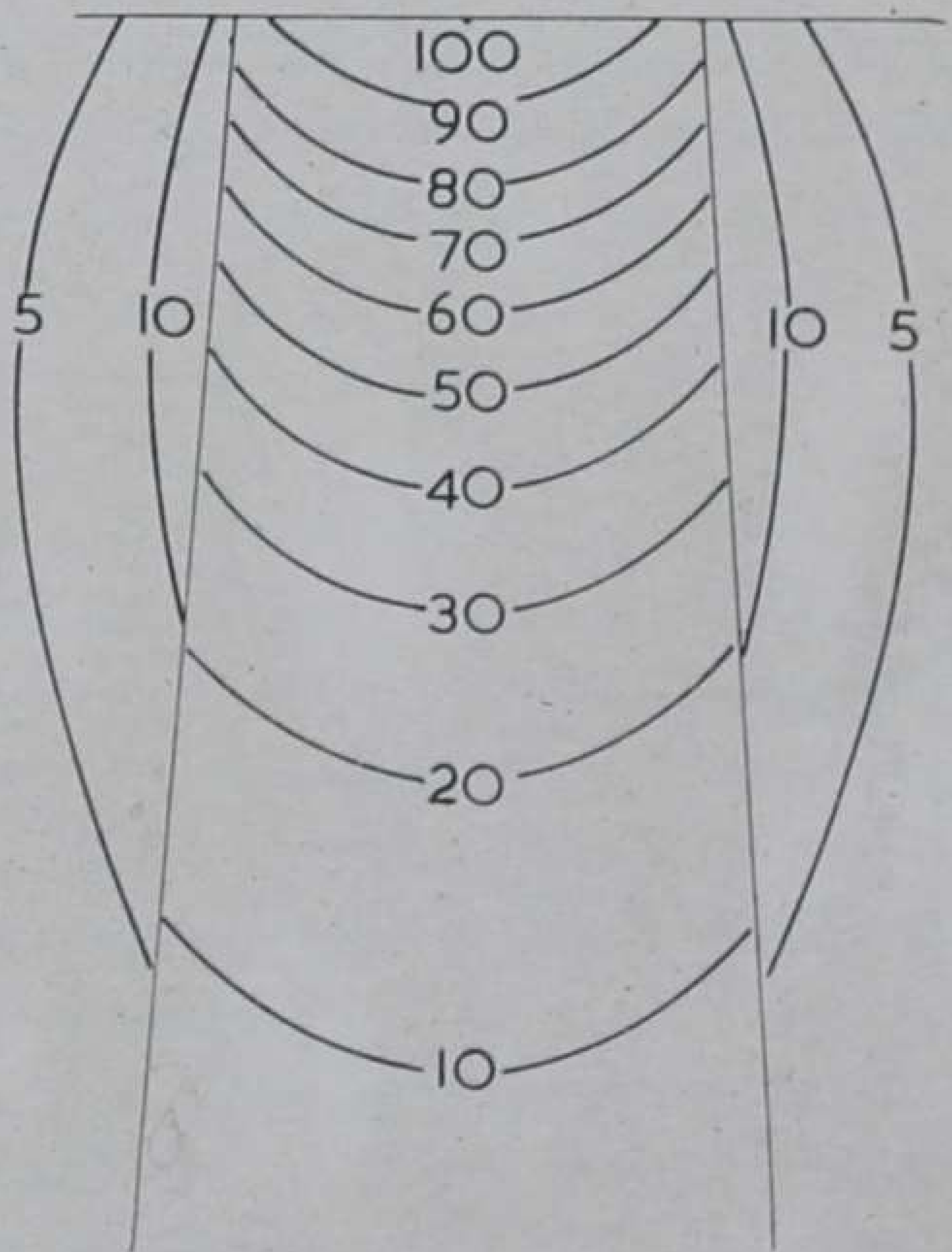


Fig. 139.—Isodose chart for 7·6-cm. diameter circle. Conditions: H.V.L. = 1·92 mm. Cu; F.S.D. = 50 cm.

It is clearly important to know the intensity of X rays at all points; to facilitate this, a diagram of an X-ray beam is drawn as shown in *Fig.* 139, in which points of equal intensity are connected by lines, the resultant curves being called isodose curves (curves of equal dose). The intensity at the surface (which is at a fixed distance from the target) is taken as 100 per cent and the lines are usually drawn through points at 10 per cent intervals. It is of little practical use to measure these points in air, as human tissue is composed of different atoms. Ideally, they should be measured in human tissue, but this is rarely possible, so that a substance having similar properties with regard to X rays as human tissue is used by the physicist in his measurements, e.g., water.

Because the intensity of the X-ray beam decreases with distance, the skin surface receives a greater dosage than points deep to the skin. Accordingly, if it is desired to deliver a dose to a deep tumour, without over-dosing the skin, it is necessary to use several beams in turn, passing through different parts of the skin. These all cross at the tumour ('cross-fire'). The total dosage from the cross-fire is determined by laying the isodose curves in their correct position to represent the direction of the X-ray beams. The summated intensity at each point can be obtained readily by adding the figures where the lines cross.

Since it is essential to produce even irradiation, symmetrical arrangements of X-ray beams are usually used (*see* X-ray technique, p. 247).

Often it is not possible to arrange the beams symmetrically around the region to be treated, and it may be desirable to confine the radiated

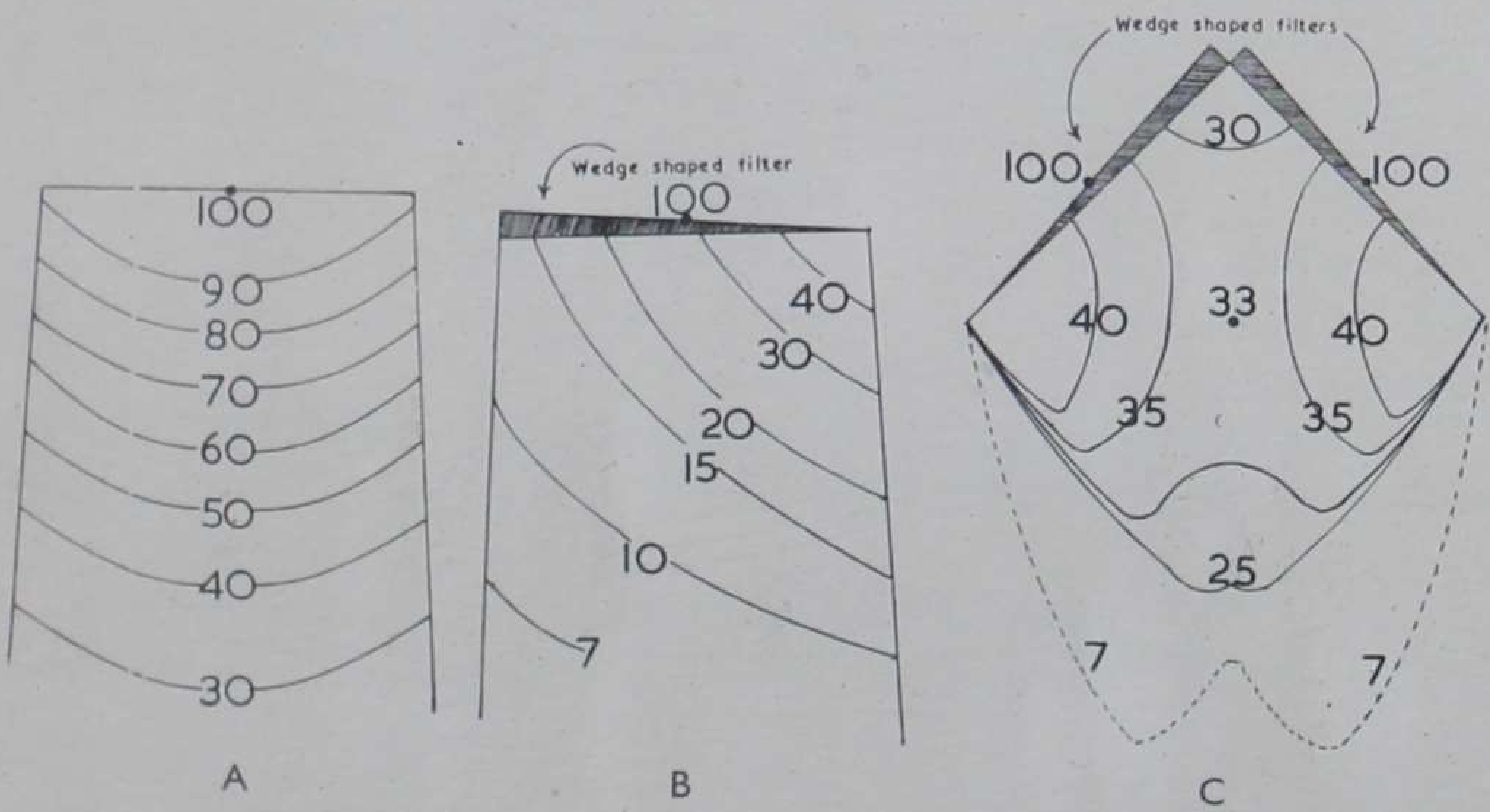


Fig. 140.—Showing how isodose curves of a beam may be inclined by the use of wedge-shaped filters. A, Ordinary isodose curves; B, Inclined isodose curves; C, Summated intensities for two beams at right angles.

zone to a small volume. This can be done by using filters to cut down the dose over those parts of the beam where it is not required. *Fig.* 140 A, B shows how the isodose curves of a beam can be inclined by the use of a wedge-shaped filter, and in *Fig.* 140 C it is seen that the summation of two such beams at right angles leads to the desired result, provided that any spare space between the wedge and the patient is filled with tissue-like material, for example paraffin wax (which has similar X-ray absorption properties).

Percentage figures give great assistance in planning treatments so that even dosage is obtained, but some unit of actual measurement is essential ; this unit is the roentgen (r) and is the usual measure of dose.

This unit is based on physical factors and is not completely adequate for the radiotherapist's use. A biological unit is sometimes used which is related to the r and is known as the erythema dose.

This is the number of r required to produce an erythema of the skin which is just perceptible. The erythema dose in r units is not a constant, because it varies not only with the particular range of X rays in use, but also with the period of time over which it is given.

The beam of X rays is directed to the patient through an applicator. If the end of the applicator where the beam emerges does not lie in contact with the skin over its whole length, air gaps result, and the isodose curves do not apply. These gaps have to be filled by wax or similar substance, as previously mentioned. Bags filled with a powder having the same characteristics as human tissue with regard to X rays can also be used. These are known as bolus bags and are in common use where wax moulding is not necessary.

RADIUM

Radium is used as radium sulphate because it is insoluble. This powder is packed into a tubular or needle-shaped container, which is hollow and sealed at both ends.

Radium, being radio-active, spontaneously disintegrates to form a chain of daughter substances, the first of which is radon. Radon

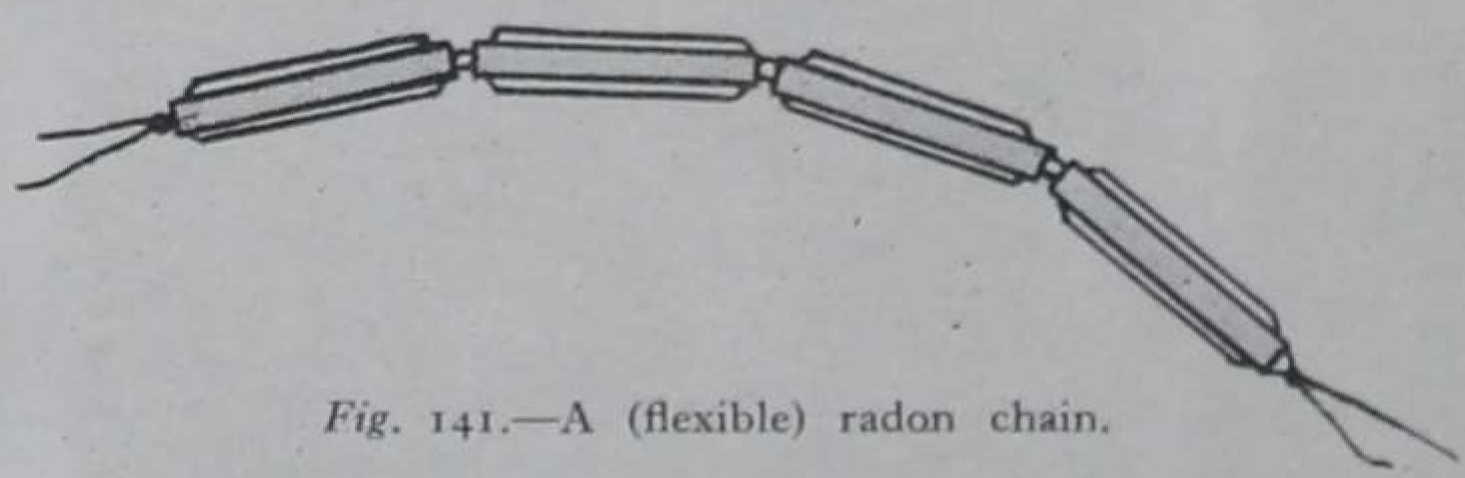


Fig. 141.—A (flexible) radon chain.

is a gas and can be sealed in containers from which the radiations are emitted. The main active break-down product of radium and radon is actually radium C, so that both radium and radon containers emit the same radiations. Radium is very valuable but radon is relatively inexpensive and is sealed in glass or gold capillaries. The glass types are again sealed in platinum containers. (Under the Radiochemical Centre, Amersham, these seeds are now replaced by gold seeds enclosed in a silk sheath.) These are known as radon seeds. The seeds may be used individually or strung together in a chain (Green's method), when virtually they are flexible needles (*Fig.* 141). Radon being a radio-active substance breaks down and reaches half its strength in approximately 3 days 20 hours, and a quarter of its strength in $7\frac{1}{2}$ days. Thus the half-life period of radon is 3 days 20 hours. Radium breaks down so slowly (its half life is 1580 years) that it is for practical purposes a constant source of radiation.

This radio-active series gives rise to alpha, beta, and gamma rays. The alpha and beta are not wanted for the treatment of breast conditions and the metal containers made of platinum or gold serve to filter them off.

Gamma rays, like X rays, fall off in intensity with increasing distance. The rays are very penetrating, and so the absorption is much less than with X rays. Isodose curves may be drawn and the dosage is measured in r units as with X rays. In *Fig.* 142 the isodose

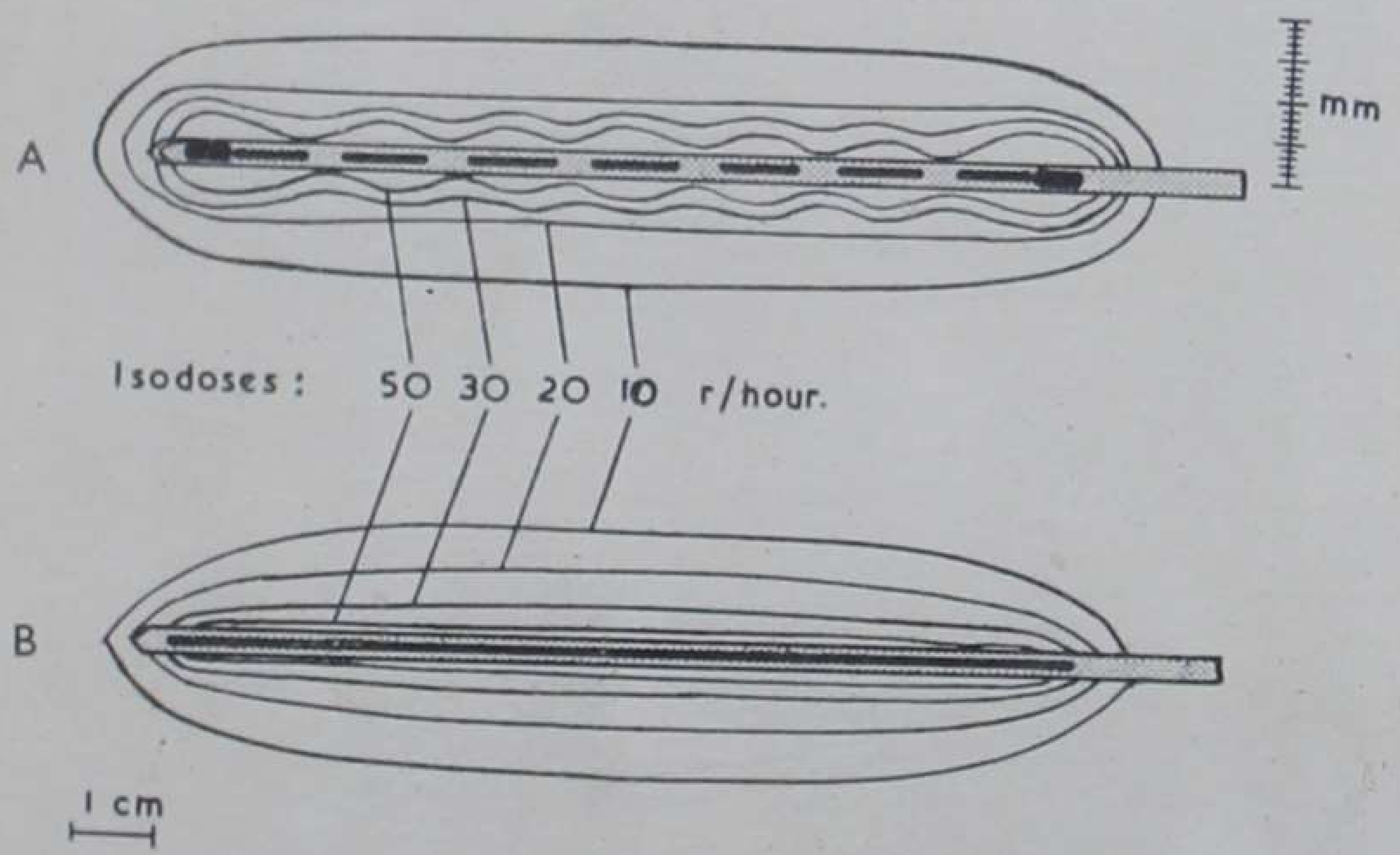


Fig. 142.—Two 9-mg. radium needles, showing the advantage of end-loading. A, With end-loading ; B, With no end-loading.

curves surrounding two types of a long radium needle, of the kind used in breast treatments, are shown. Example B shows the curves obtained with a needle in which the radium is evenly distributed along its length, whereas example A shows the effect of inserting additional radium at each end. By this means the dosage is prevented from falling off at each end. The use of hollow needles filled by suitable small radium cells makes such end-loading possible for any length of needle that may be required (Green's method).

When radium was first used in medicine the dosage unit was given as a product of the amount and the time for which it was used, i.e., milligramme-hours. This unit is now obsolete since the falling-off of intensity with distance is not taken into account.

It has been explained that even irradiation of the particular region is essential. This is obtained by the symmetrical arrangement of radium sources, or by so arranging their strengths that an even dose is obtained (*Fig.* 143). It will be readily understood that the intensity immediately on the surface of a needle is very high, and for the purpose of calculation a zone of 5 mm. from the source is generally used. (A small zone of necrosis occurs around any needle whether it contains radium or not.)

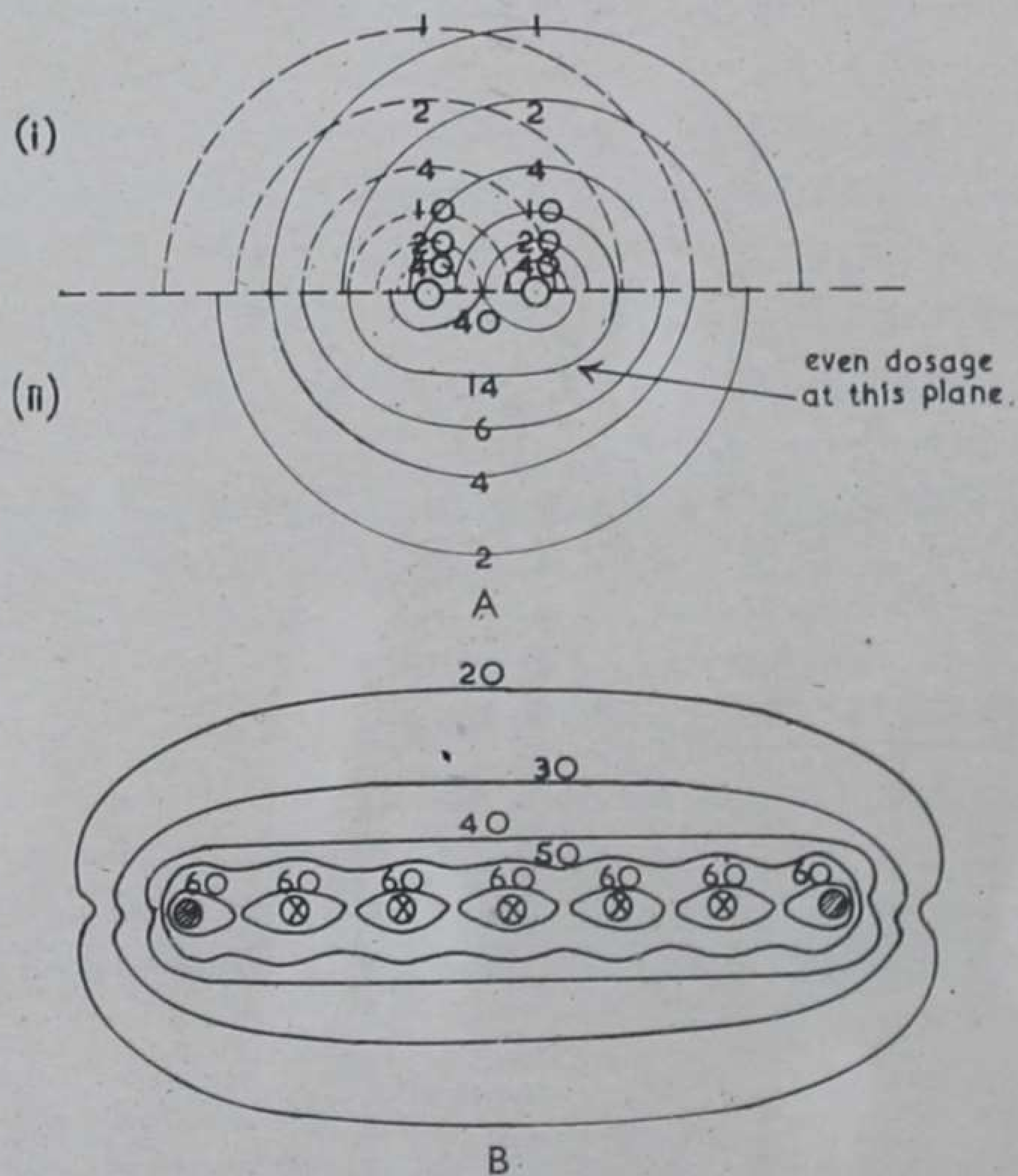


Fig. 143.—Showing how radium needles may be arranged to procure even irradiation. A, Summation of isodoses surrounding two radium needles, here seen end on: (i) The isodoses of the two needles shown separately; (ii) The summated isodoses. B, Summated isodoses for a set of parallel needles, seen end on. End needles each contain 10 units of radium, inner ones 7 units—to prevent fall in dosage at sides of area treated.

III. RADIOTHERAPY

GENERAL PRINCIPLES

Mode of Action of Radiation.—X rays and radium inflict damage on normal and malignant cells by virtue of the atomic disruption in the cell nuclei due to the impact of X and gamma rays. Normal cells in the resting phase or early phase of activity are relatively insensitive and tend to recover from irradiation damage. Several 'hits' may be required to produce severe damage, and even then recovery may occur. If death of the cells does ensue it is delayed. Actively dividing cells, however, are in the most sensitive phase and a single 'hit' on the nucleus may result in the breakdown of the chromosomes, followed by shrinkage and death of the cell.

Sections of breast cancers show microscopically cells of various types—undifferentiated and active, and differentiated and inactive (*Fig.* 144). In rapidly growing tumours the direct effect on the cells is of great importance, but this alone does not account for the full action of radiation. The tumour bed, comprising normal tissue with its all-important blood-supply, doubtless plays a large part in the destruction of cancer cells. Histologically, macrophages can be seen devouring damaged cells, and if there is a good blood-supply they are abundant. In favourable circumstances, therefore, irradiation can lead to the

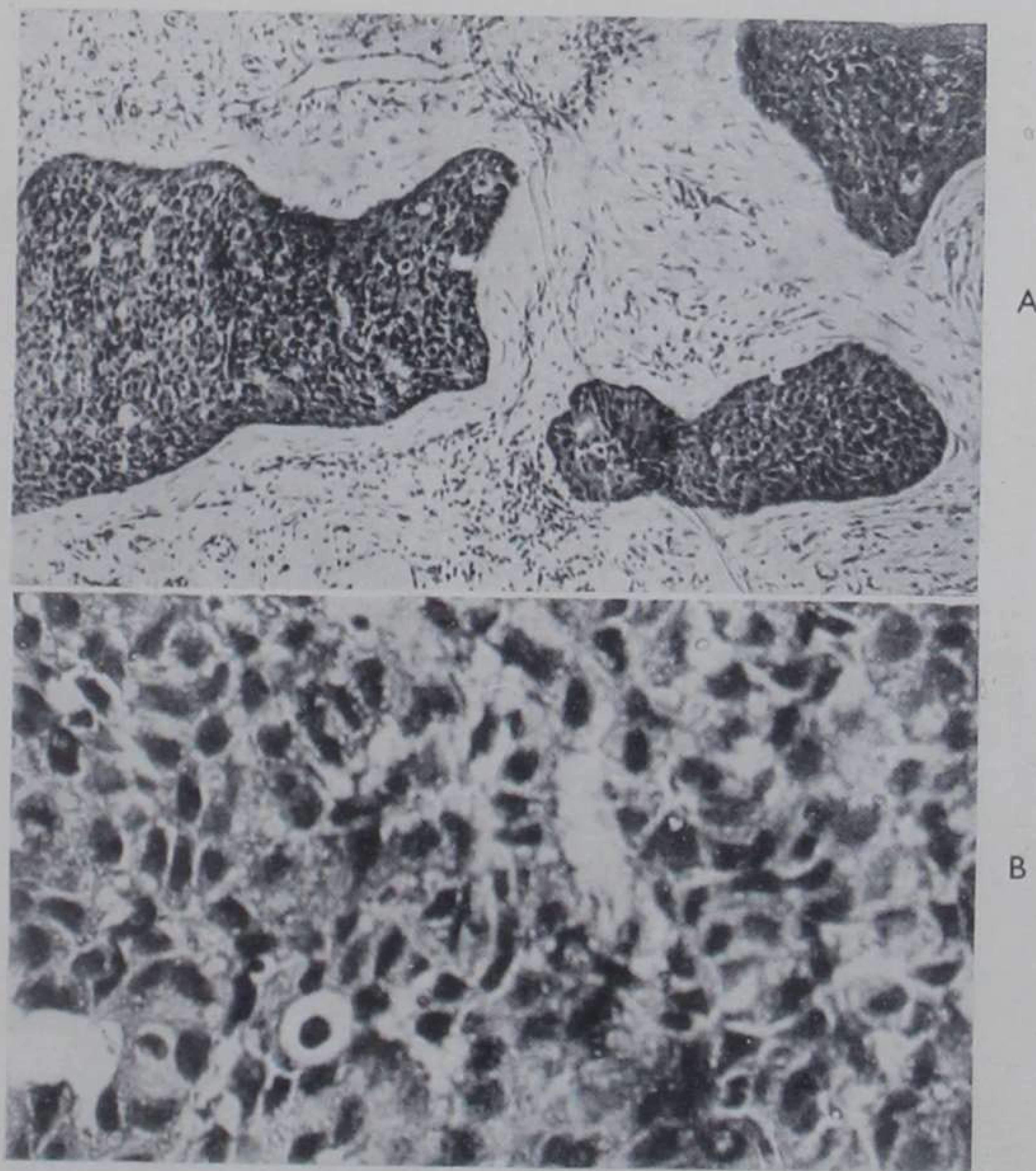


Fig. 144.—Solid trabecular breast carcinoma, before irradiation. A, Note abundance of stroma around solid blocks of tumour cells. (× 75.) B, Cellular detail of the same. (× 315.) (*Figs.* 144–146 *from sections by Dr. P. M. Peters.*)

disappearance of a breast cancer, but if there is infection in the tumour bed the macrophages are distracted to this rather than to the results of radiation injury.

The most favourable conditions are a limited size of tumour, little surrounding fat, a good blood-supply, and absence of infection. It is clear that a large hard tumour in the centre of a massive breast is unsuitable for treatment by radiotherapy alone, and these facts explain why the response of the axillary nodes may be better than that of the primary growth.

Nevertheless, although irradiation alone can eliminate a proportion of breast cancers, a sharp distinction should be made between *radio-sensitivity* and *radio-curability*, for a lesion although not highly sensitive to moderate doses may shrink and disappear with high dosage.

In treatment, an intense dose of irradiation is applied homogeneously over the whole of the diseased area so as to affect each

A

B

Fig. 145.—The same tumour on the 8th day after irradiation—dosage 200 r four days a week, total 1000 r. A, Note degenerating columns of growths diagonally across field and on the right. Some of the tumour cells have survived. Note inflammatory reaction in the stroma. (× 75.) B, Cellular detail of the same. The cavity produced by the tumour destruction is filled with loose cancer cells and neutrophil polymorphs. (× 315.)

cancer cell. In the case of radium the radiation is continuously administered over a number of days, and in the case of X rays divided doses are given over a number of weeks. Radium implanted in the tumour irradiates less tissue with less constitutional disturbance, and the dosage can be completed in a week. X rays cover a much greater volume of tissue and produce greater constitutional effects. In order to minimize these the dosage is spread over two or more weeks. This 'fractionated' method of dosage, in addition, aims at irradiating cells as they reach the stage of cell division, i.e., when sensitivity is at its maximum.

Tumour Response to Irradiation.—Small doses of X rays have no important effect on cancer cells, and so far as treatment is concerned

Fig. 146.—The same tumour on the 15th day after irradiation—total dosage 1800 r. A, The location of the dead growth trabeculæ is marked by areas of structureless eosinophil material derived from dead tumour cells and dead polymorphs; such an area can be made out below the surviving column of growth. (× 75.) B, Detail of the same, showing necrotic tumour below and surviving tumour top right. The stromal cells are now plasma cells, lymphocytes, and eosinophil polymorphs. The spindle-shaped fibroblasts are proliferating. (× 165.)

have no place in the management of a case of mammary carcinoma. If a dose is not physically uniform, growth of malignant tissue may continue in areas of low dosage, or necrosis occur in those of high dosage. Speaking generally, under-dosage is a greater factor in loss of life than intensive treatment with high dosage.

At any given time there are comparatively few cells in a stage of division, so that a single dose of irradiation destroys only a few cells. When, however, the dosage is spread over a period of time, and continuously applied as in the case of radium or by repeated exposures to X rays, many cells reach the division stage and are destroyed. This protraction of treatment should not be too extensive, e.g., six weeks, for cells normally destined to divide are liable to be inhibited but not destroyed. Moreover, a fibrotic reaction is promoted in the connective tissues, with the result that a mass of inhibited malignant cells becomes encased in fibrous tissue (*Figs.* 145, 146).

These facts explain the different technique in radical and palliative therapy. In radical treatment an intensive dose is given in a comparatively short time, and in palliation protracted small doses are given to encourage fibrosis. Excessive dosage achieves neither, and in

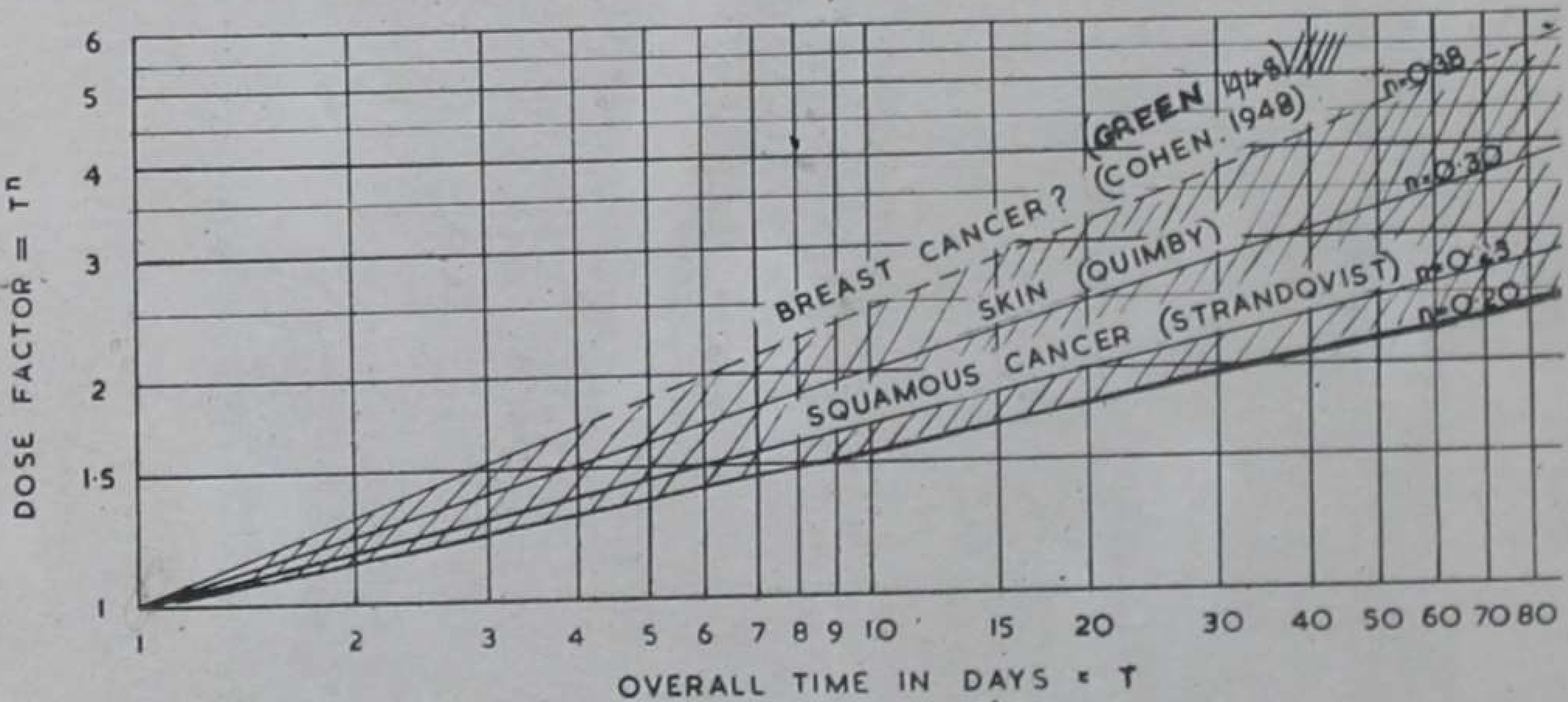


Fig. 147.—Equivalent clinical dosage for various treatment times. The variation in response of breast cancer to irradiation as compared to normal skin and squamous cancer is shown. Cohen indicates a high figure (top line). Green indicates a wide variation in sensitivity for different breast cancers as shown between the values of 0·2 and 0·4 n.

order to obtain the best results high dosage with minimal damage to the tumour bed should be achieved.

The total dose employed depends upon the time of its administration, for a given dose delivered in one exposure has proportionately a greater effect than the same dose spread over a period of time. The longer the overall time the greater the total dose has to be to achieve the same effect, because the normal powers of repair have to be overcome.

It has been shown by Strandqvist that the effective dose to destroy a squamous-cell carcinoma of the skin is doubled if spread over 20 days (*Fig.* 147). Similar data for breast cancer are unknown, but can be assessed from graphs constructed from clinical observations and theoretical data; these also show the different recovery-rate of the skin and tumour tissue based on the time-dosage ratio.

A study of these in planning treatment enables one to choose the optimum conditions.

Cutaneous Response to Irradiation.—The response of the skin to irradiation depends upon the quality and quantity administered. The reactions described are those which follow the treatment of carcinoma of the breast with normal conditions.

Rarely, within an hour or two of the application, a pricking sensation may be felt in the skin, which shows a faint erythema.

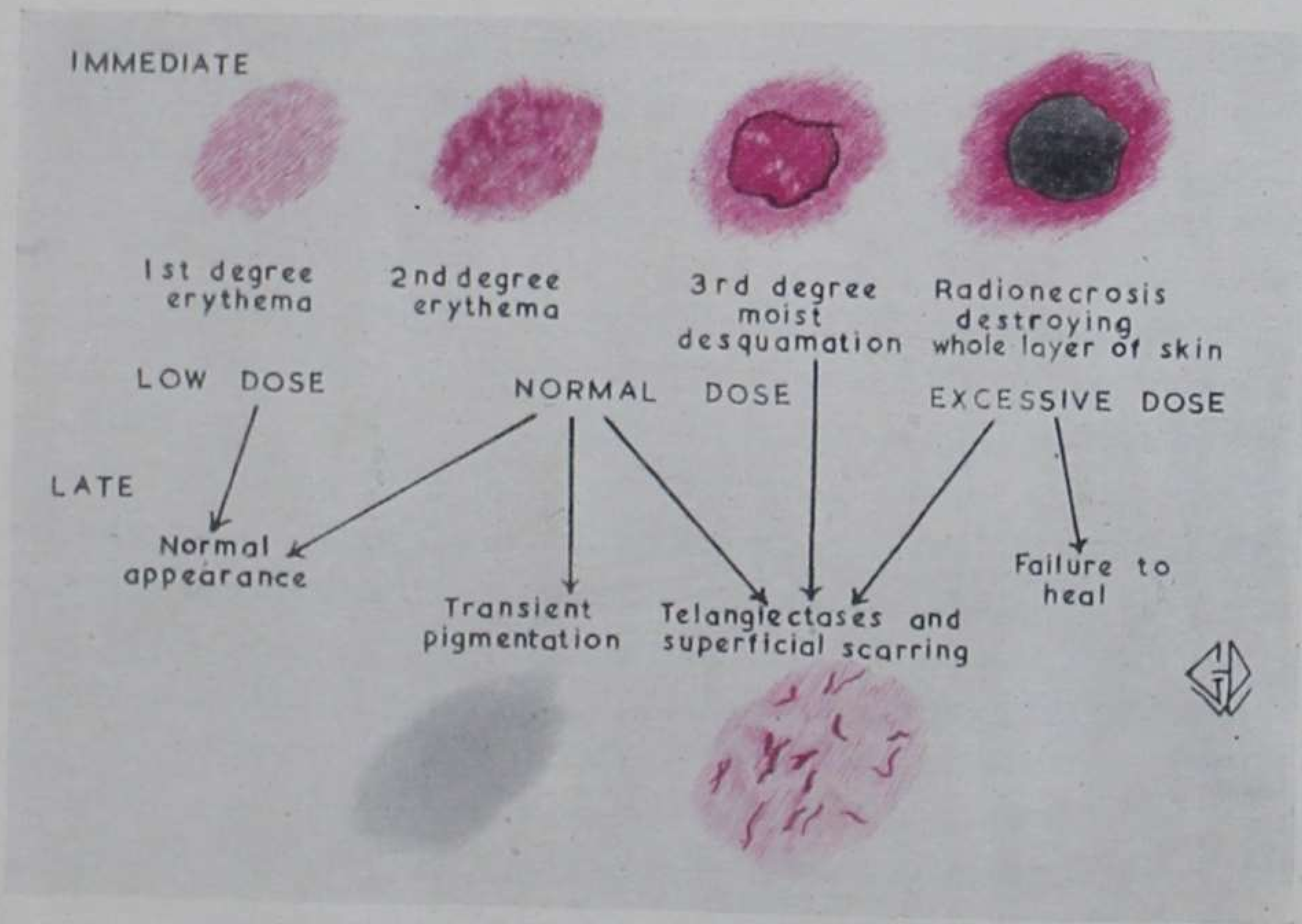


Fig. 148.—Cutaneous effects of irradiation.

These changes last for two or three days only and constitute the primary wave or primary erythema.

Following a latent period of about a week or more, the true erythema or reaction occurs. At first this is just perceptible and is known as a 1st-degree reaction. The erythema develops, and when bright red the 2nd degree is reached. This may be followed by a moist desquamation, the 3rd degree. Normally the skin then heals, the overall time for these changes being about six weeks. Some patients do not pass through all the stages, for the type of skin determines in part the degree of reaction—e.g., the fair patient, who sunburns easily, shows the most reaction. Many cases treated for breast carcinoma show a 2nd-degree reaction only. Should the reaction continue, radio-necrosis occurs and the skin is destroyed, the 4th degree (*Fig.* 148).

Since the dose required to produce the faintest perceptible erythema depends on biological factors, this 'erythema dose', now used as a unit, has definite advantages over the physical r unit.

The late effects of skin irradiation depend upon the degree of response evoked. Following a 2nd- and 3rd-degree reaction telangiectases and superficial scarring may occur. A radio-necrotic ulcer, if untreated, may heal after a considerable length of time, but usually active interference becomes necessary. (*See* Chapter XII, p. 288.)

In considering cutaneous reactions an important clinical detail has to be borne in mind. It will be understood from the PHYSICS section that if any large (metallic) atoms are present on the skin at the time of irradiation their disruption leads to a stream of electrons (beta rays). These penetrate the skin but their energy is soon expended by the production of a useless but intense irradiation of the skin alone. Patients submitted to radiotherapy should not have dressings containing, for example, iodine, biniodide, mercurochrome, or silver nitrate. Zinc strapping in particular must be completely removed. Small residues should be eradicated with methylated ether, and non-metallic sticking plaster with a rubber or synthetic base (Herts Chemical Co.) used instead.

Response in other Tissues.—Following a full dose of irradiation a chronic œdema or leathery thickening of the connective tissues beneath the skin may ensue. This is due to a diffuse fibrosis, and in the event of injury a deep necrosis is apt to follow. Osteoporosis may be produced in the humerus and ribs, with the liability, though small, to spontaneous fracture. This phenomenon should be borne in mind so that it is not confused with a fracture at the site of secondary deposits. Fibrosis of the lungs, secondary to irradiation, is now extremely rare since direct transthoracic beams of X rays have been abandoned in favour of glancing beams. Instances of alleged pulmonary fibrosis now seen are in fact due to secondary deposits.

Radio-necrosis.—The production of radio-necrosis is influenced by both constitutional and local conditions. Adiposity, diabetes, anæmia, syphilis, and a thin tender skin, for example, influence the accessibility of the tumour or the blood-supply. Locally existing fibrosis, œdema, or sepsis adversely affect the blood-supply and tissue response.

Before starting any course of irradiation the urine should always be tested, and if glycosuria is proved treatment for this should be instituted immediately and observation maintained. So far as is possible the conditions should be made favourable for irradiation—e.g., a blood transfusion for anæmia or penicillin therapy for sepsis—and the plan of irradiation will depend on the response to such general treatment. Radium implantation should not be employed in the presence of even slight sepsis ; such cases should be treated by small and increasing doses of X rays until the sepsis has cleared. Further, the volume of tissue treated has an important bearing on the reaction and has to be taken into account to avoid the risk of radio-necrosis. Only 6000 r from radium can be given to a whole breast, but 8000 r can be given to a skin ulcer under 2 cm. in diameter without producing necrosis. Bone is relatively intolerant to irradiation, since it absorbs more than soft tissue ; for this reason radium needles when placed deep to a mammary tumour should not be immediately against the ribs.

Management of Radiation Reactions.—The erythema arising in the irradiated area is treated with 1 in 500 proflavine in spirit. A watery solution may be employed on an unhealed skin area, but it is less effective. The unpleasant yellow colour of the flavine can be avoided by the use of 5-amino acridine in the strength of 1 in 1000 (water or spirit), which, too, is more actively bacteriostatic and affects the leucocytes less adversely. For moist desquamation penicillin ointment is applied for one day, and then a bland ointment, which does not encourage bacterial growth, is applied on lint twice daily. A suitable ointment is Radiotherapy Ointment (Green's formula) made up by Allen & Hanbury.—

Radiotherapy Ointment.—

℞ (1) Zinc Oxide	5 oz.
Borax	120 gr.
Lanolin	10 oz.
Yellow Vaseline Petroleum Jelly	5 oz.
Ol. Theobrom.	240 gr.
Liq. Hamamelidis	240 m.
Aq. Dest.	4 oz.

Mechanical mill for 2–3 hours until smooth.
Sig. Spread thickly on lint and change twice per day

(2) Add 10 per cent benzocaine if pain.

(3) Add 1–1000 5-amino acridine if mild sepsis.

Proflavine in paraffin can be used, though this dressing is apt to make granulations œdematous and indolent. It is not as effective as the above ointment.

Attention to general treatment is important. Extra nourishment, intake of fluids, and iron therapy are useful.

PRE-OPERATIVE X-RAY THERAPY

Moderate Dose and Immediate Operation.—If the local disease is not clearly limited, or if doubt exists as to the extent of lymph-node spread, a single exposure to X rays is given up to 1000 r tissue dosage followed by operative removal. This is approximately a mild erythema dose, but is sufficient to affect adversely the actively growing neoplastic cells. Mitosis is significantly arrested, cell division aborted, and a proportion of actively malignant cells are killed outright. The malignant cells, therefore, near the margin of the field of operation, which may be spilled or left behind—the forerunners of local deposits—are inactivated.

Since there is a latent period between the initial erythema and true erythema, any operative procedure should be planned between the third and seventh day after irradiation. If operation is undertaken in the presence of the erythema the tissues will be found to be œdematous and hæmorrhagic, and thus more liable to infection and to delay in healing.

The care, so essential in every operation for malignant disease of the breast, should be even more meticulous after pre-operative irradiation. Gentle handling of the tissues, careful attention to hæmostasis, and closure of flaps without tension to preserve an adequate blood-supply are all obvious but necessary points to be emphasized. Skin sutures should be left in situ until such time as satisfactory healing has commenced, which may take up to three weeks, and removal of a few sutures at a time is a wise precaution. Exposure of irradiated areas to strong sun or ultra-violet light must be avoided.

Full Dose and Delayed Operation.—The operability of a carcinoma mammæ may be in doubt because of its size, involvement of skin, extent of spread, or fixation to the chest wall. Such cases are given a full dose of X-ray therapy, up to 3000 r tissue dosage in two weeks, to the breast, axilla, internal mammary nodes, and supraclavicular region. The patient is then kept under observation, and after two months, when the reaction has subsided, many lesions will be found to have shrunk and become mobile. It is desirable to remove the residue in which potentially active malignant cells are locked in fibrous tissue. Ewing has stated that such cells are not viable and slowly die, but clinical experience has shown that the malignant process continues in a persistent fibrous mass.

Preferably, then, any persistent hard residue which is mobile and not of the frozen chronic œdema type is excised together with the limited area of telangiectatic skin and a volume of irradiated tissue.

After an excision, whether local or by a mastectomy, and which may necessitate rib resection with its attendant risks, a primary closure may be feasible or obtained by immediate grafting. For a large area, or if in the event of radio-necrosis* a block removal with a diathermy knife and electro-desiccation is performed, cover should be postponed until grafting becomes possible.

If, however, there are other definite contra-indications to an operation, a residual mass, although poorly radio-sensitive, may respond to further radiotherapy. (*See* Radium Treatment, p. 257, *and also* Chapter XII, p. 288.)

POST-OPERATIVE X-RAY THERAPY

Immediate.—Clinical experience has shown that, however early the disease appears to be when first seen, the late results indicate that dissemination has already occurred in some cases. There are no means of determining in which patients this is so, and most cases at any rate should receive post-operative therapy as soon as the wound has healed. This early treatment has the added advantage that hypertrophic scars are avoided.

Examination of tissue removed at operation shows that the presence of growth in the tissues over the upper abdominal wall is very rare, and since an inordinately long scar necessitates a wide field of irradiation—with consequent upset to the patient—limitation of operative exposure in this area is suggested.

Late.—Many cases are seen months or years after operation with nodules of growth on the chest wall, enlarged lymph-nodes, or with distant deposits. In all these cases radiotherapy can produce material improvement.

The treatment of such malignant disease on the chest wall depends upon the size and extent of the tumour. An isolated nodule is best treated by a radium or radon seed implant, but if multiple or confluent, nodules are best treated with X-ray therapy. The thin isolated nodules can be treated successfully with superficial X-ray therapy, the type used depending on the thickness of the lesion ; the thinner it is the softer the X rays required. A range of X rays produced at 30–100 kv. is available and an adequate dose is 5000 r in one week.

If, on examination, a granular feel of the skin is noted round a single nodule this usually indicates the presence of further very

* In the event of radio-necrosis a biopsy should be performed and the tissue for examination should be removed to a depth sufficient to exclude underlying malignant tissue.

early nodules. In such cases, and in those where multiple nodules are evident, X-ray therapy covering the whole area is required. The dosage employed depends upon the general health of the patient as well as the extent of disease, and the greater the affected area and the poorer the patient's condition the less and more protracted the dose. When glancing fields of medium size are employed a dose of 3000 r in 2 weeks is possible, but in cases of cancer *en cuirasse*, where wide fields have to be used, a dose of only 3000 r in 4 weeks may be achieved and the integral dose must be carefully watched for it is essential to avoid constitutional upset as far as is possible.

In those patients who present a painful diffuse swelling over the upper third of the sternum, commonly extending more to the right

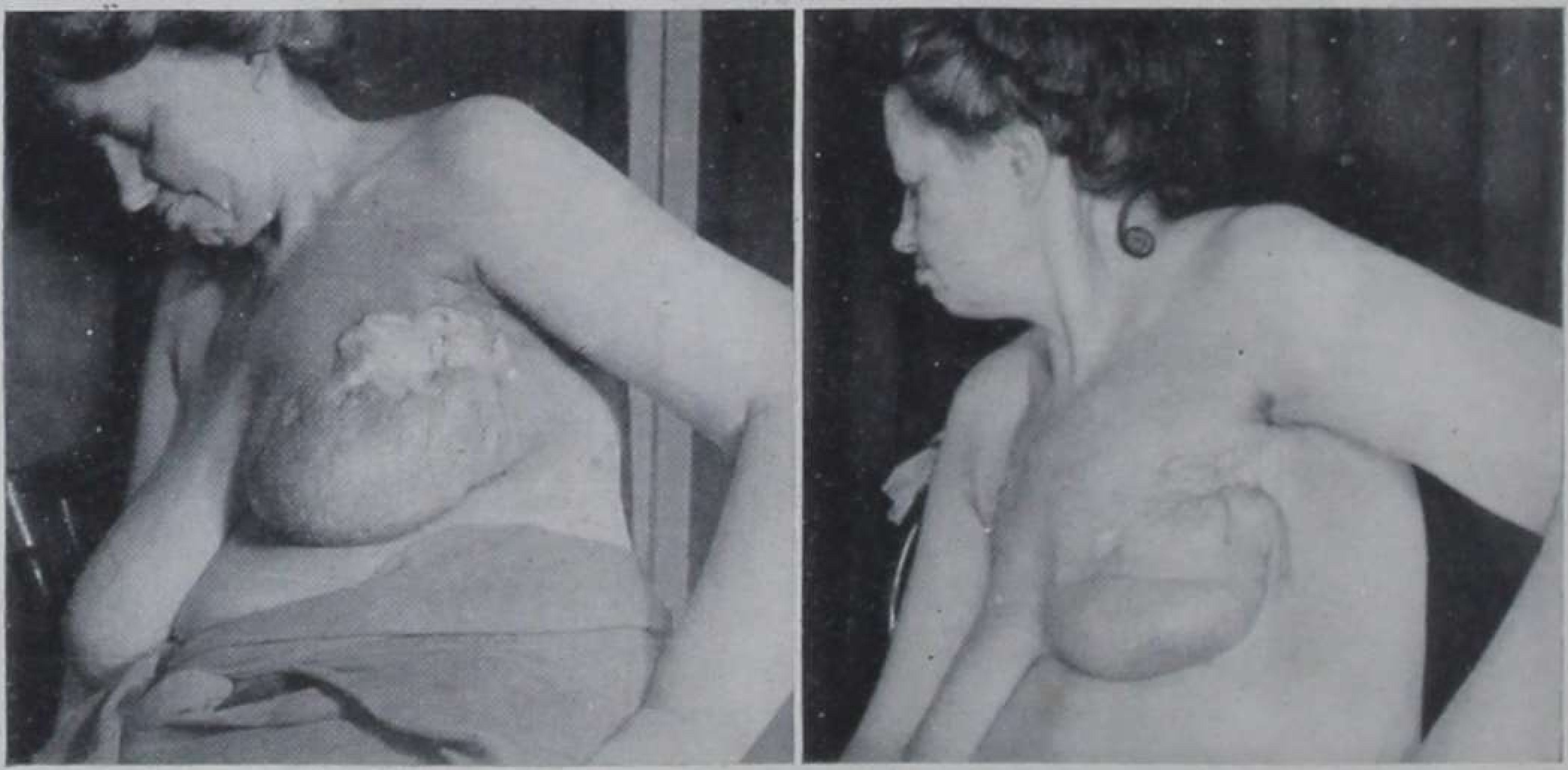


Fig. 149.—An example of palliative treatment by deep X rays. Before and after treatment.

than to the left, a full dose of 3000 r in 2 weeks can be given by two fields at right angles using wedge filters. In almost every case the pain disappears and the swelling subsides.

In the case of massive axillary and supraclavicular nodes deep X-ray therapy to full dosage is given and most cases respond; this affords great relief to those patients in whom the gross œdema of the arm thereby diminishes.

Much suffering can be alleviated by treating large ulcerated surfaces, for although the ultimate prognosis is usually hopeless, the offensive discharge diminishes and the ulceration will often heal. This also applies to the comparatively few patients with carcinoma of the breast who do not seek advice until the primary tumour has fungated. *Figs.* 144–146 show sections of a fungating growth (measuring 14 × 9 × 5 cm.) of such a patient (*Fig.* 149) in which the ulceration healed after treatment and the patient lived quite comfortably for 5 months, though intrapulmonary deposits were known to exist at the time of the first attendance.

TECHNIQUE OF RADIOTHERAPY

X-RAY TREATMENT

Control of Settings.—Since the X-ray method necessitates exposures over a number of days, precautions have to be taken to ensure that the required treatment conditions can be reproduced

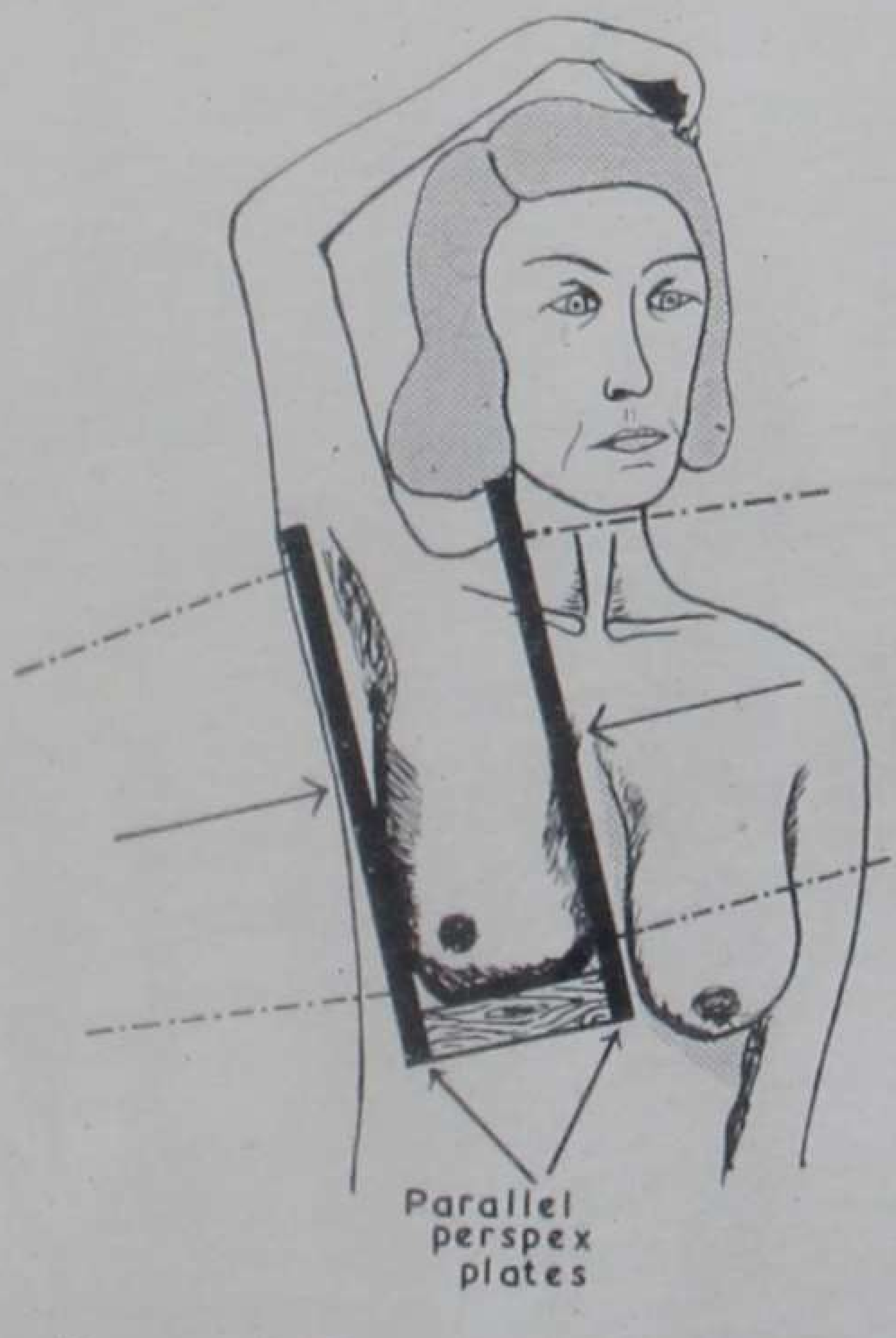


Fig. 150.—Application of paralle fields to the breast and axilla.

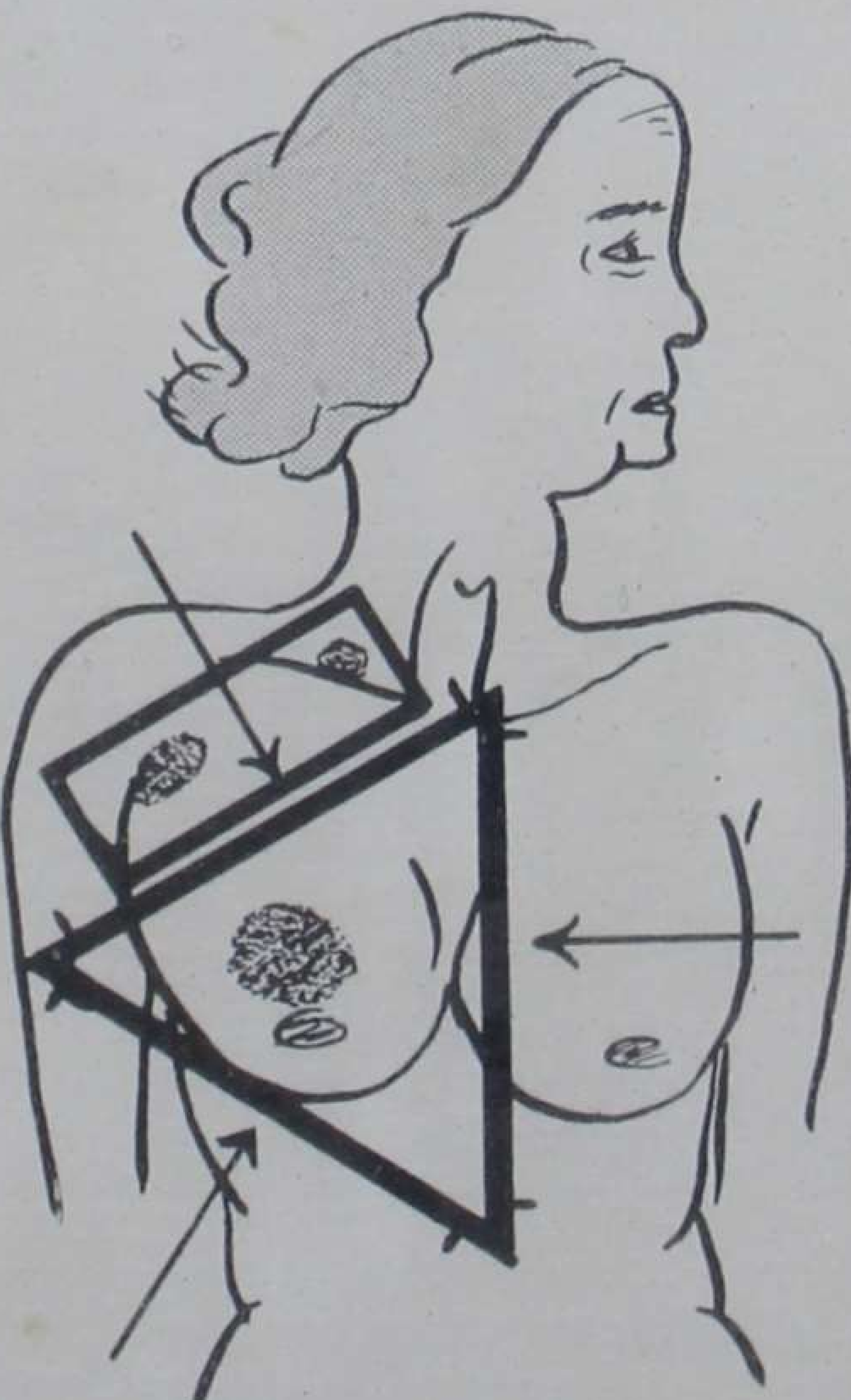


Fig. 151.—Application of triangle of fields to the breast.

accurately. To achieve this the site of application on the patient is marked with a red dye (basic fuchsine) the lines being intensified as they gradually wear off over a period of days. The position of the patient is carefully noted and the direction of the X-ray beam is recorded from the angles shown on scales attached to the X-ray tube.

Illustrations of Breast Technique.—*Figs.* 150–157 show the combination of fields used at the Royal Northern Hospital. It will be clear that the choice of field arrangement depends upon the site of disease and its extent, the variations of which demand several alternatives.

The two parallel fields shown in *Fig.* 150 are particularly suitable for old people in whom the breast and axilla only need to be treated; these shallow glancing fields reduce the body or integral dose, and therefore constitutional effects, to a minimum.

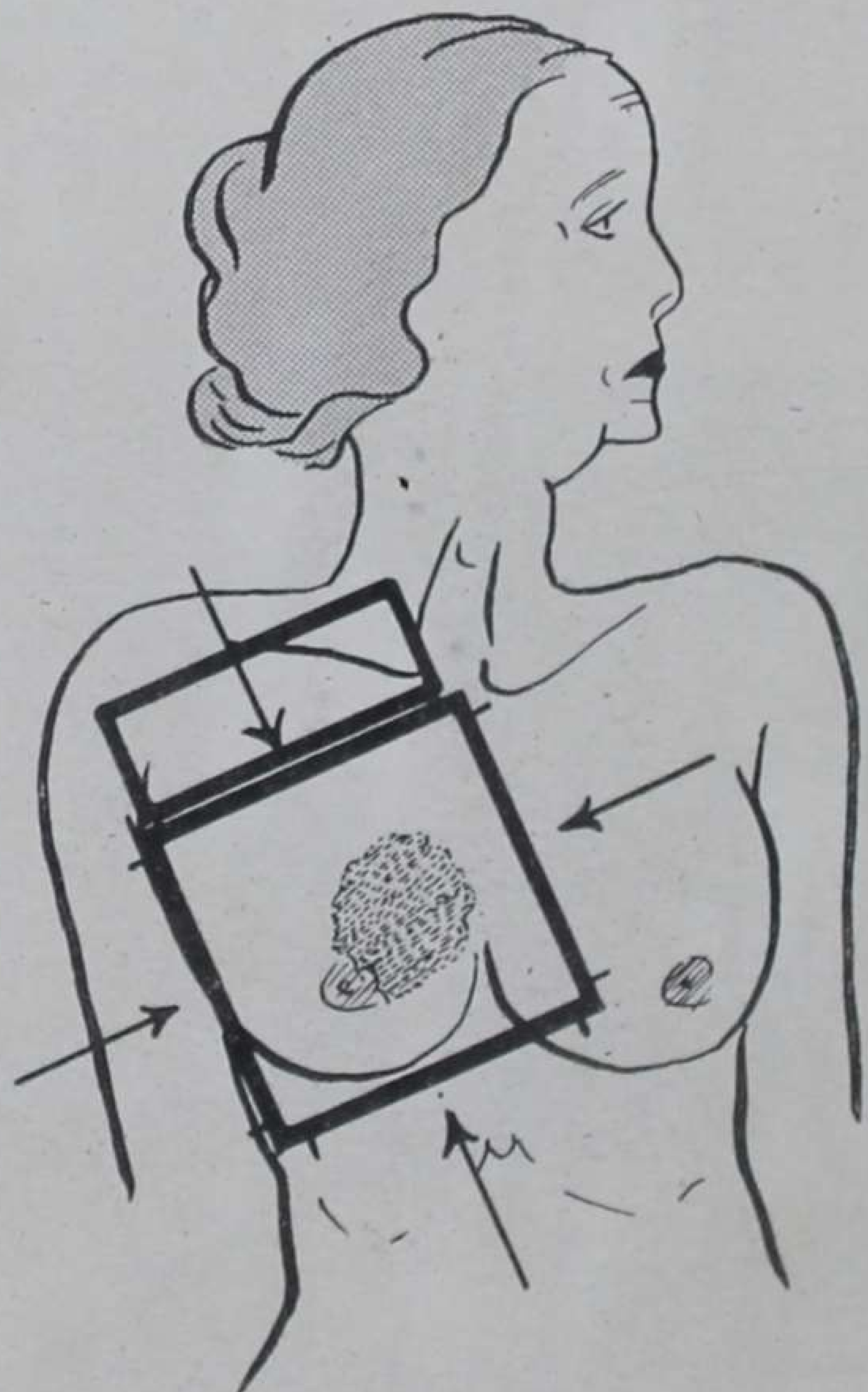


Fig. 152.—Application of square of fields to the breast.

The triangle of fields to the breast is the one most commonly employed, as this irradiates the internal mammary nodes and the chest wall satisfactorily with the minimum integral dose for intense local treatment (*Fig.* 151). The axilla is treated first, 3000 r in 2 weeks, followed by the chest wall, 3000 r in 2 weeks. This reduces the integral dose per week and is well tolerated. If the breast lesion is large the triangle may be replaced by the square arrangement (*Fig.* 152).

The rectangular and pentagonal arrangements of fields (*Figs.* 153 and 154), though theoretically ideal, are difficult to apply in practice, since the constitutional effects of irradiation of such an extensive volume of tissue are poorly tolerated by the patients ; these methods are, therefore, not commonly employed.

Irradiation of the axilla and supraclavicular regions is usually accomplished by the use of parallel fields, one anterior (*Fig.* 151) and one posterior (*Fig.* 155), to form a sandwich. In the case of very round-shouldered subjects, the posterior field is divided into two so

Fig. 153.—Application of rectangle of fields to the breast.

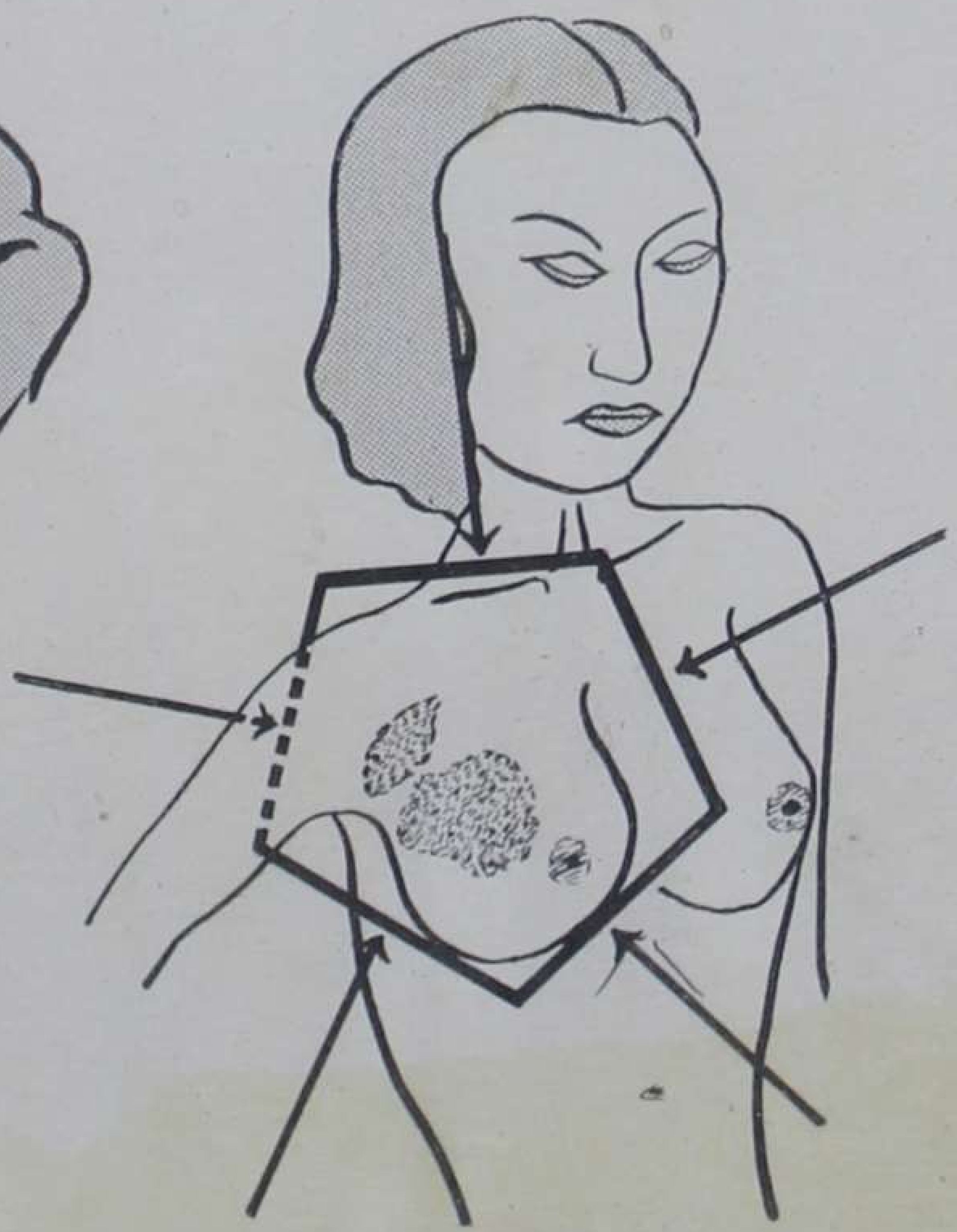


Fig. 154.—Application of pentagon of fields to the breast.

that a better depth dose can be achieved (*Fig.* 155). Occasionally the breast may be included in such fields (*Fig.* 156).

In very fat subjects it may be necessary to place an additional field pointing directly into the axilla to avoid overdosing the skin, and when this is done the incident skin dose is calculated so that the direct axillary skin dose is 50 per cent of the anterior and posterior fields. This method, however, is avoided whenever possible, as the even physical distribution, obtained by sandwich fields alone, is upset.

In treating the supraclavicular nodes with the internal mammary nodes, two beams at right angles, using wedge filters, are used (*Fig.* 157) (*see* PHYSICS, p. 233).

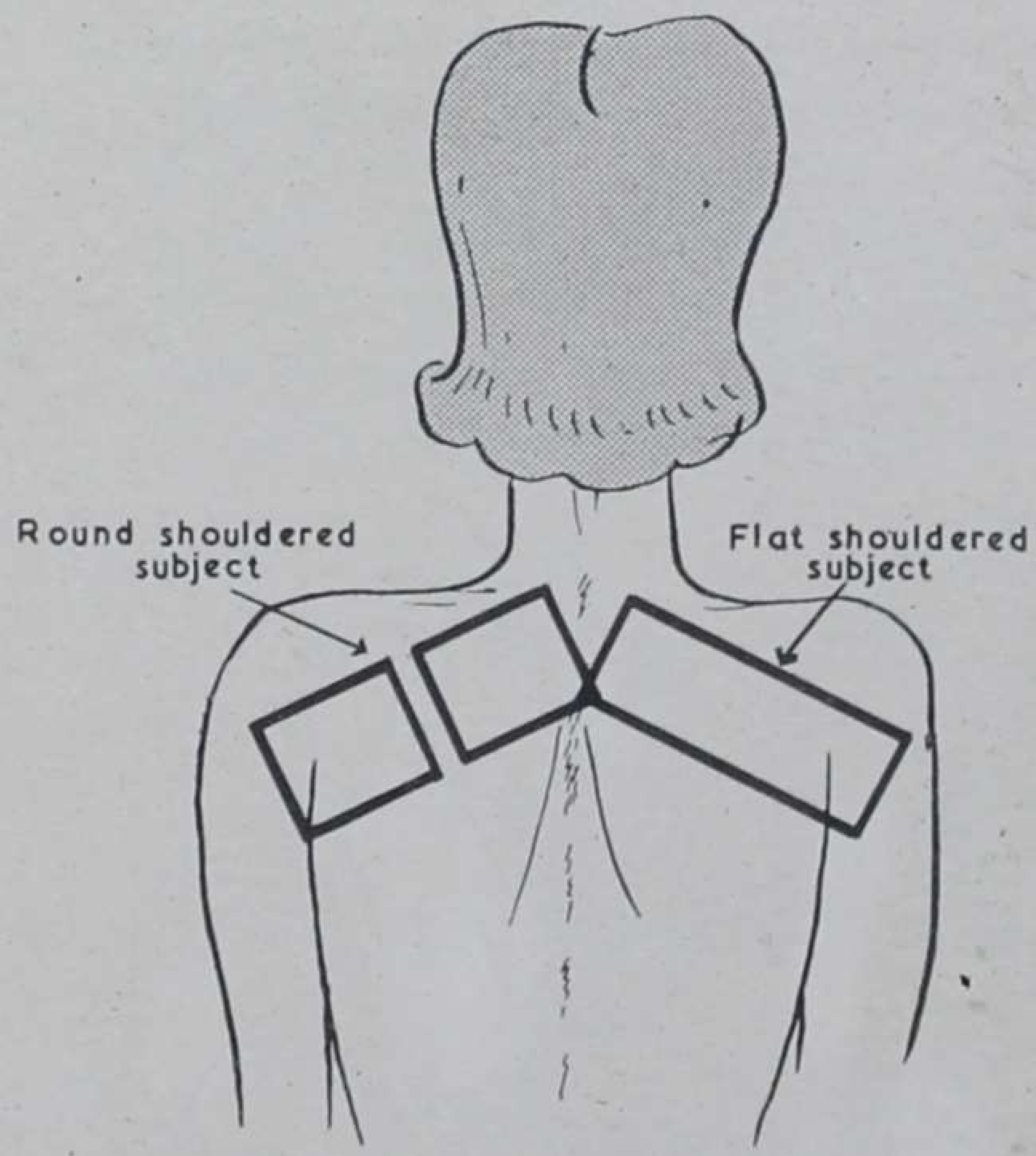


Fig. 155.—Application of posterior fields in axilla and supraclavicular sandwich.

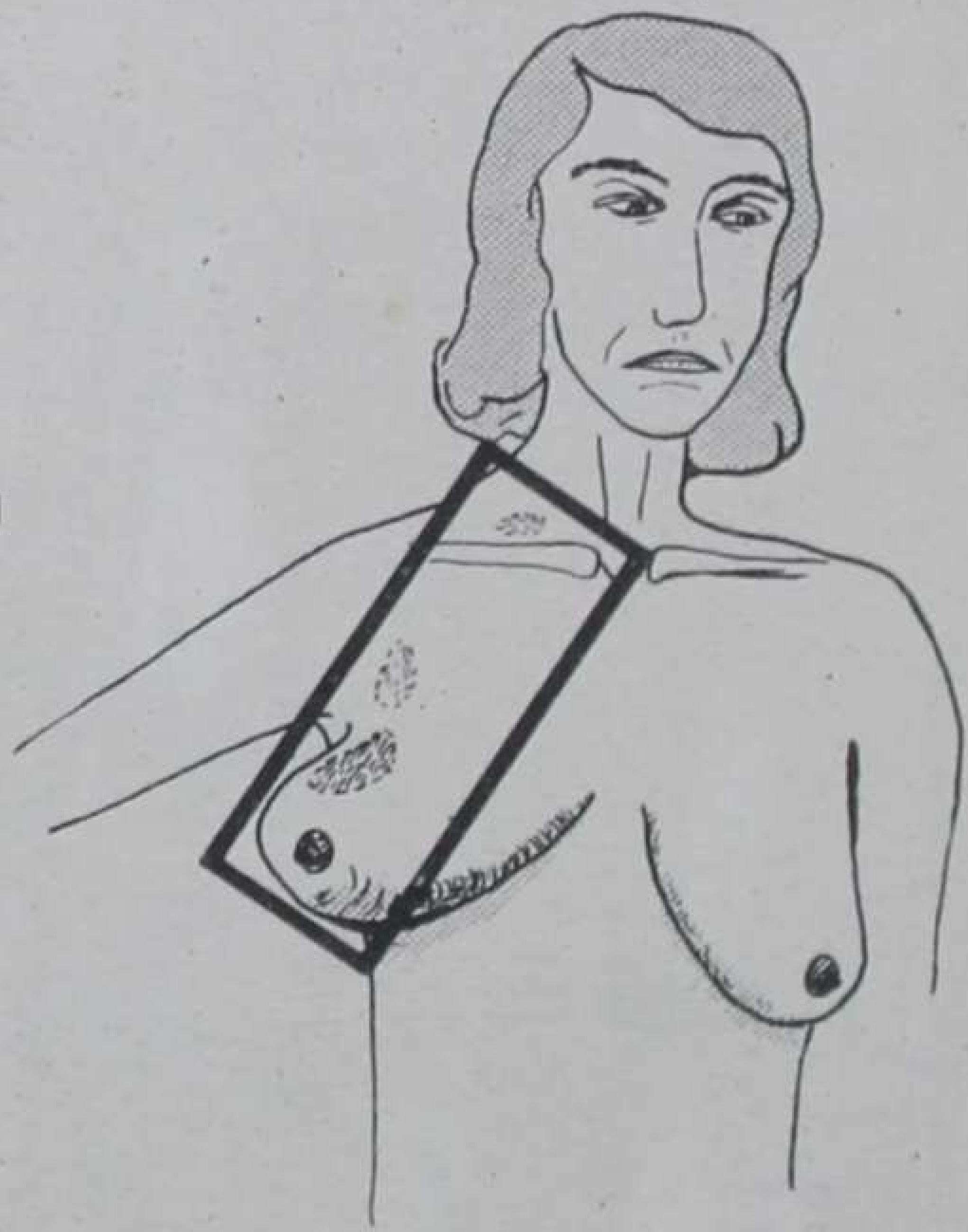


Fig. 156.—Application of parallel fields to the breast, axilla, and supraclavicular region.

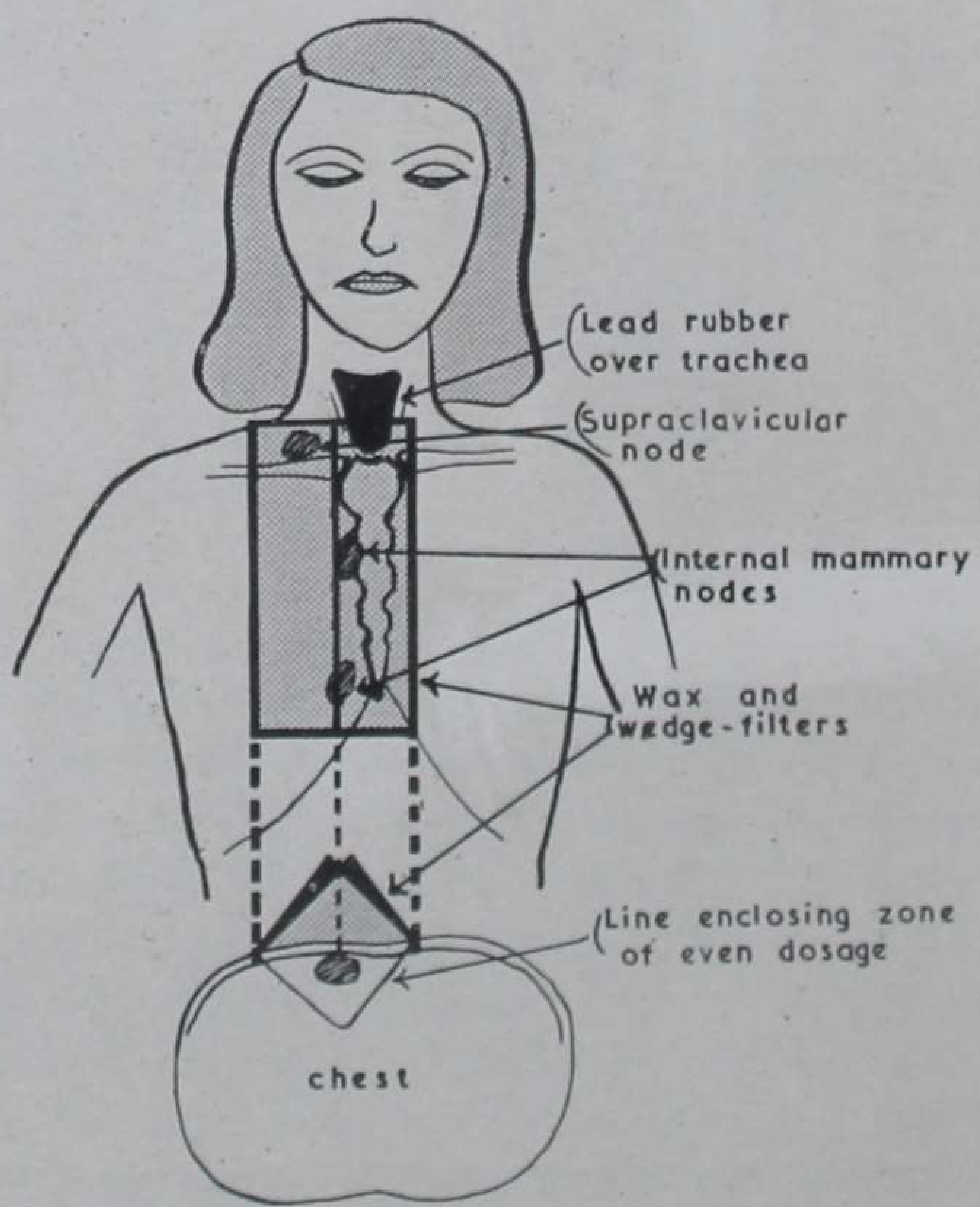


Fig. 157.—Method of X-ray treatment to internal mammary and supraclavicular zones.

The isodose charts for such arrangements of fields are shown in *Figs.* 158–162.

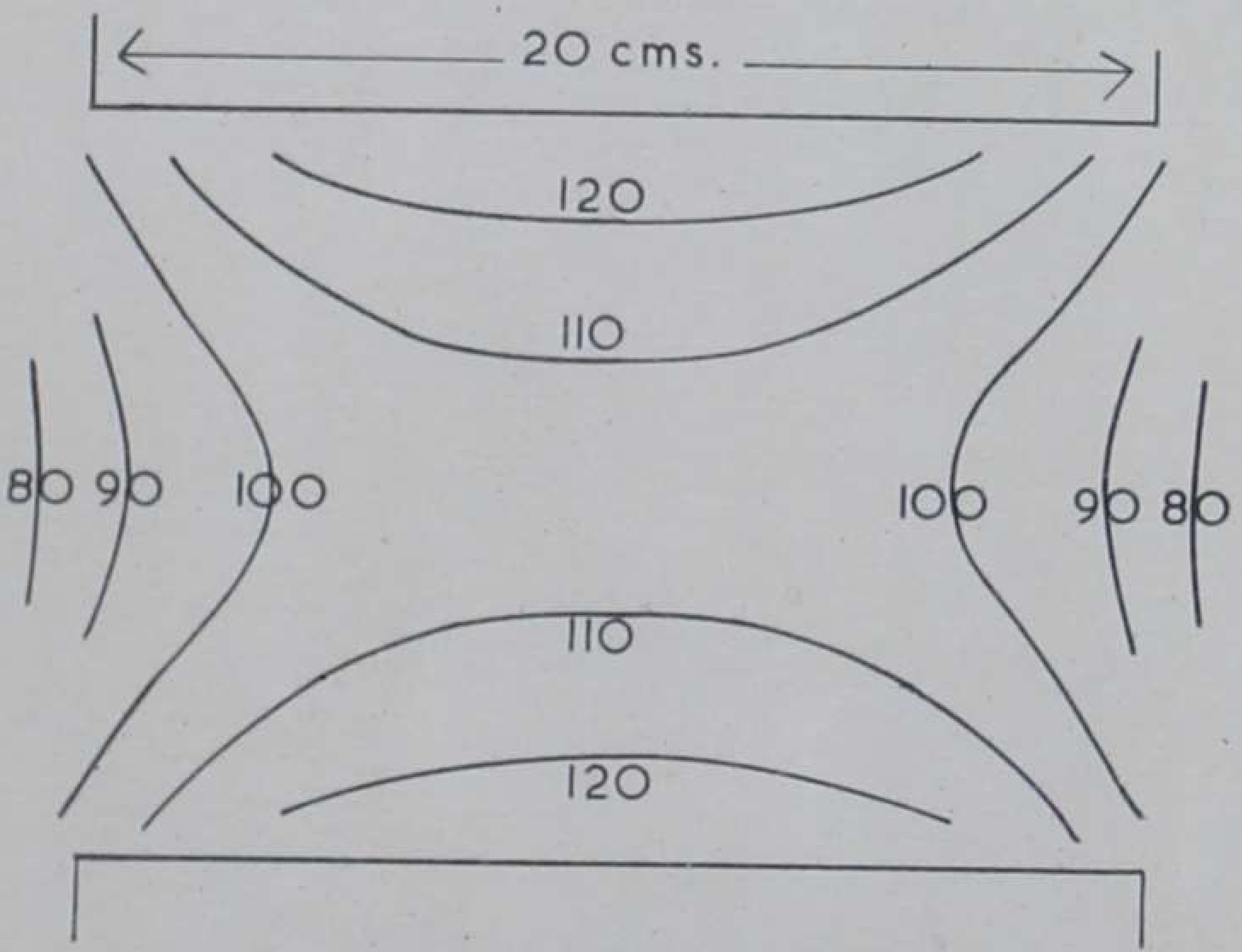


Fig. 158.—Isodose chart for parallel fields to the breast and axilla. Two 8 × 20-cm. applicators at 50 cm. f.s.d. Fields opposing, 14 cm. apart. Dose in r per 100 r (incident with back scatter) at applicator surface in each position.

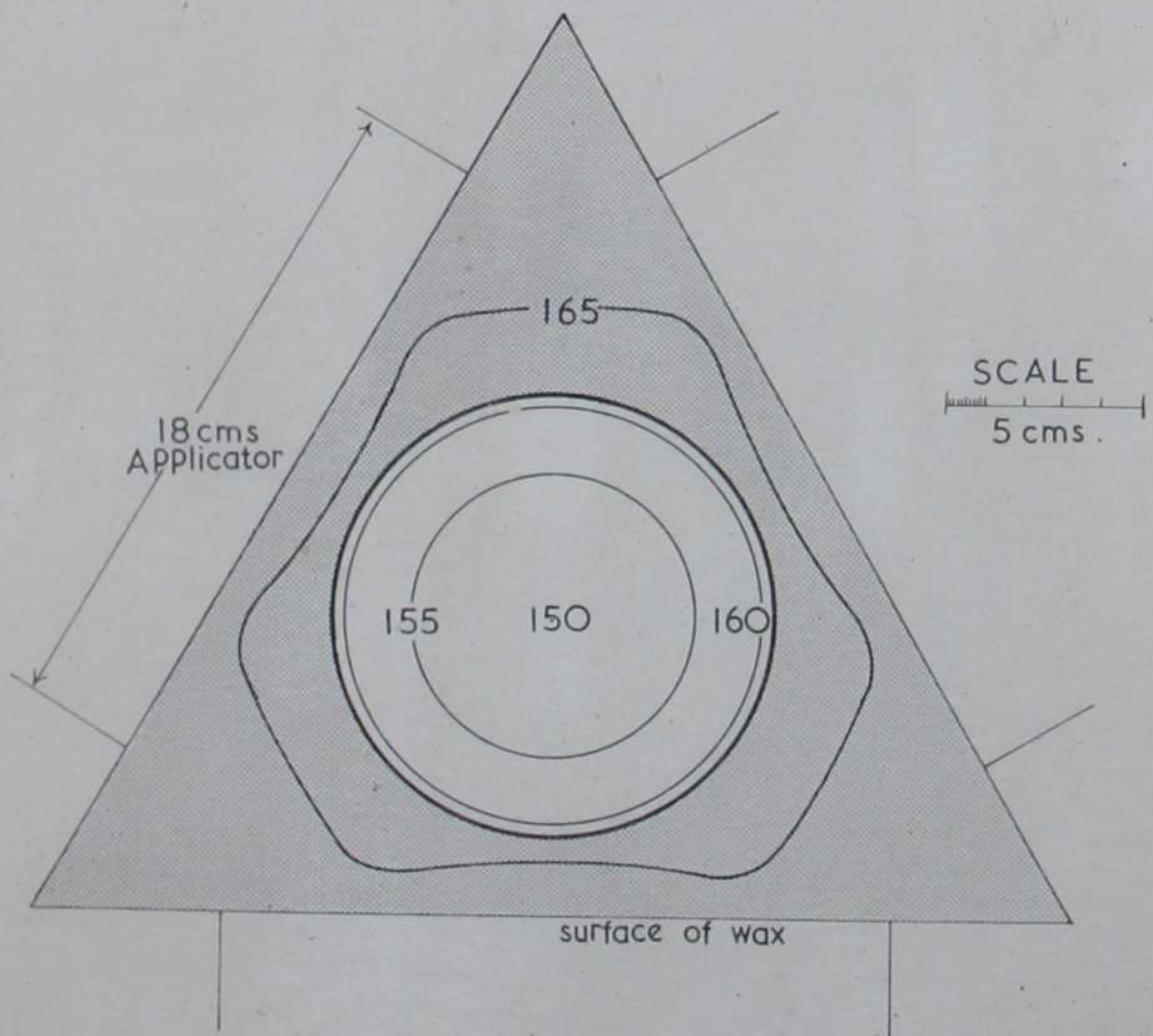


Fig. 159.—Isodose chart for triangle of fields to the breast. 10 × 18-cm. applicator at 50 cm. f.s.d. Dose details expressed as in *Fig.* 158.

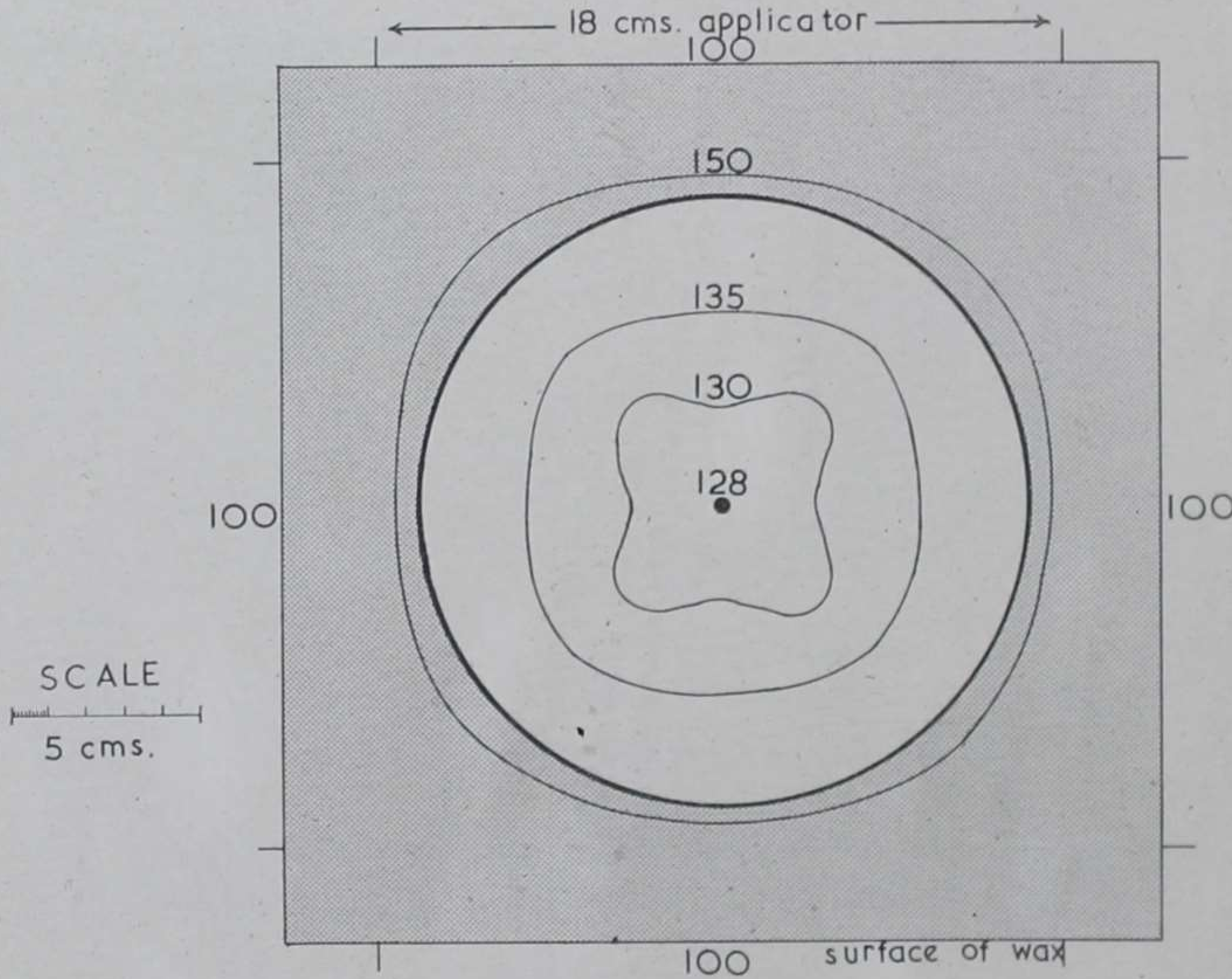


Fig. 160.—Isodose chart for square of fields to the breast. 10 × 18-cm. applicator at 50 cm. f.s.d. Dose details expressed as in *Fig.* 158.

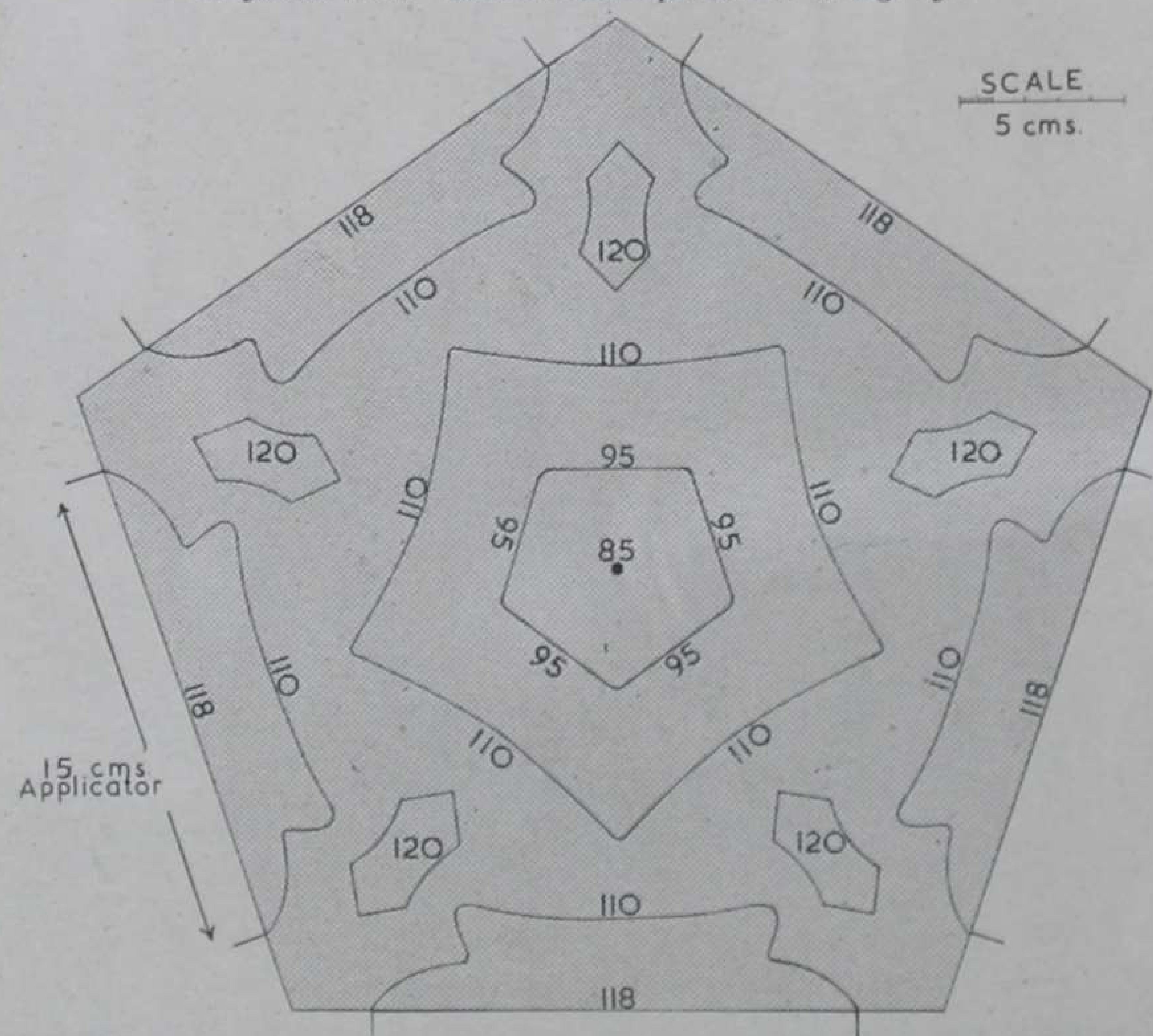


Fig. 161.—Isodose chart for pentagon of fields to the breast. 15 × 8-cm. applicator at 50 cm. f.s.d. Dose details expressed as in *Fig.* 158.

The choice of type of X ray to be used in the treatment of a given case depends upon the site of the lesion. For those which are situated deep to the deep fascia 'deep' X rays, usually produced at

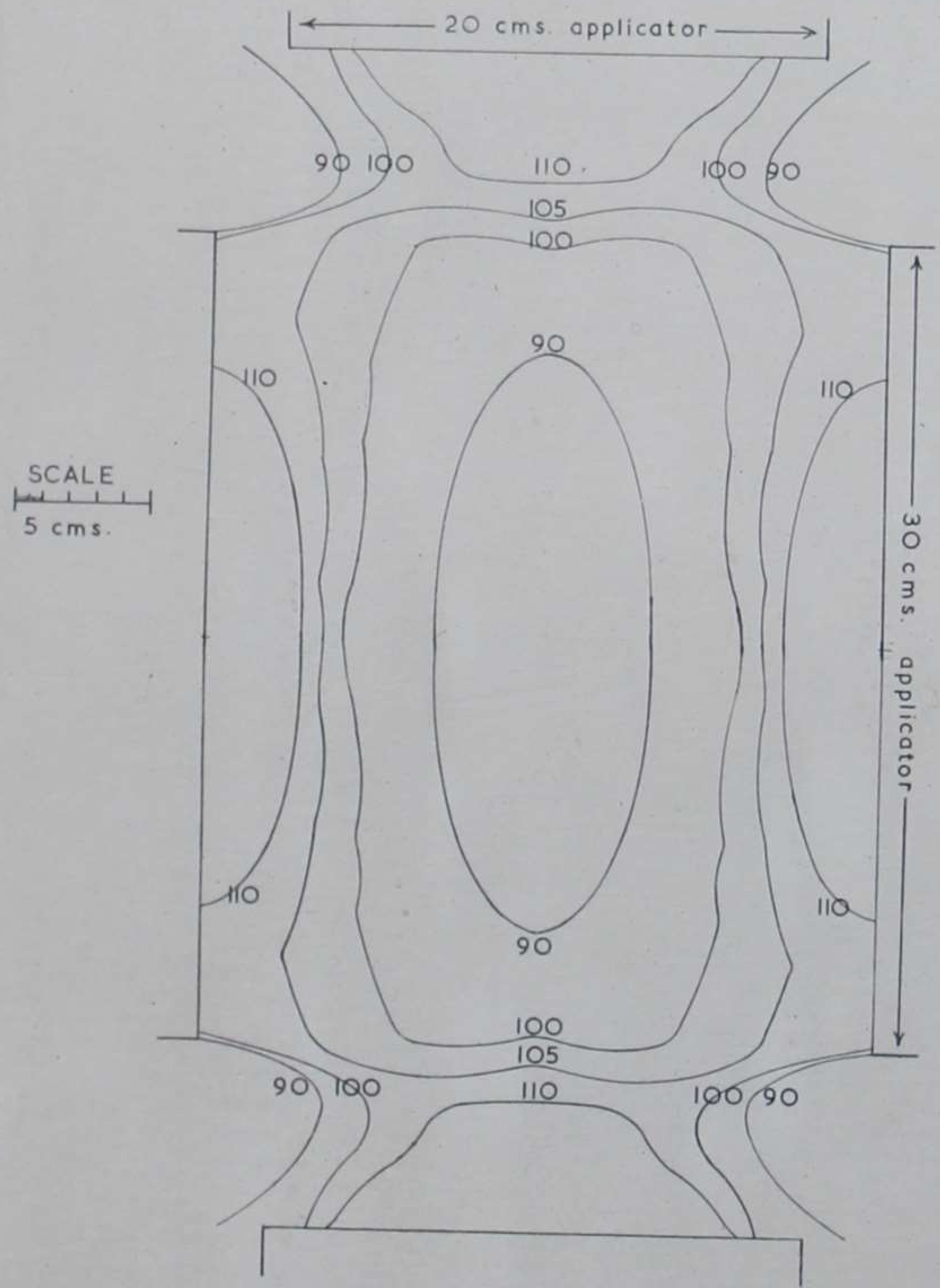


Fig. 162.—Isodose chart for rectangle of fields to the breast. Applicators at 50 cm. f.s.d. Dose details expressed as in *Fig.* 158.

about 200 kv., have to be used, whereas for superficial lesions 'superficial' X rays, produced at voltages up to 120 kv., are desirable. This will be understood by reference to *Figs.* 163 and 164. The kilovoltage across the beryllium-window X-ray tube shown in *Fig.* 164 is easily adjusted so that X-ray beams of varying, but known, quality are produced. By choosing the appropriate voltage the rapidity with which the depth dose falls can be adjusted so that an adequate dose can be delivered to the tumour without excessive dosage of the skin. At the same time the integral dose can be kept to a minimum.

The physical factors leading to the estimation of dose received are accurate when drawn on paper, but under treatment conditions difficulties, such as the configuration of the patient, arise and the

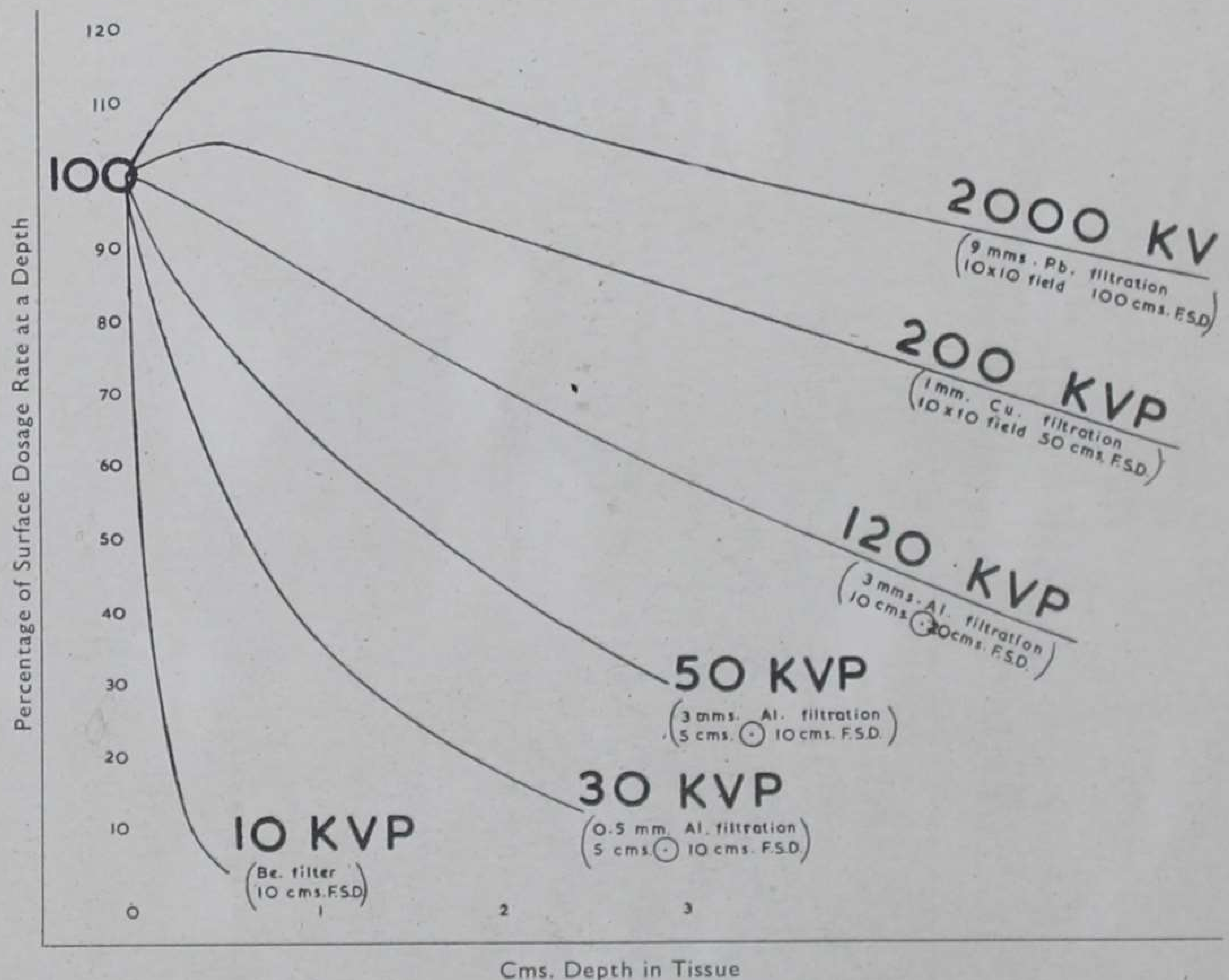


Fig. 163.—Showing the increase in depth dose with increase in voltage. (2000 kv. is experimental only.)

estimated dose is incorrect. Whenever possible the dose is measured by placing a small instrument at selected points on the patient which gives a direct reading of the dose-rate at that point (dosimeter).

Technical Appliances.—

The Directional Caliper.—Accurate settings are greatly facilitated by the use of this instrument (*Fig.* 165). It consists of a horizontal arm securely fixed to the X-ray tube-head along which a vertical telescopic arm can travel. A scale on the horizontal arm gives the distance of the vertical arm from the anode and a scale on the telescopic portion of the vertical arm gives readings of the distance the ball end is from the central axis of the beam. With the help of beam-spread charts the caliper can be set so that a glancing field can be accurately placed, for example a layer of tissue 2 cm. thick in the edge of the beam. The glancing fields used on the chest wall are set in this manner at

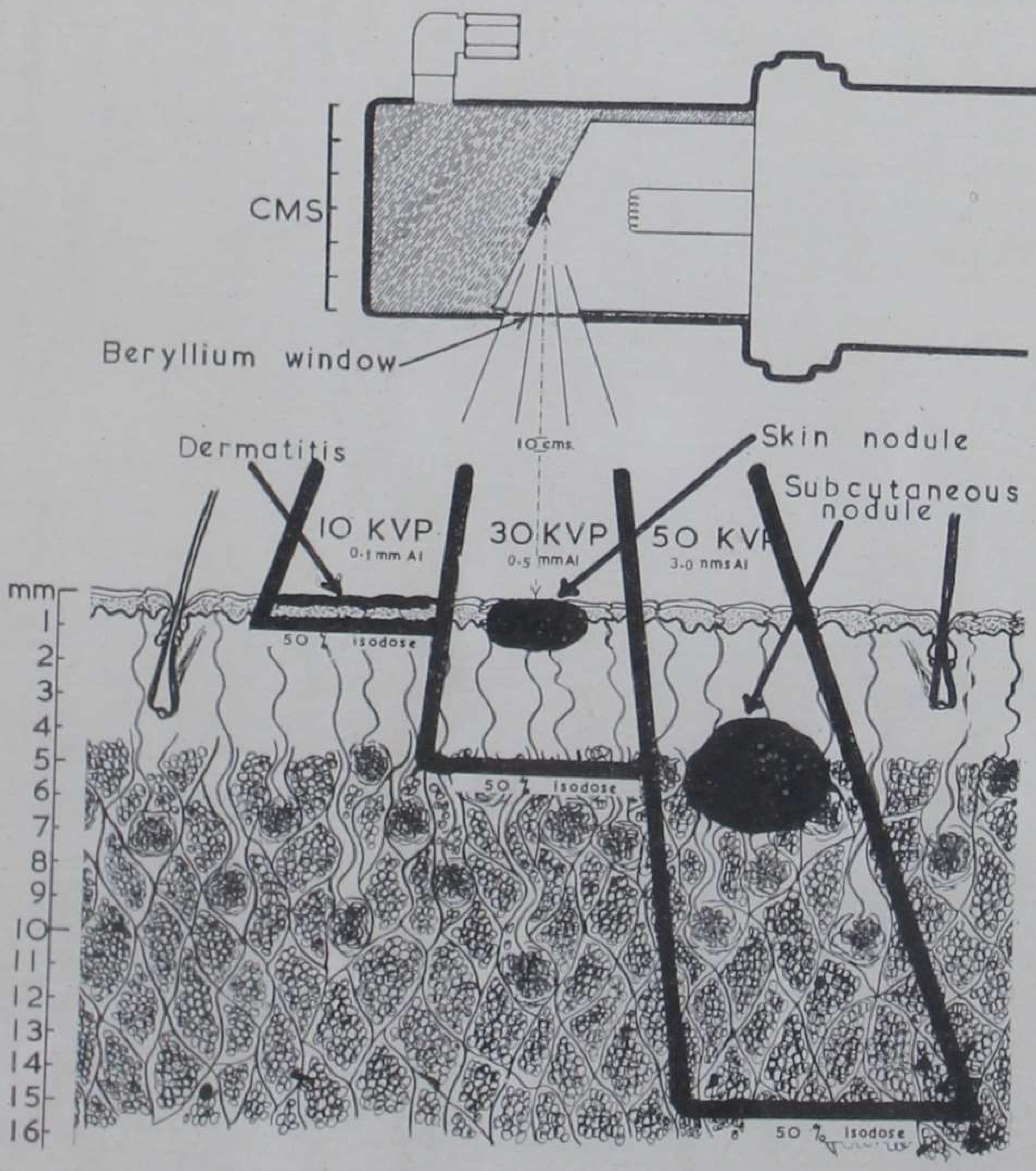


Fig. 164.—Three examples of treatment of breast conditions with low-voltage beryllium-window X-ray tubes, showing the wide range provided by the machine.

the first treatment and tube angles are then recorded for the future settings.

The Cut-away Applicator.—The normal applicator can only lie in contact for the whole of its length if the patient's chest is flat. This is rarely the case, so that a cut-away applicator was designed (*Fig.* 166). With this a free space is provided in which the curve of the chest wall can be accommodated, and a flexible lead rubber sheet replaces the inferior wall of the applicator to protect the areas which are not to be treated.

Plaster and Wax Moulds.—When the normal applicator is used the resultant air gaps have to be filled with material of similar density

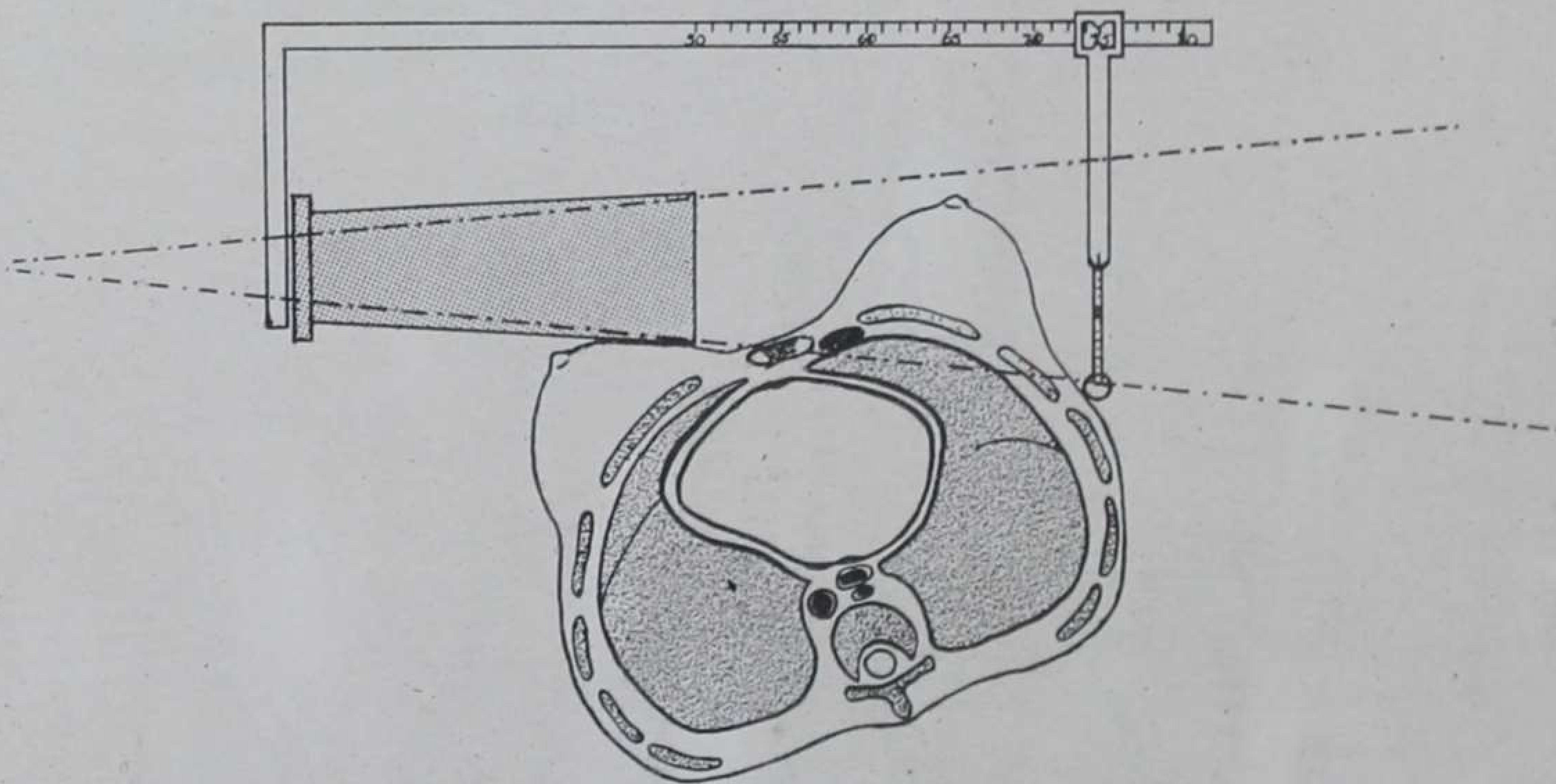


Fig. 165.—Use of directional caliper for glancing fields in treatment of breast and internal mammary nodes.

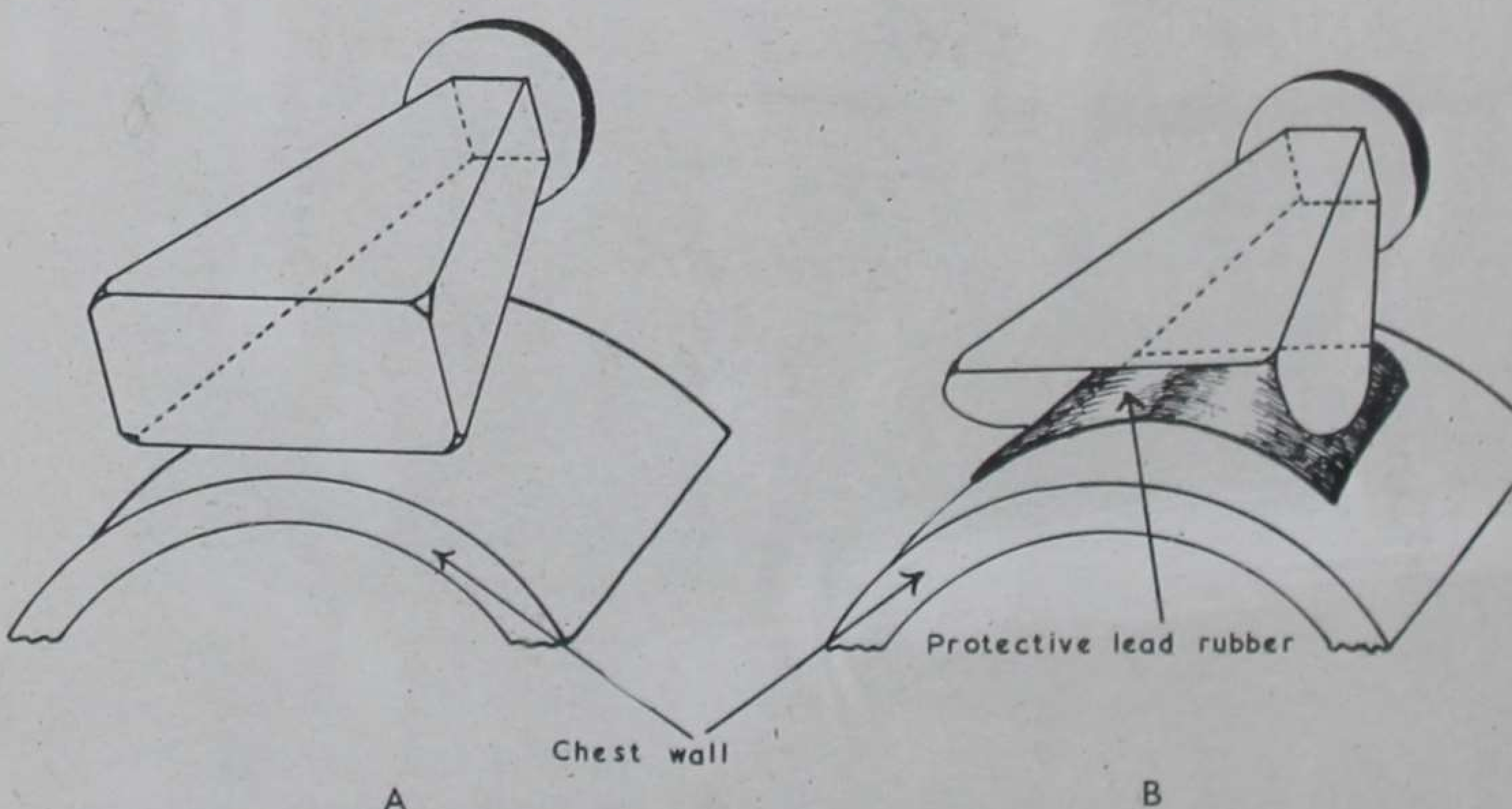


Fig. 166.—Use of cut-away type of applicator for curved surfaces. A, Standard type applicator; B, Cut-away type applicator.

to human tissue, for otherwise the physicist's isodose curves do not apply. This is commonly, though imperfectly, done by packing the gaps with bags containing a powdered mixture of chemicals. A superior method is to use paraffin wax, the density of which is close to that of human tissue ; this is moulded to fit the patient and the applicator. The construction of the blocks entails much labour, but the advantages of their use are great for special cases.

The construction of any type has a number of similar stages. First, the patient's skin is marked with dye to indicate the treatment zone and fields required with the patient in the treatment position ; the skin is greased with vaseline petroleum jelly and a thin plaster-of-Paris shell applied. When this has set (after a quarter of an hour) it is removed from the patient and a wall is constructed of plaster bandages to enable a plaster-of-Paris cream to be poured in. After this has set (after about half an hour) the shell is removed and a cast of the patient with skin markings is obtained.

A wall is then built on the cast using cardboard or other suitable material, and the inside of the cavity painted with a solution of X-ray film base in acetone. This prevents the wax from adhering to the walls. Areas such as the larynx, or telangiectatic areas from previous treatment, not to be treated, are covered with lead rubber, which is incorporated in the final wax mould. Wax, at a temperature where the main mass is liquid but the surface shows a thin ' skin ', is poured in. After a further twelve hours the walls around the wax are removed and a wax mould fitting the patient's contour is obtained.

The further steps depend upon the type of applicator surface required, the wax being shaped by means of a heated metal plate on a wooden handle. In the case of a wax for use with X-ray beams at right angles with wedge-filters, a right-angled hot plate is used.

Plaster casts are also of great value in planning treatment, for they can be sawn through and hollowed out to re-construct the tumour. The arrangement of fields to ensure complete coverage is thus greatly facilitated.

Radium Treatment

Irradiation of the Breast.—

Post-X-ray Residues.—It has already been stated that whenever possible a residue remaining after X-ray therapy should be removed, but if major surgery is contra-indicated or refused, intense local treatment by radium provides an alternative. It will be appreciated that in the technique of radium implantation accurate spacing of the needles is essential since the intensity of radiation falls rapidly with distance. If the needle points converge, a so-called " high spot " with local necrosis may occur, whereas divergence leads to a volume of under-dosage which is ineffective. The problem of mixed necrosis and malignancy cannot satisfactorily be solved by radiotherapy, and the surgical excision of a wide area by diathermy becomes necessary.

At the Royal Northern Hospital a technique is employed the principles of which govern all radium implantations. Needles are inserted through guides, constructed for the individual case if necessary, made of perspex or metal to fit any curved contour. The perspex type most commonly used is longitudinally cut, the two halves being held together by screws. At insertion the lesion is clearly marked on the skin, and by measurement the line of insertion of

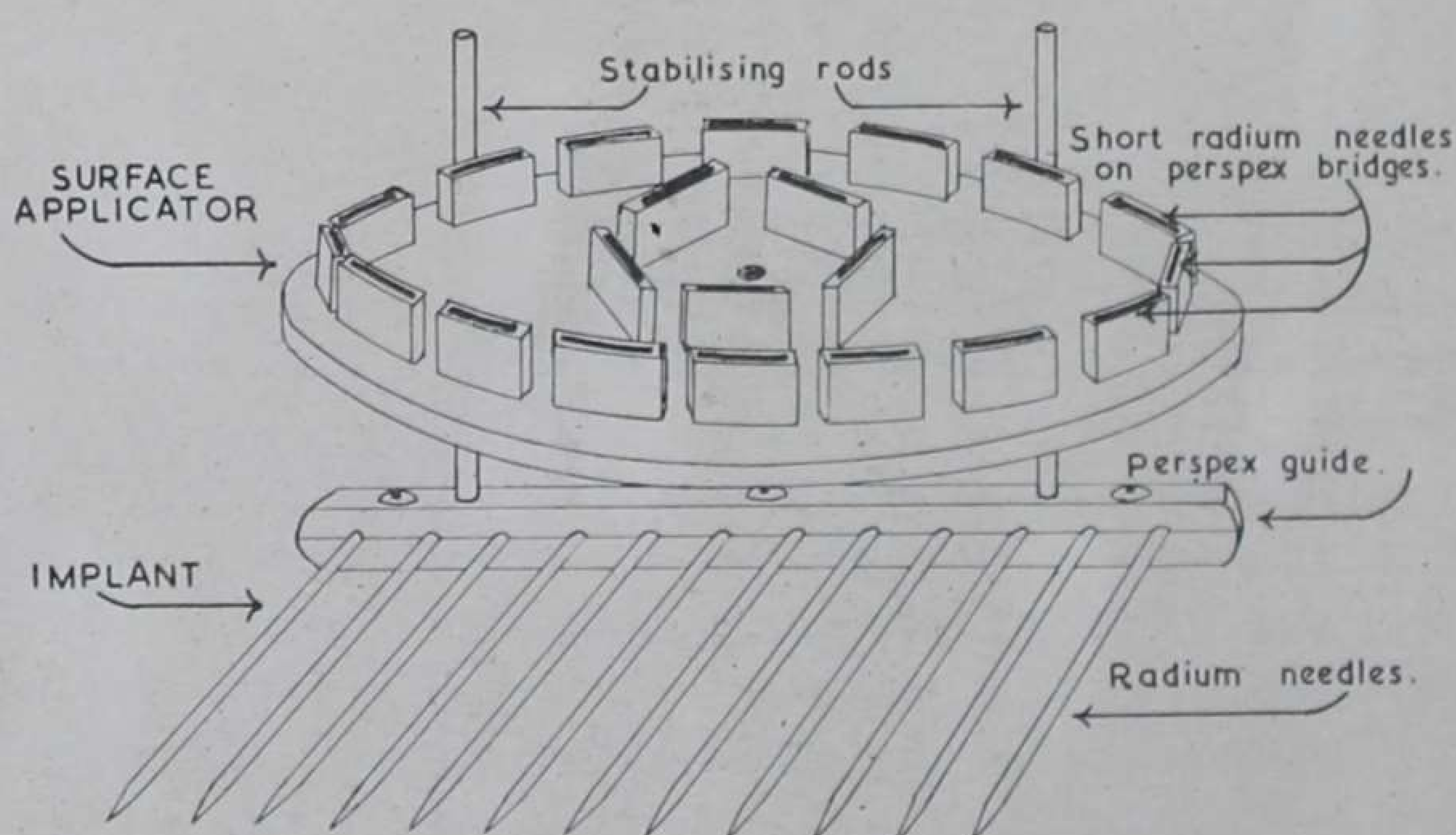


Fig. 167.—Combined implant and surface applicator. The grid of radium needles is placed deep to the breast tumour. This grid may be curved to fit the chest wall in large breasts. The perspex plaque is then placed over the breast and compressed to the required distance.

the needles is determined. The skin is punctured with a tenotomy knife and the end needles are inserted first through the guide into the tissue at the correct plane. When all needles have been introduced the screws are tightened to clamp the needles in place. The width of the perspex holder in breast cases is 1 cm., so that the needles are parallel as they are introduced and subsequently remain parallel. It should be pointed out that the needles are hollow and loaded with radium cells according to the physicist's instructions. Sufficient space is allowed at the eye end of the needle to be filled with ' blanks ' and ensure that the skin around the point of entry does not receive excessive dosage, as would occur with the permanently loaded type of radium needle. *Fig.* 167 illustrates a combined implant and surface applicator, and *Fig.* 168 shows a radiograph of another after insertion of the needles with the surface plaque in place. The results of this method of achieving the physicist's requirements are consistently good and simple to attain.

In the treatment of breast residues three methods are available. First, the commonest used is the combined single-plane implant and surface applicator. The implant is placed deep to the mass and by means of the applicator shown in *Fig.* 167 the two planes are held parallel, and it is usual to arrange the radium loading so that for all practical purposes there is even irradiation between them. The

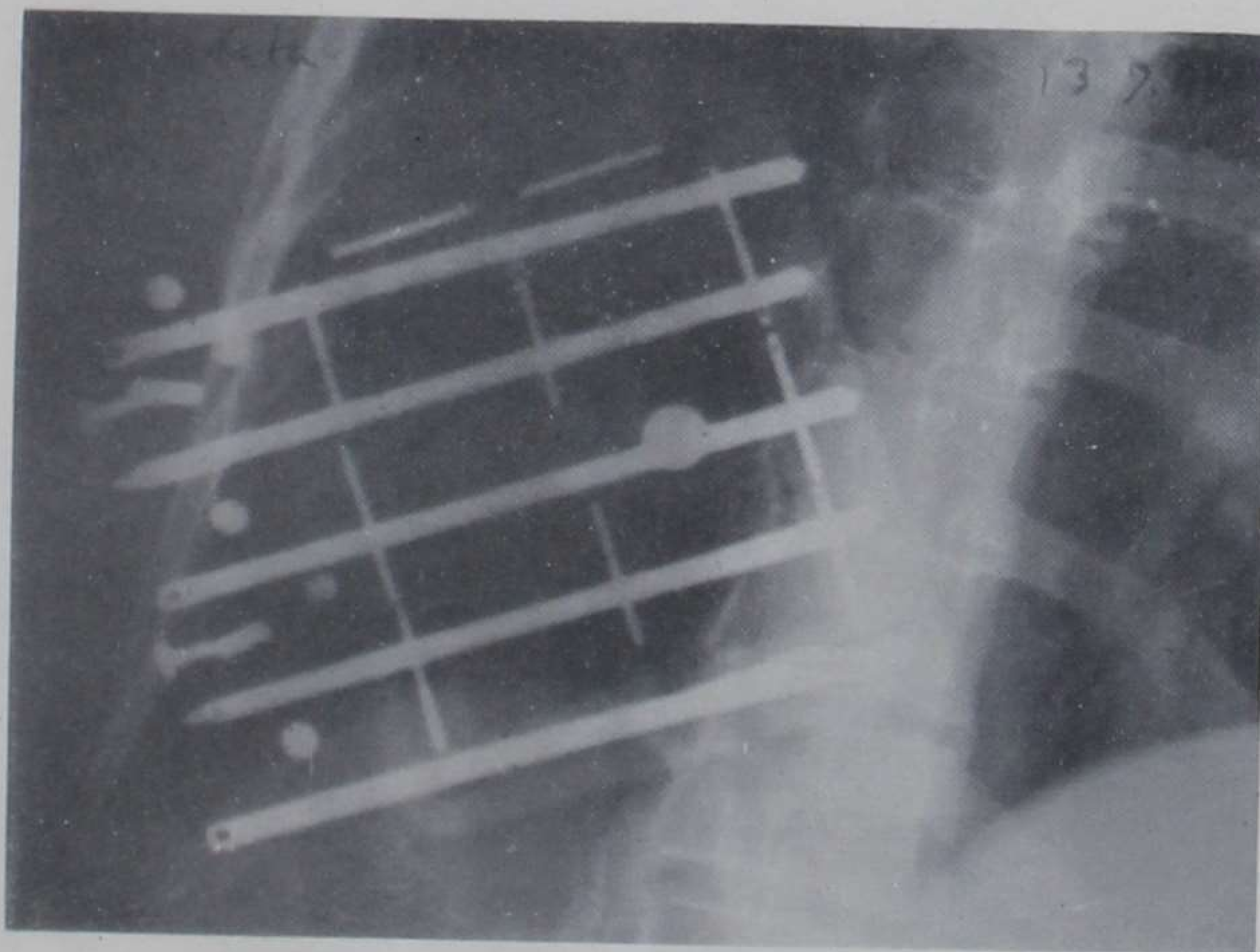


Fig. 168.—Radiograph showing radium needles in position in breast with the overlying surface applicator.

total dosage given is determined by the skin tolerance, but an adequate dose to eradicate the growth can be achieved, usually 6000 r in one week. Because of the time-dose ratio it is possible to reduce this time and dosage and still achieve the same biological effect. This is particularly valuable in the patient who is old or in poor general health, for the integral dose upon which the constitutional effects depend is lessened. It is possible to arrange the loading of the radium so that a graduated dose is obtained from the skin level to the deep plane. This method causes less skin reaction but carries a risk of deep necrosis, and in such treatment a dose of 8000 r at 5 mm. from the deep plane is considered safe.

Secondly, a two-plane implant is used occasionally provided the lesion is not close to the skin. A high tumour dosage can be achieved with minimal skin reaction. This method is used by Cade and Keynes.

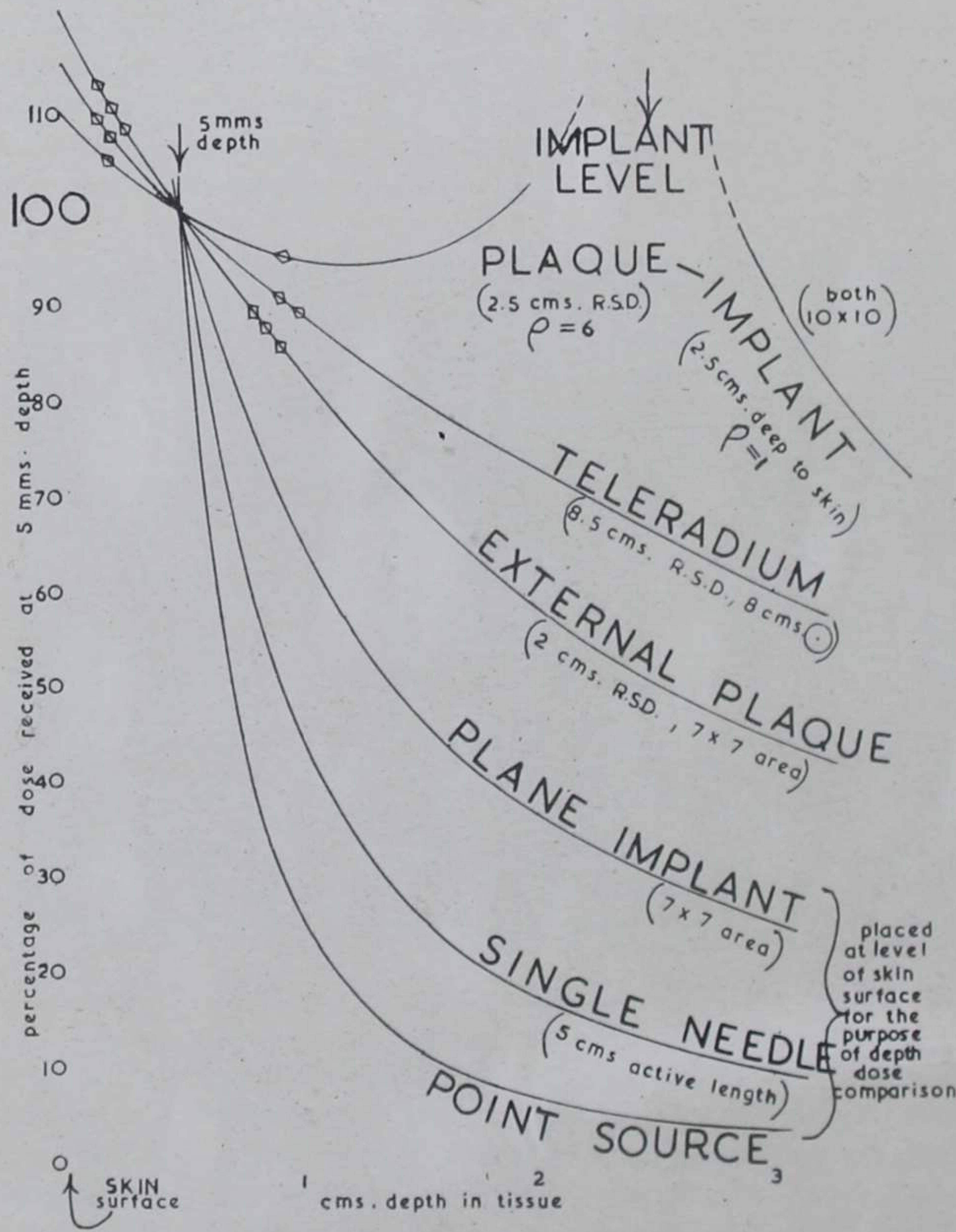


Fig. 169.—Graph of depth dosage with varying radium methods, showing the superiority of the plaque implant method for uniform dose.

Thirdly, in a thin breast it may be possible to use a single plane alone. There is the danger, however, of intense irradiation of the underlying ribs if adequate dosage from the point of view of the neoplasm is used.

The superiority of the plaque-implant method is seen graphically in *Fig.* 169. A point 5 mm. below the skin surface is taken and the dose received at the point by different methods of application is taken as 100. The curves show clearly how the depth dose falls according to the source of irradiation. It is most rapid if a point source of radium is used, less rapid with a needle source, and least with tele-radium when radiation from the skin surface alone is used. For example, at 2·0 cm. deep a point source gives only 6 per cent whereas teleradium gives 72 per cent. When a surface plaque and interstitial

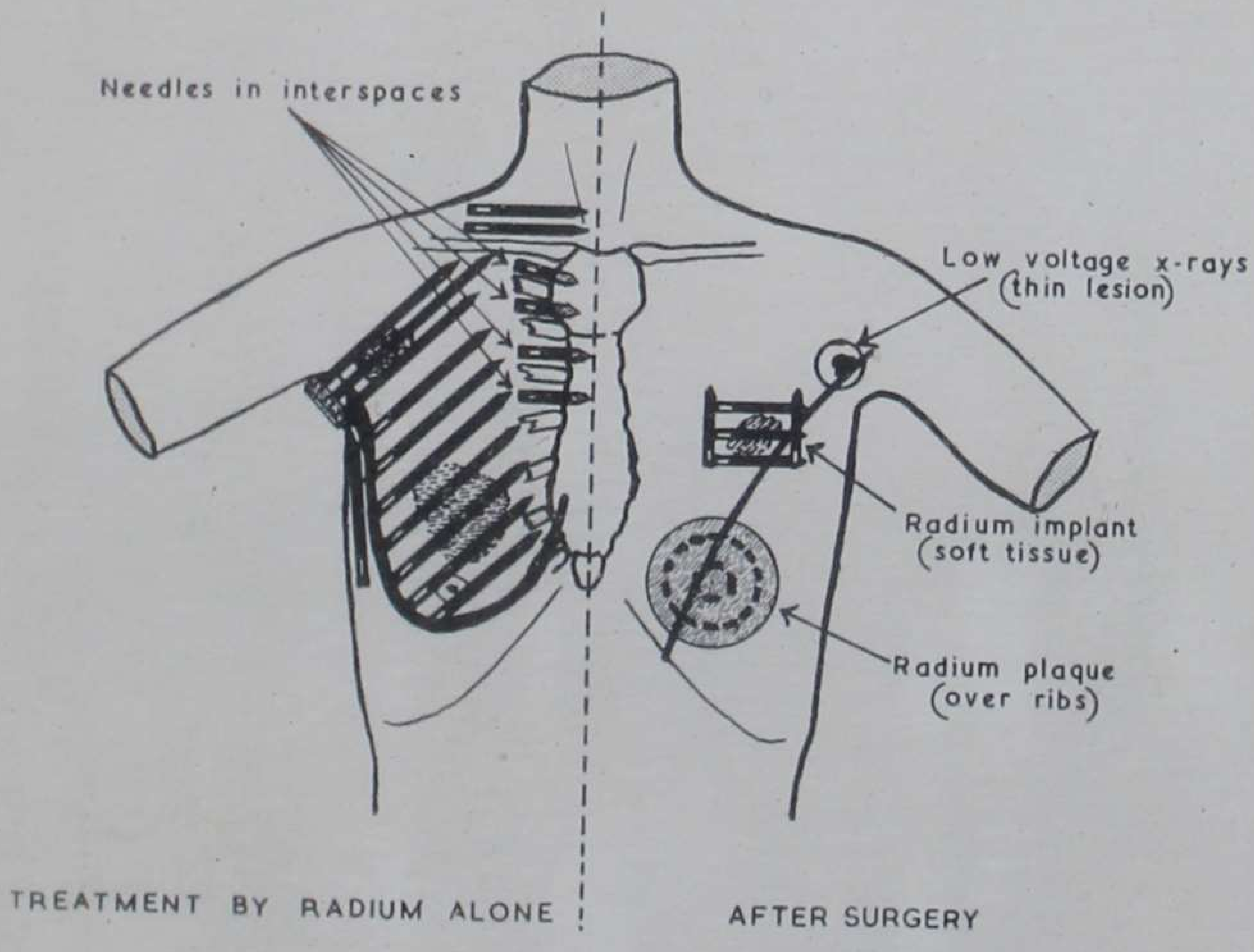


Fig. 170.—Radium and low-voltage X-ray treatment to the breast.

implant are employed the figure is 102 per cent, due to the addition of radiation from the two planes. It will be seen on the plaque-implant curves that nowhere between them does the dose drop below 94 per cent. The skin dose is only 110 per cent, and it will be seen how rapidly the dose falls on the deep side of the implant. By this method an approximately homogeneous dose is received by the tumour which is situated between the two planes of radium.

Primary Tumour.—The method has been used in the past when an attempt was made to treat the disease radically with radium alone. Such an implant is depicted in *Fig.* 170, but the method has largely been abandoned for two reasons: first, the mathematical spacing required for even dosage cannot be attained in practice ; and secondly, due to the large amount of radium required, the integral dose is so high that the patients may be considerably upset by the treatment. It is however possible to treat a primary tumour in Stage I cases by the plaque-implant method if an operation is declined.

Chest Wall Nodules.—Isolated nodules on the chest wall are treated by single plane implants, surface applicators, or small combined plaques and implants according to their size. In many cases

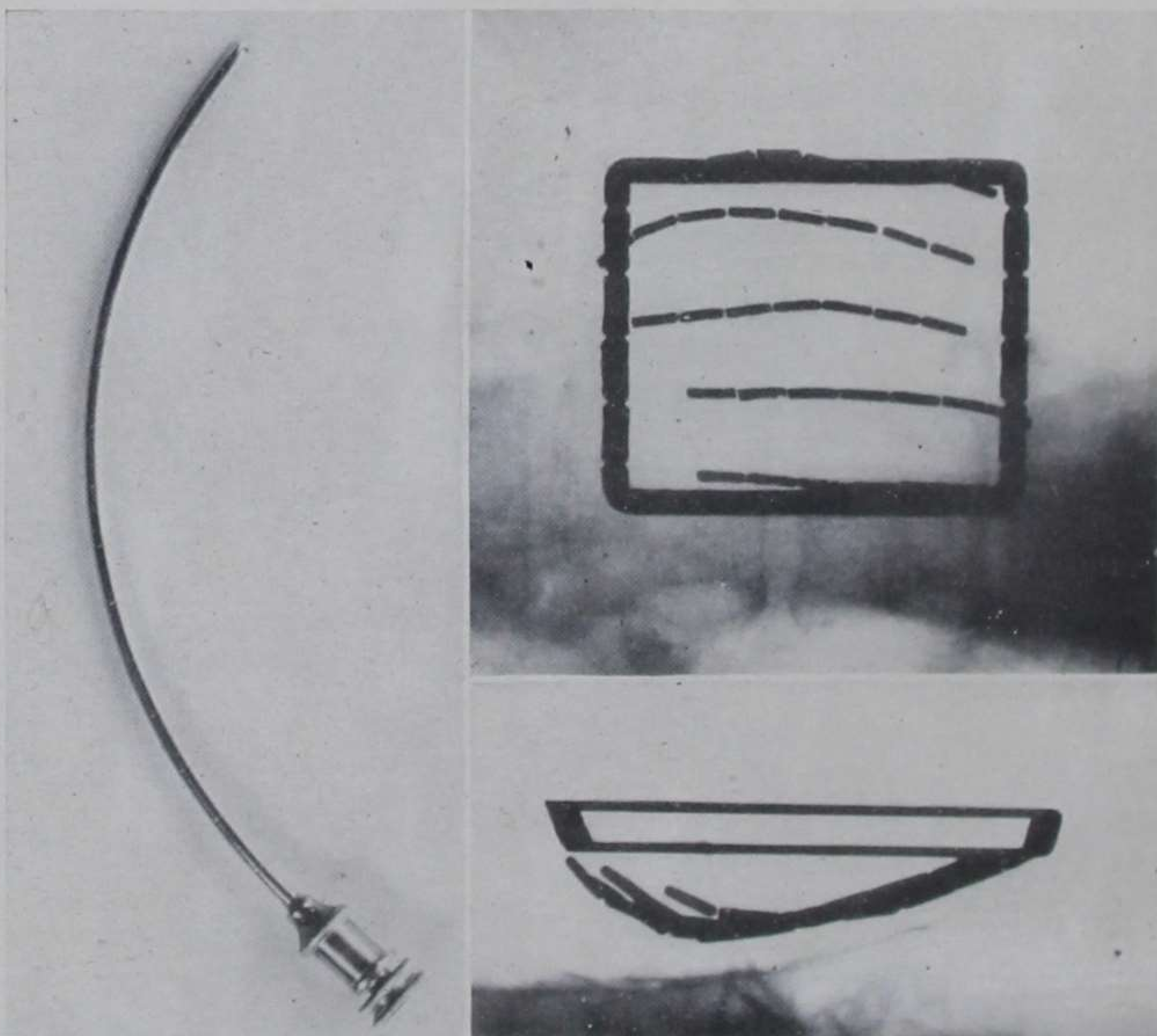


Fig. 171.—Local radon seed-chain implantation under a breast nodule. The chains are fixed to a wire frame. The cannula is used to insert the chains.

when in-patient treatment is not desired or beds cannot be obtained the radon seed method is of great value, as it is simply performed and the patient can return home.

In the physics section it was explained how radon seeds may be strung together to form a chain which is virtually a flexible radium needle. Since radon is a gas and can be compressed, seeds of different intensities may be obtained ; this is of great value to the physicist in his calculations and allows curved contours to be followed accurately. Their introduction is easily performed under local anæsthesia and causes little disturbance to any patient.

The operative technique is different to that of radium implantation, the insertion being achieved as follows: The lesion is carefully marked and the required position of the seed chains drawn as in radium implantation. A straight or curved cannula is passed into the tissues and in lesions on the chest wall the cannula emerges through the skin on the distant side of the tumour. The trocar has a bevelled eye through which the seed-chain thread is passed and on withdrawal the seeds pass into the cannula. This is carefully withdrawn and the loose thread on the chain is held so that the seed chains remain in situ. In cases where the point of the cannula remains buried the trocar is removed and a pusher, flattened on one side to allow room for the seed-chain thread, pushes the seeds down. Both cannula and pusher are graduated in centimetres so that the seeds can be placed at any required depth. To anchor the chains the threads are tied to a metal frame or wire looped at the required spacing. *Fig.* 171 demonstrates a curved cannula as used and a radiograph of a completed implant in the abdominal wall.

Irradiation of the Axilla.—It is usual for small axillary nodes to disappear following X-ray therapy with high dosage, but when the nodes are large there is a residue which is treated by radium implantations. The needles can be simply placed along the axillary walls, and care taken to avoid damage to the axillary vein and brachial plexus. This method, however, is not compatible with a planned arrangement of the needles, and leads to an appreciable variation in the dose throughout the axillary tissue.

At the Royal Northern Hospital a perspex plate, pyramidal in shape to conform with that of the axilla, is used. The plate is drilled so that the holes are equidistant and parallel and as the needles are inserted through these they are guided and held parallel. The plate remains in place during the whole of the treatment time, and by this means the geometrical distribution demanded by the physicist's calculations is obtained (*Figs.* 172, 173).

There is, even with this method, a variation in the dosage throughout the axilla, but it is less than that of many techniques, and a total dose of 6000–7000 r in 3 to 7 days can be readily attained without risk.

Radium Planning.—It will be appreciated that the planning of this treatment has to be complete and is of great importance. Accordingly one session is devoted entirely to radium planning, when the Radiotherapy and Physics Staff meet, with the patient, to discuss and select the best distribution of radium to give even dosage. In difficult cases a model of the lesion may have to be made, but usually a three-dimensional full-scale drawing suffices. Jigs or

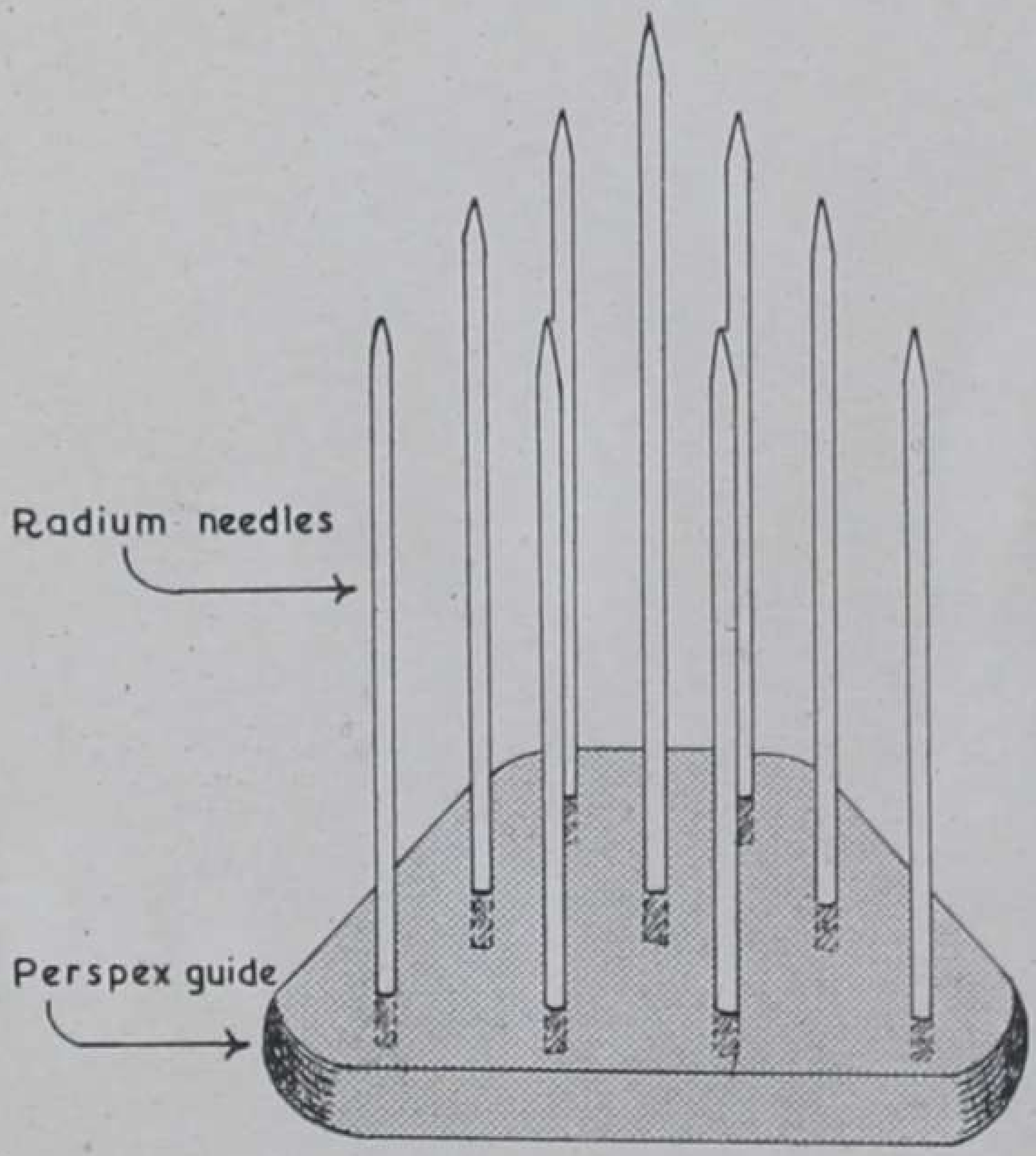


Fig. 172.—Axilla implant. A group of needles with a large centre needle is held in a perspex plate and in the approximate shape of the axilla.

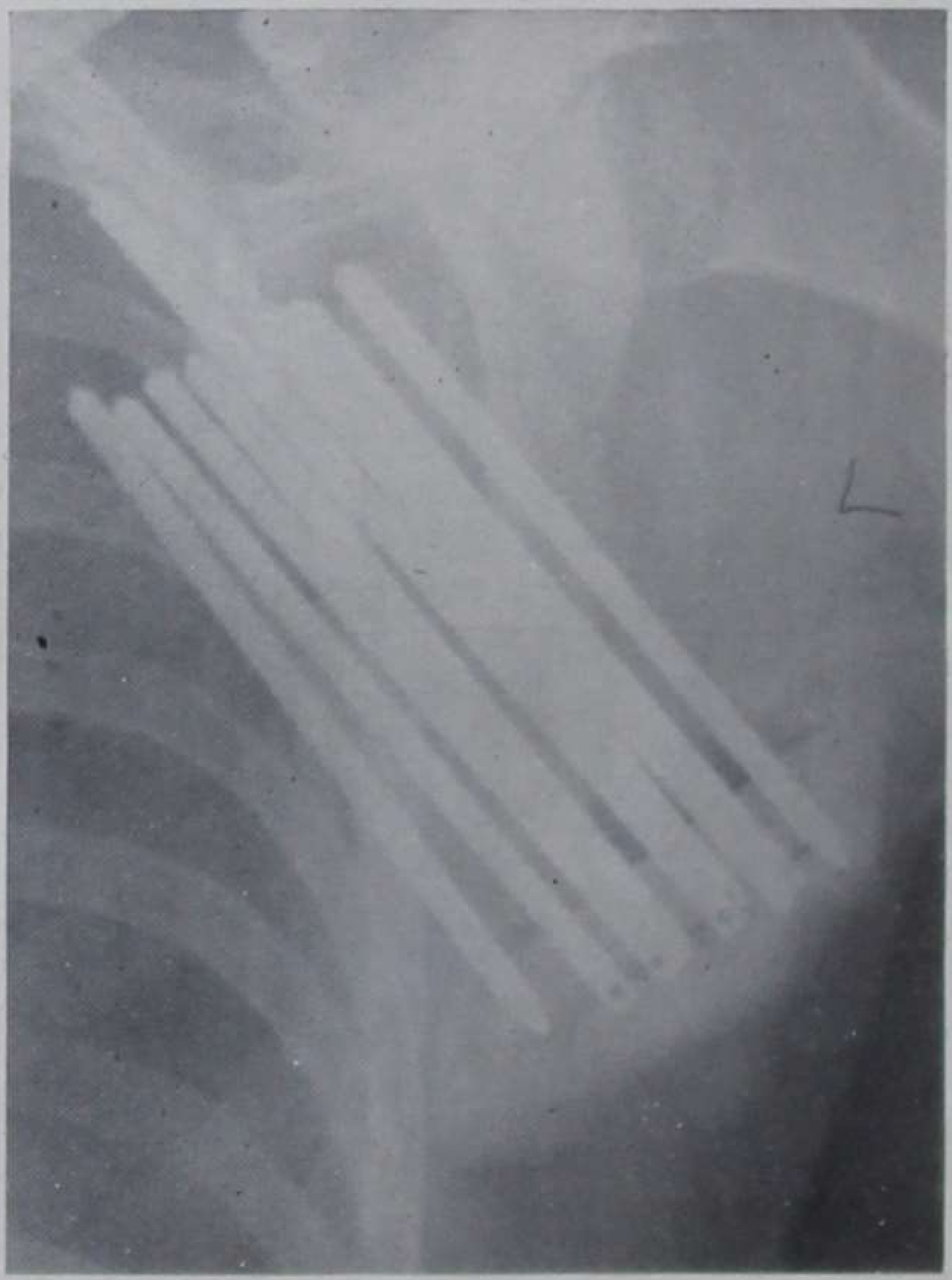


Fig. 173.—Radiograph showing radium needles in position in axilla.

other pieces of apparatus required to hold the radium are made in the department's workshop.

Theatre Technique.—Radiotherapy is a highly specialized subject throughout, the theatre technique being no exception.

Since radium is valuable, and dangerous if mislaid, a radium card is issued with full particulars of the amount and arrangement clearly written which accompanies the radium wherever it goes. At each stage a responsible person signs the card to denote acceptance of responsibility. The radiographer who loads the radium from the safe and takes it to the theatre, the theatre sister, the nurse who accompanies the patient back to the ward, the ward sister, and the radiographer who receives the radium after removal and replaces it in the safe, all sign.

The needles are loaded and threaded on a lead-protected bench, then taken to the theatre in a lead container, and kept there in a lead tray to protect the personnel handling them. After sterilization in pure dettol (repeated boiling causes distortion) the needles are handled with special long forceps.

The radiotherapist sterilizes the skin with dettol or cetavlon, avoiding substances such as iodine (*see* CUTANEOUS RESPONSE TO IRRADIATION, p. 241). The anatomical landmarks and tumour are then clearly marked with gentian violet and the needles inserted through puncture holes in the skin made with a tenotomy knife. After fixation of the radium in position by sutures or wiring, dressings are applied.

A radiograph is then taken, preferably by a portable apparatus in the theatre, so that if the film shows the radium to be misplaced a re-insertion, again checked, can be performed.

CHOICE OF METHOD IN RADIOTHERAPY ALONE IN BREAST CANCER

AIM	METHOD	USED IN PATIENTS WHO ARE: In Good General Health	USED IN PATIENTS WHO ARE: Senile or Ill	RESULTS
RADICAL THERAPY	X rays and radium to residue	Yes	Usually	Comparable to surgery
	Radical radium implant	Yes	Sometimes	
	Local radium or radon seed-chain implant	Occasionally	Yes	Good local results
	Local intensive X rays. Radon seeds to residue	Occasionally	Tolerated by most	Growth arrest in many. Occasional disappearance of tumour
PALLIATIVE THERAPY For advanced growths with poor prognosis. For psychological reasons if distant metastases present	Intense X-ray therapy to whole area	Yes	No	Palliation in nearly all. Prolongs life in comfort
	Small-dose X-ray therapy local or wide fields	No	Yes	Shrinks growth. Prolongs life

SECONDARY DEPOSITS

Sites

Bone.—The commonest site for distant deposits from a mammary cancer excluding the chest is undoubtedly in the bones. Pain is an early and constant sign, especially in the weight-bearing bones such as the spine, pelvis, and femora (*Fig.* 174). At first the pain

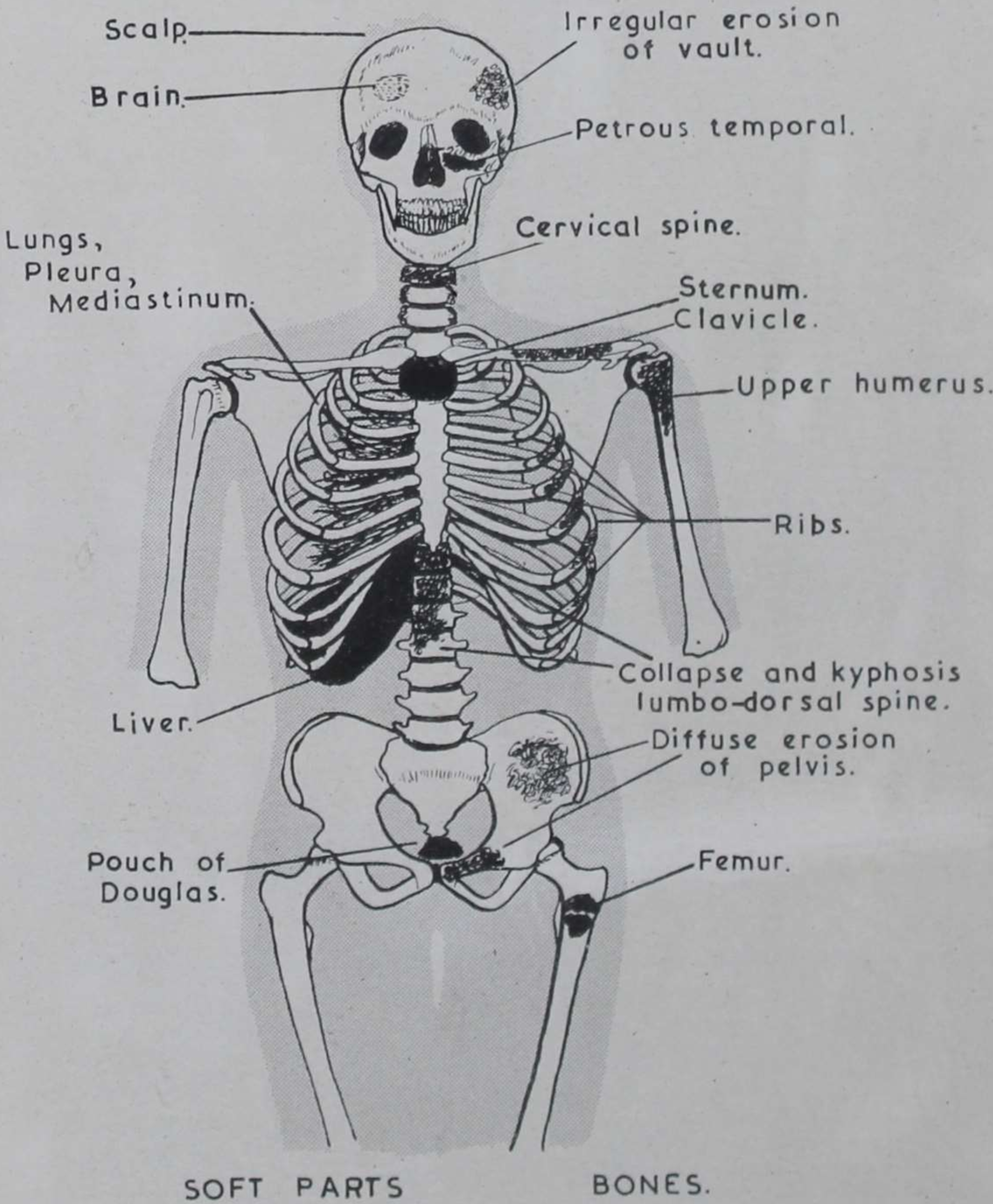


Fig. 174.—Common sites for secondary deposits in breast cancer.

is slight and intermittent at the site of the deposit, but later, particularly in the event of vertebral collapse, the pain is referred along the segmental nerve distribution in the trunk or limb. Occasionally these complaints together with some deprivation of general health precede the finding of a breast mass, or again, although a mass has been found, the " rheumatic " pains in the back receive scant attention. Limitation of movement and an inability to lift heavy weights are generally noted.

A pathological fracture may be the first sign of a secondary deposit, and the shafts of any of the long bones, including the neck of the femur, and less often the small bones, may be affected. Such a fracture may not be recognized at first as pathological, since in X-ray films the erosion is apt to be obscured by the line of fracture; in some cases, however, when pain has been evident prior to the fracture the radiographic evidence is obvious. Nevertheless a pathological fracture, although the most dramatic sign of a secondary deposit in bone, is in fact rare.

An osseous deposit, if accessible to examination, may present a swelling such as can sometimes be felt in the sternum, skull, or ribs. If not actually palpable the site is tender on pressure. Ribs containing deposits are often exquisitely tender, and springing of the ribs, by pressure on the sternum and spine, will generally elicit a sharp pain in those affected. This examination is performed by placing the palm of the left hand over the lower dorsal spine and the right hand over the lower part of the body of the sternum. Firm but gentle pressure, to avoid possible injury, is applied until the ribs are felt to spring. If pain is complained of the site is noted and marked for X-ray examination. Palpation may reveal a depression, a swelling, or crepitus.

In the lower limb gentle percussion with the closed fist on the heel may cause pain at the site of a deposit in the femur.

In making an early diagnosis of secondary deposits in the spine, hyperæsthesia can be a sign of considerable value. If a pin is gently scraped down the back from the neck to the buttock sharpness will be complained of as the nerve-supply corresponding to the site of the spinal lesion is crossed. Absence of this sign suggests that pain in the back is due to other causes, e.g., osteo-arthritis.

Compression of the vertebræ by firm pressure on the neck and shoulders causes pain in the affected segment. Further examination of the spine is conducted with the patient sitting on a couch with the legs hanging over the edge. With the body relaxed the shoulders are grasped and the body turned from right to left and vice versa, the spine being rotated through its full range. The patient then leans slightly forward, and by exerting pressure with the right hand over the sternoclavicular joints and the left hand in the lumbar curve

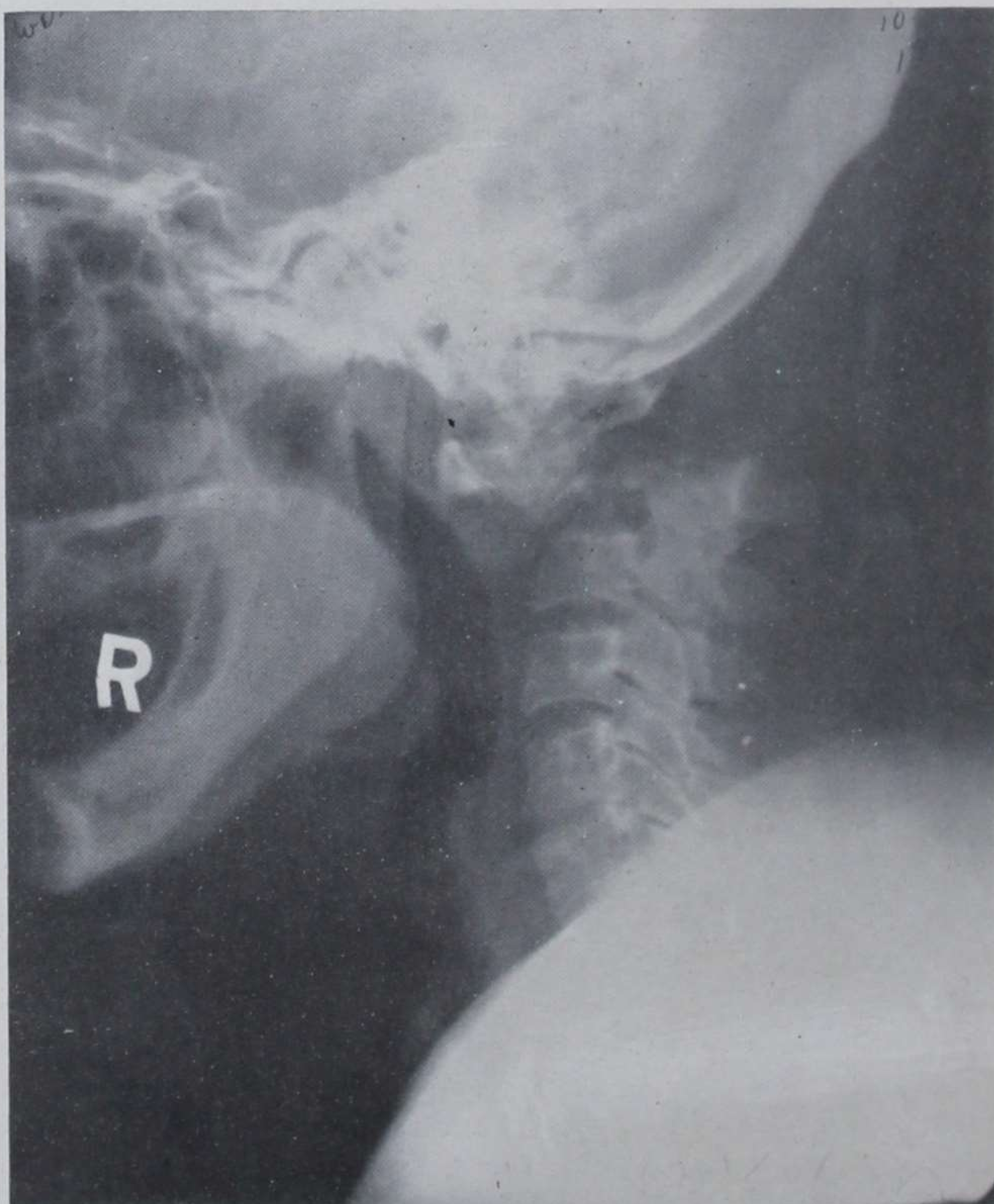


Fig. 175.—Radiograph of fracture-dislocation of cervical spine due to secondary deposits from carcinoma of the breast. There were no neurological signs.

extension is tested. Finally with the patient leaning to the left pressure is applied to the right side of the root of the neck and vice versa. By such tests strain is exerted on different parts of the spine, and the site of pain, if complained of, is noted. If vertebral collapse has occurred a kyphotic or scoliotic deformity may be obvious.

Radiological evidence of secondary deposits in bone may not be definite for some two months after the onset of symptoms, though special techniques can be employed to increase the clarity of the radiographs. In the early stages, however, careful clinical examination is of greater value since negative radiographs do not exclude the presence of secondary deposits. In some instances a tomograph may be of value.

In biochemical investigations the E.S.R. is found to be elevated in cases of established secondary deposits, but the test is of little diagnostic significance. Where there are gross and diffuse erosions of bone the alkaline phosphatase is raised.

Pathological Fracture-dislocation of the Cervical Spine.—This is an alarming condition and deserves special mention. A vague history of stiffness of the neck and pain on movement may be obtained and on examination the head is seen to be thrust forward with obvious neck deformity. Radiographs then reveal a sharp angulation, usually in the upper half of the cervical spine, but not infrequently, in spite of gross deformity, there are no clinical signs of pressure on the spinal cord (*Fig.* 175).

TREATMENT.—

Radiotherapy.—In cases of secondary deposits in bone radiotherapeutic treatment gives considerable relief from pain.

This is its main object, since relief can only be obtained inadequately by sedatives, but permanent freedom is achieved only in rare instances. If pain, hyperæsthesia, stiffness, or limitation of movement are present, then prompt treatment is indicated despite negative radiographs, and the benefits obtained are usually dramatic especially when the deposits are limited and the patient is ambulant. In some patients who are already confined to bed by extensive erosions this statement is also true. To quote two cases; one with a secondary deposit in the fifth lumbar vertebra continued well and comfortable for five years after irradiation; and another, bedridden and in great pain from widespread pelvic and spinal deposits, was able to get up and later walk, and to continue in relative comfort for about two years. (*Fig.* 176 demonstrates the re-formation of a clavicle after X-ray therapy.) If, however, the patient's general condition is poor and rapidly deteriorating, radiotherapy is contra-indicated.

In the event of fracture, radiotherapeutic and orthopædic measures are combined, particularly in cases of vertebral collapse with danger of spinal cord injury.

A well-padded plaster, while conforming to the orthopædic requirements, must be fashioned preferably to permit irradiation through uncovered skin. Such treatment not only relieves pain but the advance of the malignant process is arrested and allows re-calcification to occur.

In the case of a fracture-dislocation of the cervical spine traction is applied by bandages passing under the chin and occiput to a Balkan

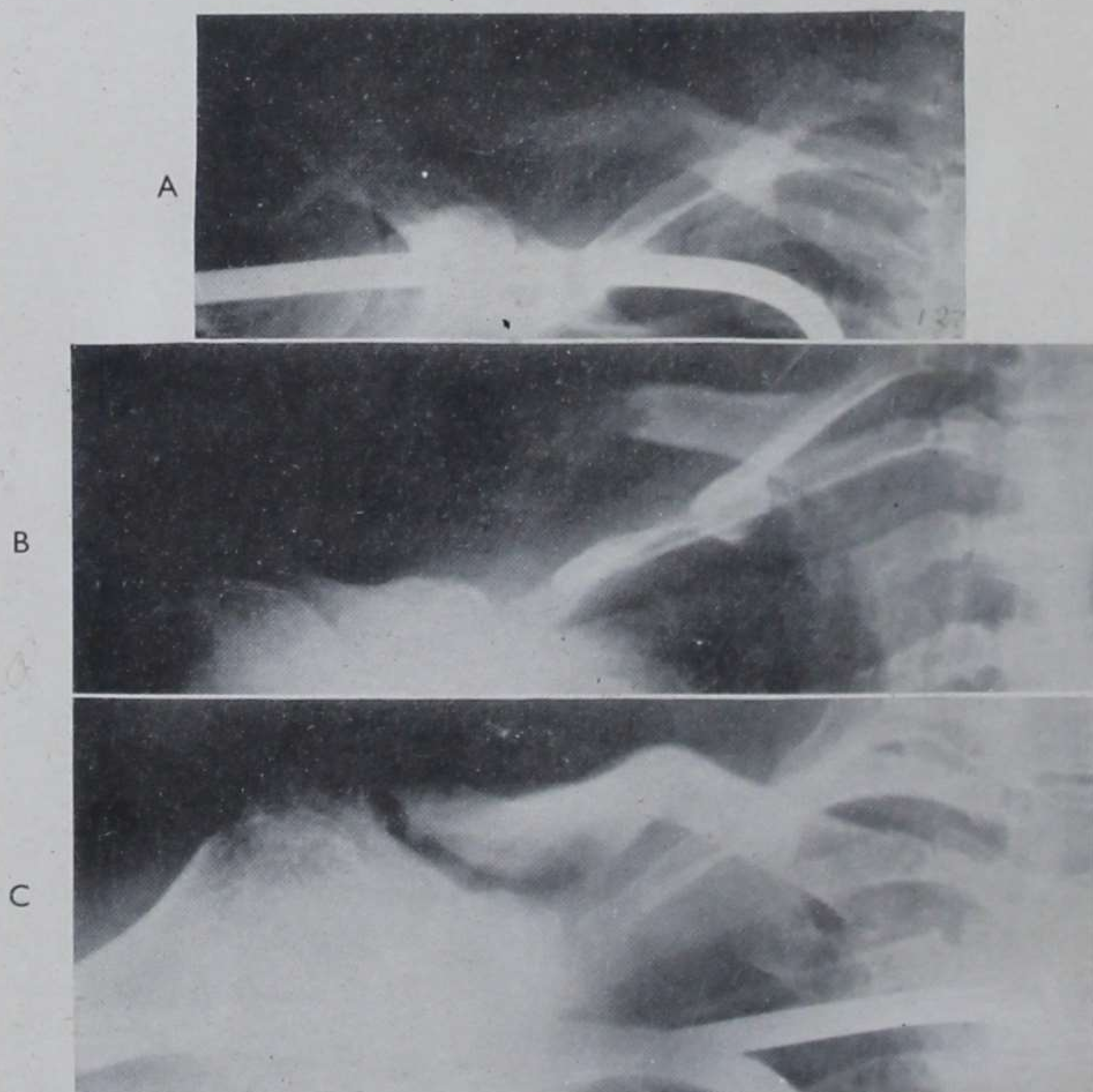


Fig. 176.—Radiographs showing complete re-formation of the outer end of the clavicle after X-ray therapy for a secondary deposit from carcinoma of the breast. A, Before treatment; B, During treatment; C, After treatment.

beam. When the neck has been extended the position is maintained by the application of a thin plaster-of-Paris shell which includes the whole head and upper thorax, care being taken to allow sufficient space under the chin and in front of the larynx for comfort in eating. The site of the lesion is accurately localized by radiographs, and deep X-ray therapy, 2000 r in one to two weeks, given. In some instances the fracture unites.

Drugs and Diet.—Sedatives and depressants of the central nervous system such as phenobarbitone may usefully be combined with aspirin or veganin. Pethidine and hyperduric morphine are given, though frequent use of the latter may be regarded as faulty management. Syrup triplex (iron and strychnine) is helpful in general debility, and in the case of osseous deposits a plentiful supply of milk and green vegetables should be taken together with calcium gluconate and calciferol to provide calcium.

The Chest.—

Mediastinal.—The first complaint is often a feeling of uneasiness, slight pain, or tightness in the chest, and later difficulty in breathing occurs. In the early stages a radiograph may not reveal any abnormality, but on careful inspection two findings may be noted. First a vague faint shadow near the upper part of the hilum and secondly a slight increase in the density of the right upper lobe due to partial collapse with consequent deficient aeration. If there is definite pain and a straight X-ray fails to give clear evidence a tomograph through the chest may show nodes at an early stage of enlargement.

A radiograph demonstrating the presence of a definite shadow in the region of the hilum with early collapse, as often seen in the right upper lobe, is not uncommon, and perhaps only then is full significance attached to the earlier symptoms; but at this stage cough, dyspnœa, and general failure of the health are usually apparent. Careful clinical examination, then, is essential in order to make an early diagnosis.

These intrathoracic manifestations are associated with cases in which the lymphatic spread has carried the disease to the supraclavicular nodes, and it is assumed that by further direct or embolic lymphatic spread the growth reaches the thoracic nodes.

Infiltration from the Hilum.—The symptoms of cough and feeling of uneasiness and tightness in the chest without pain or external physical signs may be associated with radiographic appearances similar to those of chronic bronchitis. The film shows radiating lines and a network suggestive of lymphatic permeation spreading from the hilum on either side. Such appearances are commonly found with advanced infiltrating growths where a *peau d'orange* or cancer *en cuirasse* infiltration of the skin are features of the case.

In the early stages, as stated, a confident radiological diagnosis is impossible, but when, with increasing clinical evidence, repeat films taken after two or three weeks show a small effusion, little doubt is left.

Intrapulmonary.—In some cases, without more than a complaint of lassitude and slight loss of weight, with poor facial colour but without physical signs, a radiograph of the chest will show separate fluffy deposits in the lungs. These deposits are almost certainly the result of blood-borne embolisms and associated maybe with those growths which form masses in, rather than infiltrate, the breast.

At a late stage definite signs are present, such as cough with sputum or hæmoptysis, when the failure of general health is evident.

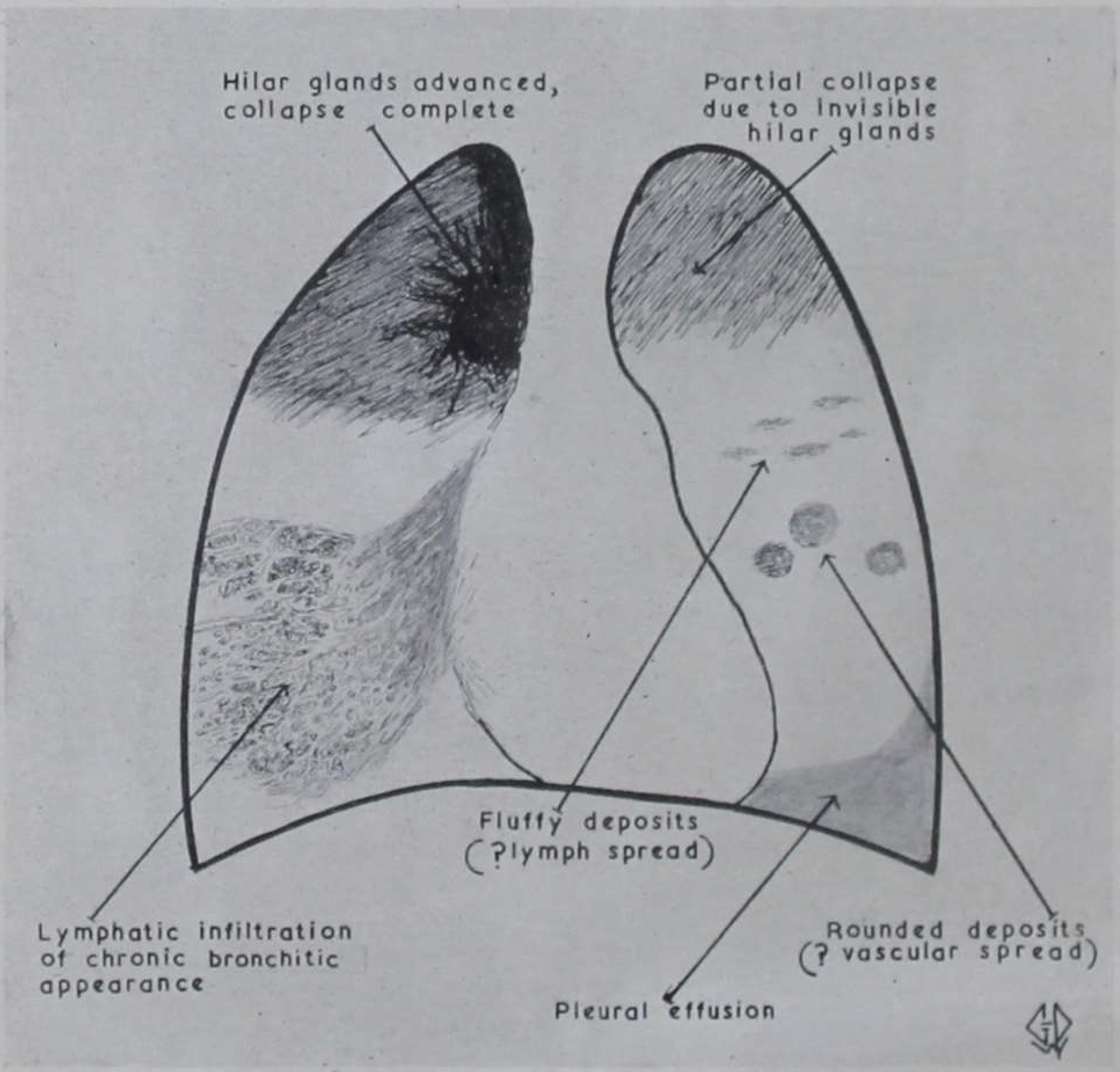


Fig. 177.—Secondary deposits in lung fields from breast cancer.

Pleural Effusion.—An effusion may occur alone or together with other evidence of secondary deposits such as the infiltrations from the hilum, especially when these extend downwards. The effusion is usually small at first, up to an inch or two in height, obliterating the costophrenic angle. Later it becomes more massive, and on aspiration the fluid is often blood-stained and on microscopical examination of the centrifuged cellular deposit cells suggesting malignancy may be seen.

Mixed.—Although these types of intrathoracic deposits have been classified in the light of the authors' clinical experience, the differentiation in many cases is not so clearly defined. Mixed types would be expected and are commonly found. *Fig.* 177 is a composite picture illustrating the classified types.

TREATMENT.—The treatment of intrapulmonary deposits is of little practical value. As yet these findings are but a measure of the progress of the disease and of its prognosis. An increased knowledge, however, of the paths of spread may lead to an advance in treatment.

OVARIAN IRRADIATION FOR CANCER OF THE BREAST

Sterilization has been advocated for the treatment of carcinoma of the breast in cases occurring prior to the menopause. A beneficial effect has been shown, though not consistently, both in lymphatic and bony metastases. Ovarian irradiation after the menopause has given similar results, particularly in extensive deposits in bone, when relief of pain—though temporary—has been obtained.

A dose of 800 r in 8 days to the centre of the pelvis, measured by vaginal ionization, is given with deep X rays. In the younger group menopausal symptoms may be severe, and if not controlled by œstrogen therapy, pituitary irradiation with 150 r weekly has no ill effects and often ameliorates the symptoms considerably. (For treatment by œstrogens and androgens, *see* p. 222.)

IRRADIATION AND LEAD THERAPY

During World War I it was noted that cancer in lead workers showed a low rate of growth, and this stimulated experimental work and clinical application. To begin with, colloidal solution of metallic lead, 0·6 g. in 8 doses spread over a period of 4 months, was used. In 1926 the first results were published. The conclusion reached was that all types of malignant neoplasms were probably amenable to the beneficial influence of lead. Simultaneous irradiation measures were considered to be of great value.

Since 1928 colloidal lead orthophosphate has been used, the types of cases being gradually narrowed to those of bone neoplasm, because of bone's high absorption.

Present Standard Procedure.—An average dose of 30 c.c. of colloidal lead orthophosphate suspension containing 120 mg. of lead is injected intravenously. Three days later X-ray therapy is begun. Two months later the same procedure is repeated. This concludes the normal treatment. If in subsequent X-rays new areas are seen to be affected the same dosage is repeated. One case received 1200 mg. over 10 years.

Contra-indications.—Severe liver damage, nephritis, or marked anæmia.

Immediate Effects of Injection.—One to two hours later a sudden rise in temperature to 103° which becomes normal after 3 to 4 hours.

Other symptoms: Nausea, anorexia, and fatigue.

Effects on Deposits.—10 to 14 days later pain abates and disappears in 6 to 8 weeks. Re-ossification occurs in about 3 months, the deposits showing a very heavy calcified shadow.

Assessment of Results.—355 cases treated. Symptomatic improvement occurred in 95 per cent. Survival rates do not appear affected.

More recently radio-active colloidal lead orthophosphate has been used, but no results are offered, as it is still experimental.

These methods have not been used by the authors.

REFERENCE

REYNOLDS, L., et al. (1948), "Colloidal Lead Orthophosphate associated with Deep Roentgen Therapy in Bone Metastases from Cancer of the Breast", *Amer. J. Roentgenol.*, August.

CHAPTER XII

THE PLASTIC CONTRIBUTION TO BREAST SURGERY

By Patrick Clarkson

I. GENERAL

Plastic surgery is both a technique of handling and repairing tissues and an approach to surgical problems based on detailed pre-operative planning and pattern cutting. This planning, even more than the technique or the use of particular instruments, constitutes the specialty and determines results.

In the following pages plastic methods are described which can be used with profit in the general surgery of the breast.

GENERAL PRE-OPERATIVE CONSIDERATIONS

All patients who are to undergo plastic operations are benefited by preparation with a high protein and sulphur diet and up to 200 mg. of vitamin C a day for about two weeks before and after operation. Post-operatively, penicillin procaine is given for 3–6 days.

SUTURE OF BREAST SKIN

A good scar is obtained by completely accurate apposition of the skin edges over a flat subcutaneous bed. For this the skin edges must be non-bevelled, with neither inversion nor eversion. Of these faults inversion is the more common and the more difficult to correct.

Suture markings, though often of trivial importance, are a definite blemish on a surgical result. Faulty control of sutures can cause necrosis, provide points of entry for deep infection, or leave, eventually, parallel rows of keloid studs along a raised irregular scar.

An ideal scar in any position is hairline, supple, flat, symptomless, and of the same colour as the surrounding skin. But the skin of the breast, in spite of every precaution, tends to form hypertrophic scars of a keloid type, often more noticeably than elsewhere in the body. The result can also be influenced by the direction of the incision, the metabolic state of the patient, and by X-ray therapy. For both functional and psychological reasons, scarring should be reduced to the minimum compatible with the security of the wound and the operative necessities, and certain fundamental principles of technique should always be observed.

Technique.—To ensure a good scar the first essential is to make the incision accurately and without bevelling of the edges.

A useful point of plastic technique, applicable to general surgery, is a routine marking out of the proposed line of incision with ink dots. Small incisions should be made to follow Langer's lines provided the access given is adequate, and though the scars are not uniformly good the results are an improvement on those from radial incisions. This does not apply, of course, to the radical mastectomy. (Langer's lines run horizontally over most of the breast but downwards and inwards over the sternum and adjacent parts.)

The skin is held slightly taut by the assistant, and is incised with the knife at right angles to it—using a No. 10 or No. 15 blade. Undermining of the skin is an essential preparation in any incision to render the skin edges mobile and adjustable for accurate sutures. In a mastectomy wound the depth of fat desirable at the skin edge is about 1 cm., and the incision is carried to this depth before undermining. In this operation skin-flaps can usually be undermined to a distance of 10 cm. or more with safety.

Closure of Wound.—The materials available for skin suture are serum-proof silk (deknatal of calibres 04, 06, 09), fine nylon, S.S. wire of gauge 35 or 40, with three 0 catgut for the subcutaneous layer. The author's preference is for fine catgut in subcutaneous layers and in continuous subcuticular sutures around the areola.

Stainless steel and tantalum wire as subcuticular sutures are excellent, especially for short incisions, but for a long mastectomy scar insertion of subcuticular sutures of this type is tedious, time-consuming, and needs much practice.

A majority of breast wounds may be closed either by serum-proof silk or nylon. The former is softer, easier to handle and to knot; it is mechanically satisfactory in maintaining edge adjustment. Nylon's only advantage perhaps is that it can remain in the skin longer without causing redness or other reaction.

Skin closure is performed by interrupted sutures for which the maxim is "that one good suture leads to another". Accurate apposition of skin edges and fat in a mastectomy wound is obtained by multiple fine sutures inserted with uniform spacing and depth of about 0·5 to 1 cm. Smaller incisions can be closed by sutures (fine silk) about 3–4 mm. apart. Closure of a wound is aided by traction on the deep layers of the free edge by Gillies' hook, and by inserting the needle—held with the surgeon's hand in full pronation —at right angles to the surface through the full thickness of the flap. Larger bites of tissue than a depth of about 1 cm. for long or short wounds increase scarring and tension in the flaps.

Periareolar incisions may be closed by a continuous subcuticular suture of fine 0000 catgut. Suture marks, in a region liable to form hypertrophic scars, and also removal of sutures in a sensitive area are thus avoided. All wounds should be covered by atraumatic dressings of tulle gras or nylon derivative with dry gauze and crêpe-elastoplast pressure.

Fine sutures are removed between the 3rd and the 6th day and heavier sutures gradually up to the 10th day. Some permanent marking is to be expected from sutures left in more than four days, but the time of removal must be influenced by the tension on the skin edges and the degree of healing.

CLOSURE OF DEFECTS ON ANTERIOR CHEST WALL

A primary closure of a radical mastectomy wound in a single line should always be the aim. This is aided by removal of all breast and subcutaneous tissue over a wide area, the pectoral muscles, and by undermining the flaps. In most cases approximation of the wound edges can be made over a wide defect and without tension, but the amount of skin available varies considerably with the size of the patient, and closure of comparatively narrow defects can be especially difficult in the inner quadrants.

If on pre-operative examination it is estimated that the excision of skin will exceed five inches in transverse diameter, or if the growth is awkwardly placed in the medial quadrant of the breast, plans should be made for a deliberate plastic closure. When, too, at the operation, in spite of undermining the flaps to the limit—it is unsafe to undermine the posterior flap beyond the lateral border of the latissimus dorsi muscle—approximation of the skin edges creates tension sufficient to cause blanching, closure should be completed by means of planned flaps or by free graft. The choice will depend partly on the individual preference of the surgeon but mainly on the site and size of the defect.

A well planned and successful local flap gives slightly quicker healing, and a supple and a more certainly symptomless scar. A free graft, although less satisfactory as regards appearance, is a safer cover, and indeed must be used for all big defects.

Closure by Local Flap.—Defects of a transverse diameter of up to 10–15 cm. can be closed by either a swinging or rotation flap which transfers skin from peripheral areas where it may be present in excess. Both flaps are rectangular and cut in the same manner, but a rotation flap has a small re-entrant incision which narrows the base and permits of a greater degree of rotation and transference. A layer of fat on the flap of at least 1 cm. in depth should be left, and the diameter of the base should not be less than the length. The secondary defect on the lateral wall of the thorax left by transference of skin and fat can often be closed by approximation after undermining. If this creates tension, a free graft should be used for the cover of this secondary defect.

For the usual residual defect, approximately in the middle of a radical mastectomy wound, two standard flaps, one based medially and the other laterally, are especially valuable ; both may be required to re-surface a large area. Of the two, the lateral flap is the more generally useful. To cut a lateral flap an incision is made at right angles to about the centre of the lateral edge of the mastectomy wound and continued into the lower axilla for the necessary breadth, usually some 10–15 cm. The incision is now turned at right angles and continued downwards, parallel to the mastectomy line, for an equal distance. The flap is then elevated and transferred by hooks over the defect to ascertain whether a small re-entrant incision is necessary to ensure cover without tension. After hæmostasis is secured the flap is sutured in position in one layer.

A single lateral flap may be based either above or below, depending on the position and shape of the defect. When used in conjunction with a medial flap, to cover a very large area, the medial is usually based above and the lateral below. The two flaps thus form a giant S and are swung together to meet across the centre of the defect.

A medial swinging or rotation flap, for the closure of medial defects, is cut in the same manner, though usually with its base above. In this way the scars, which extend well towards or over the midline, lie as far as possible below the neck line. When undermining across the midline the plane of dissection should be curved anteriorly on approaching the convexity of the opposite breast ; if undermining is carried too deeply the skin is not freed. The scars of these medial flaps over the sternum are particularly prone to hypertrophy, and a lateral flap is preferable when the size and site of the defect require only one flap.

Closure by Free Grafts.—Free grafts are the most generally applicable method for primary closure of defects too large for simple approximation, combining the advantages of saving time and of avoiding the risk of ischæmia or the sloughing of flaps. As part of a pre-operative plan, preparation of the skin of a thigh or abdominal wall can conveniently be made. For a graft closure on the thorax the hand-cut skin taken with a Blair knife is suitable for almost every case; there is no advantage in the thicker and dermatome-cut skin. The donor area is dressed with 1 per cent decicain ointment and tulle gras. Thin grafts should be spread on tulle gras and are then ready for application to the defect.

(For Blair blade and dermatome technique, *see* p. 280 et seq.)

Graft Fixation and Dressing.—Grafts are lost by infection, hæmatoma, and lack of fixation. If there has been any risk of infection, as in the removal of ulcerating growths, full penicillin protection should be given pre- and post-operatively. Great care must be taken to secure complete hæmostasis before the grafts are applied. The use of diathermy over the recipient bed should be avoided, since the exudate from the pin-point areas of heat coagulation can cause some loss of graft.

A satisfactory method of graft fixation is by suture and pressure. The skin graft, on tulle gras if hand cut but bare if a dermatome graft, is placed over the defect with a generous margin of overlap and fixed by interrupted sutures through the graft, tulle gras, and wound edge. Stay sutures are left long at each corner. Blood-clot between the graft and recipient area is removed by syringing with saline. Pressure wool, small pieces at a time, is built up, moulded firmly over the tulle gras and graft, and held in place by tying the stay sutures. On this pressure pad several layers of gauze and wool are applied and secured firmly by strips of elastoplast strapping. The elastoplast is given additional fixation if the skin is painted first with benzomastiche.

The graft fixation should be arranged, if possible, so as to permit of access to the rest of the wound without disturbing the intimate pressure dressing. In the absence of signs of infection (pain, temperature, smell) the graft is left undisturbed for ten days. If at the first dressing there is a complete take, a marginal application of mercurochrome is sufficient, but any areas of loss are removed with forceps and scissors. Subsequently, daily dressings are done with scrupulous technique for the removal of crusts and scabs. When, however, the area of loss is such that healing by marginal ingrowth cannot be expected under two weeks, a re-graft should be performed after a few days' intensive dressing and penicillin therapy.

Closure by Combined Flaps and Free Grafts.—As has already been indicated in the description of the cutting of swinging and rotation flaps, a secondary defect left by the flaps should be covered by free graft if closure by approximation causes tension on the primary flap.

When it is estimated pre-operatively that there will be a shortage of axillary skin, an appropriate flap to cover the floor of the axilla should be planned. Such a flap is usually based, and hinged, behind and above; it should be cut generously, and the secondary defect deliberately closed by a free graft. The use of a free graft across the axilla itself often results in an incomplete take, and a later contracture of its borders can anchor the shoulder.

Primary Closure after Excision of the Ribs.—If growths adherent to the thoracic cage are excised, a very considerable defect of skin and parietes down to the pericardium and pleura may be left. Defects of this type can be satisfactorily closed by free grafts, but it may be impossible to provide firm pressure for their fixation. Graft glues, in addition to light pressure, can be used; that is, the graft is loosely sutured at the margins and thrombin followed by fibrinogen is perfused between the graft and recipient area. After this light pressure is maintained for some 2–5 minutes, by which time a considerable degree of adherence between the raw surfaces has generally occurred. Further light pressure is maintained on the graft by copious gauze, wool, and strapping.

In such cases, however, a local flap to cover the exposed pericardium and pleura is likely to be more effective and should be planned ahead. If the defect is likely to be large the flap may need to be delayed, that is, two of its borders are outlined and the whole thoroughly undermined. Three weeks after the end of the main operation, when the primary defect has been established, the delayed flap is duly cut, raised, swung over the area, and sutured into place. The secondary defect on ribs and intercostals or over the rectus is covered by a free graft.

Blair Blade Technique.—The essentials for cutting skin with a Blair knife are: a sharp knife (when an experienced cutler is not available in the hospital it is best to send these blades regularly to the instrument makers for sharpening); a donor site held by the assistant so as to present a good flat surface to the surgeon (this means that the thigh is flexed and abducted with knee flexed, and the hands of the assistant are placed on the under, lateral, surface of the thigh to present as flat and broad a medial surface as possible to the blade). The patient must be in deep anæsthesia, and the "grafter's enemy", the abductor longus, well relaxed. A board held in the surgeon's left hand about 2 cm. from the blade edge further flattens the skin surface and produces the requisite tension needed for accurate cutting. A rhythmical and uniform 'see-saw' motion of the right arm held against the surgeon's flank does the cutting. The skin should be of such a thickness that as it comes off the blue colour of the blade is perceptible through it. Any tendency to cut deeper is checked

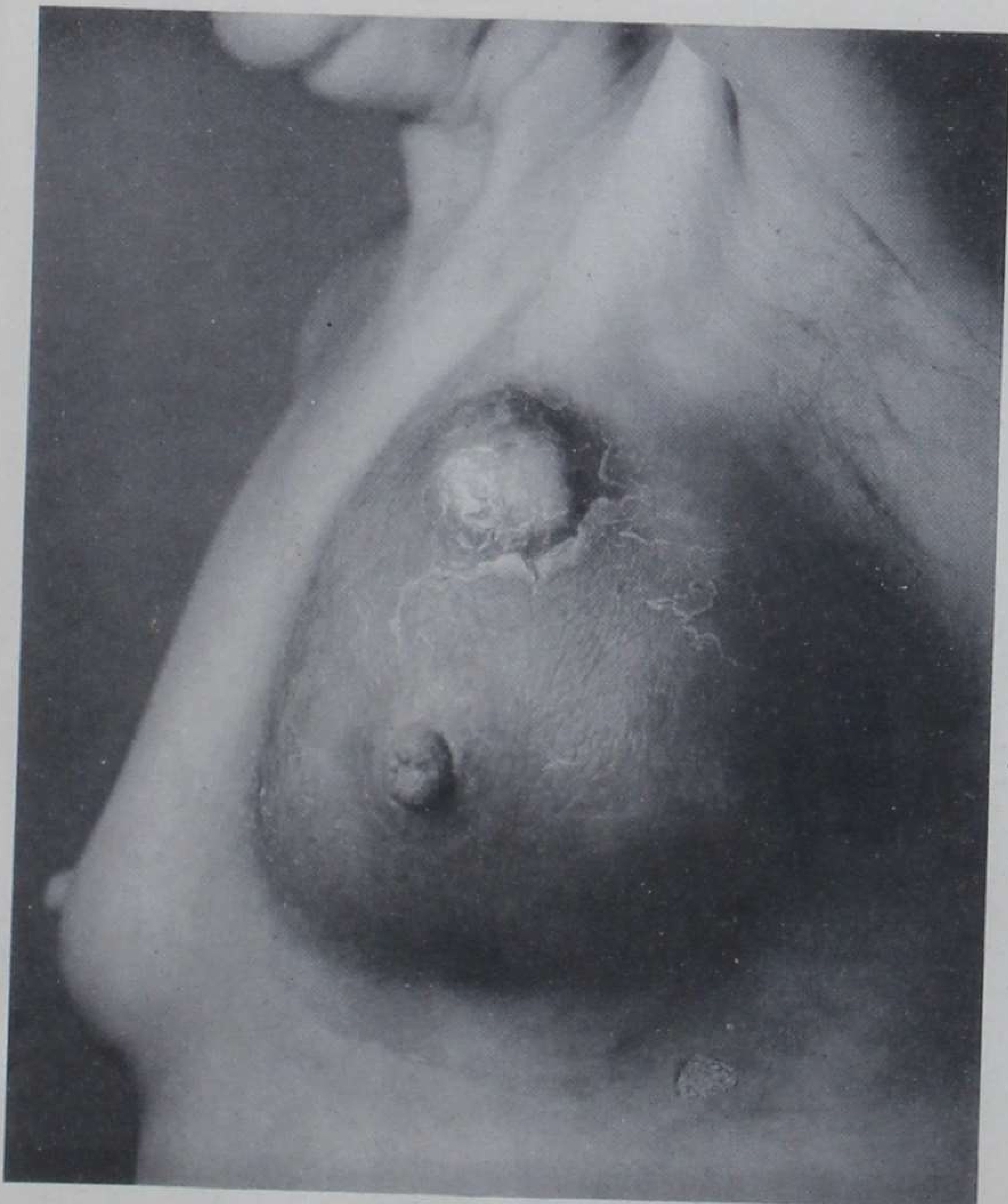


Fig. 178.—Massive carcinoma of the left breast.

by the index finger of the right hand lying along and pressing down the blunt edge of the blade.

Dermatome Technique.—Large defects are often more effectively covered by free grafts cut with a Padgett dermatome. The following are the basic points about dermatome technique :—

The donor site should be the opposite thigh in order that the graft may be cut by the assistant while the surgeon is performing the main operation. The blade should be set to cut relatively thin, at 14–16 thousandths of an inch, in order to avoid hypertrophic and keloidal scars in the donor site. Drum and skin are washed with ether. Dermatome cement is then spread evenly by brush on the donor site and on the drum. A period of time (2–5 minutes) is allowed for the cement to dry and reach its maximum stickiness. The drum is applied to the donor area and firmly pressed home over its front half and its front edge is then rolled up to produce a fold of skin. This fold is cut by a swinging motion of the blade held by the right hand. The drum is slowly rotated in the left hand while the right hand cuts the graft with a steady 'see-saw' motion of the

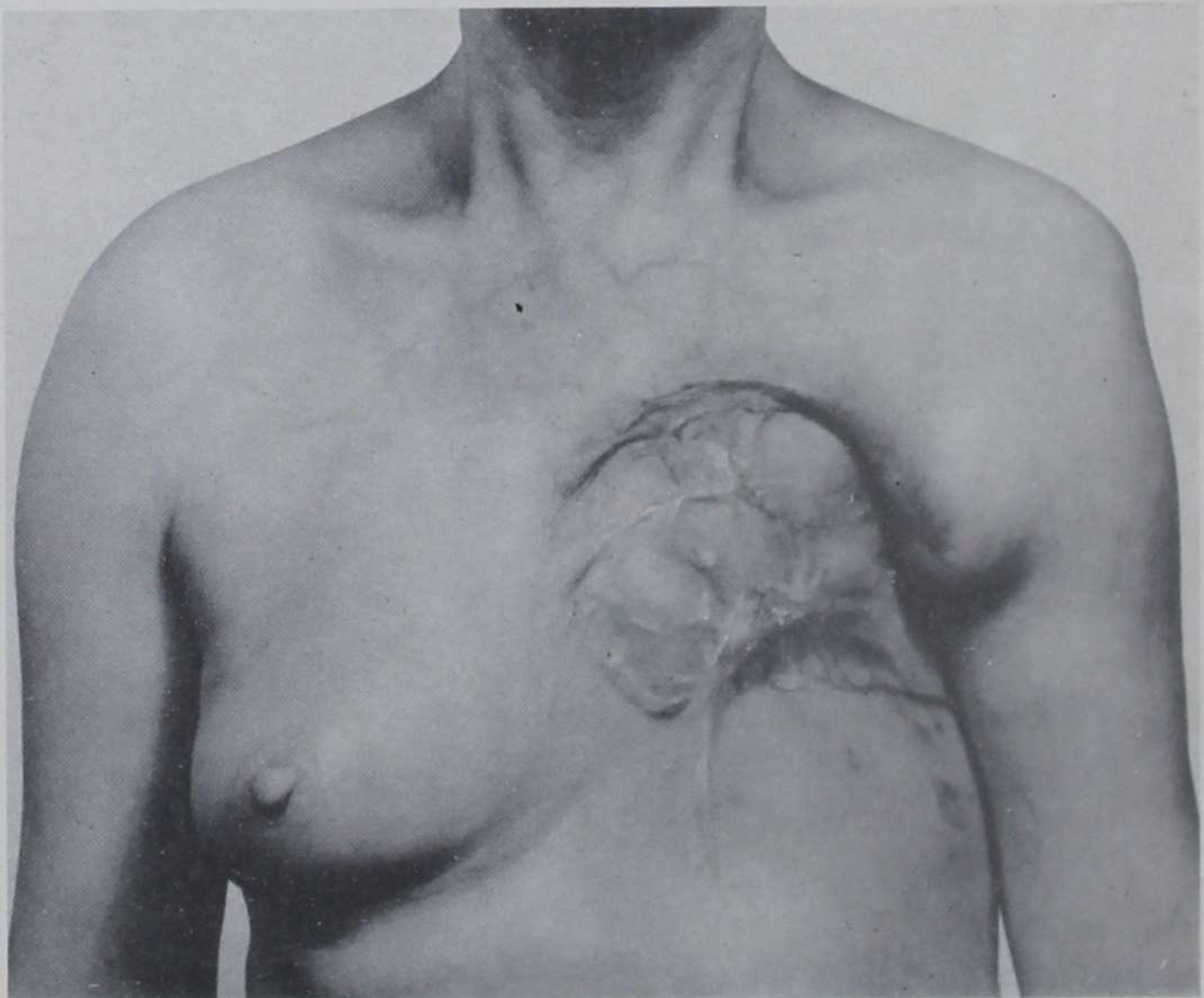


Fig. 179.—The same 4 months after operation and dermatome graft closure.

blade. On the completion of the full drum (an area of 10 × 20 cm.), or of an area of graft of sufficient size, the graft is cut from the thigh with scissors. During the cutting of the graft an assistant holds straight hæmostats parallel to each side of the drum. This prevents the deep side cuts which are sometimes seen when the dermatome is used.

Case.—**Dermatome Graft Closure of Massive Carcinoma of the Breast** (*Figs.* 178–180). (*Case treated in conjunction with Mr. H. J. B. Atkins.*)

The patient lived in the Channel Islands and had refused treatment during the early stages of the growth because of the German occupation.

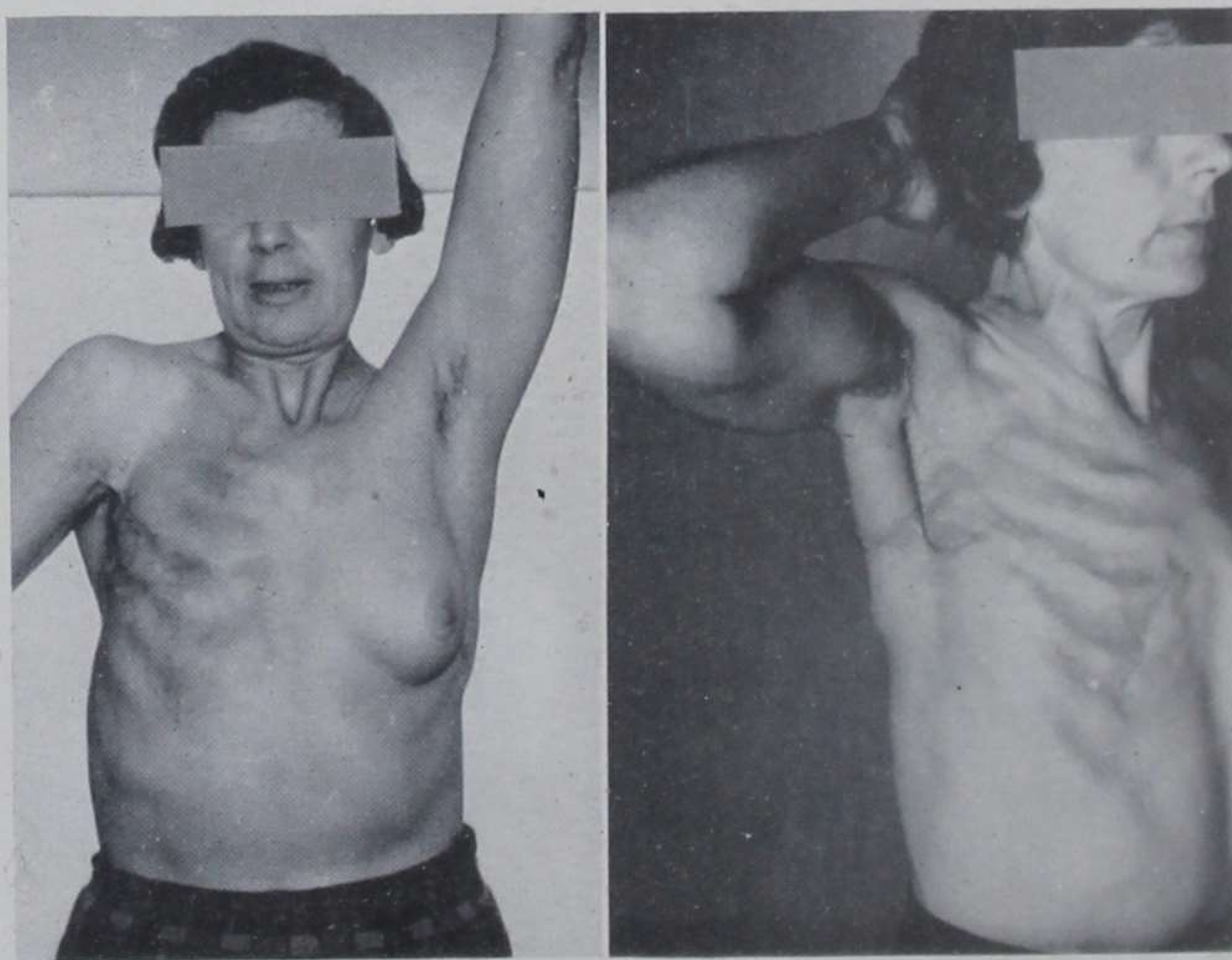
At operation Mr. Atkins removed the whole left breast and pectoralis major and minor; the axilla was untouched. Most of the skin of the left side of the front of the chest was removed, and after approximation of upper and lower ends of the wound there was a defect of about 70 square inches. The base comprised intercostals and the periosteum over otherwise bare ribs.

Fig. 180.—The same $2\frac{1}{2}$ years after operation.

Two complete dermatome drums were cut from the right thigh and were fixed in position by clips and a basting suture. Saline-soaked cotton-wool over tulle gras was applied and pressure maintained by strips of elastoplast, whose skin attachment was reinforced by Dresso-fix. There was some patchy central loss (about 10 per cent of the graft) and these areas were regrafted with hand-cut skin. Healing was not complete for a month after operation. She was given pre- and post-operative irradiation; 30 months post-operatively there is no local or general evidence of recurrence.

CORRECTION OF FAULTY BREAST SCARS

A breast scar may be wrongly sited and extend from chest to arm below the anterior axillary fold across the floor of the axilla; in which case it will, almost invariably, limit shoulder abduction.



A B

Fig. 181.—Release of axillary scar and brachial neurolysis following radical mastectomy. A, Shows a patient a year after a radical mastectomy for cancer of the right breast. This operation was followed by sloughing of the flaps, particularly in the floor of the axilla. Abduction of the shoulder was limited to 15° as shown in the photograph. There was severe and persistent intercostal and brachial neuralgia causing sleeplessness and almost completely disabling the patient. At the repair operation the axilla was cleared of scar tissue, necessitating resection of part of the axillary vein. The adherent chest scar was replaced by local flaps and dermatome grafts, placed on the ribs; a rotation flap was swung across the floor of the axilla.

B, Photograph taken 18 months after the operation. There is a supple scar which is painless except in cold weather. Abduction of the shoulder-joint is 90°.

It must be emphasized that the best result from all points of view in such cases is only obtained when the breast promontory is restored, by tube-pedicle tissue. If the patient is not prepared to undergo the operative programme necessary for this, then local flaps and free grafts as above can often give a satisfactory result.

If a long lateral flap including the floor of the axilla has undergone necrosis, the arm will again be anchored to the side, with perhaps severe brachial and intercostal neuralgia (*Fig.* 181). Or the scar may be keloidal, itching, tender, and unsightly. Massive necrosis and infection of flaps give rise to irregular, broad scars, diffusely adherent to ribs and intercostals (*Figs.* 182, 183). Faulty scars also result from irradiation necrosis, causing a chronic, painful, ulcerated area with, in some instances, necrosis of underlying ribs.

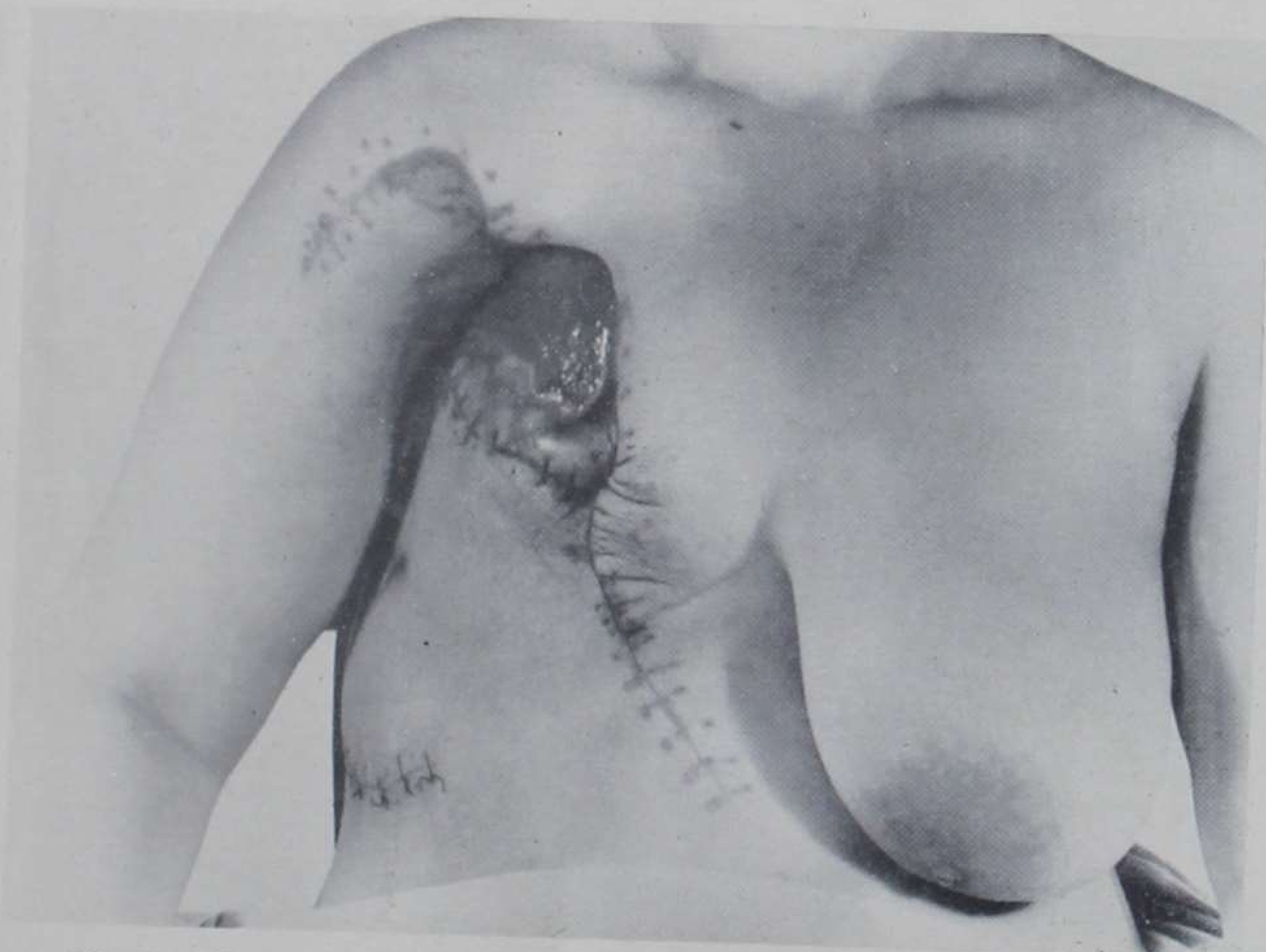


Fig. 182.—Repair of sloughing flaps. Rotation flap with dermatome graft to secondary defect used for repair of massive necrosis of radical mastectomy flaps. The figure shows the flap, which is based above and posteriorly and has been ' delayed '. The massive defect tunnels up into the apex of the axilla and is unsuitable for cover by a free graft.

Fig. 183.—Same case as *Fig.* 182. Shows the first dressing ten days after the second operation, when the delayed flap was swung over the re-excised defect. There is quiet, dry healing of the whole flap, including the apex of the axilla. Dermatome graft over the inferior secondary defect has been an edge-to-edge take. There is good abduction of the shoulder.

The basic principles in the repair of any faulty scar are the excision of all scar tissue and its replacement by tissue which is well vascularized, or can become so.

In most cases when mastectomy scars have to be revised, the most satisfactory replacement of the scar tissue is by a massive tube pedicle which, in addition to covering the defect from excision of the scar, has sufficient tissue to permit of the restoration of a mammary prominence.

Correction of Breast Keloids.—The treatment of a keloid comprises surgery and irradiation. Gillies and Levitt have drawn attention to the value of X-ray therapy in improving the appearance and quality of a breast scar. A pre-operative dose (800–1500 r) is given along the line of the proposed incision, followed by a further dose

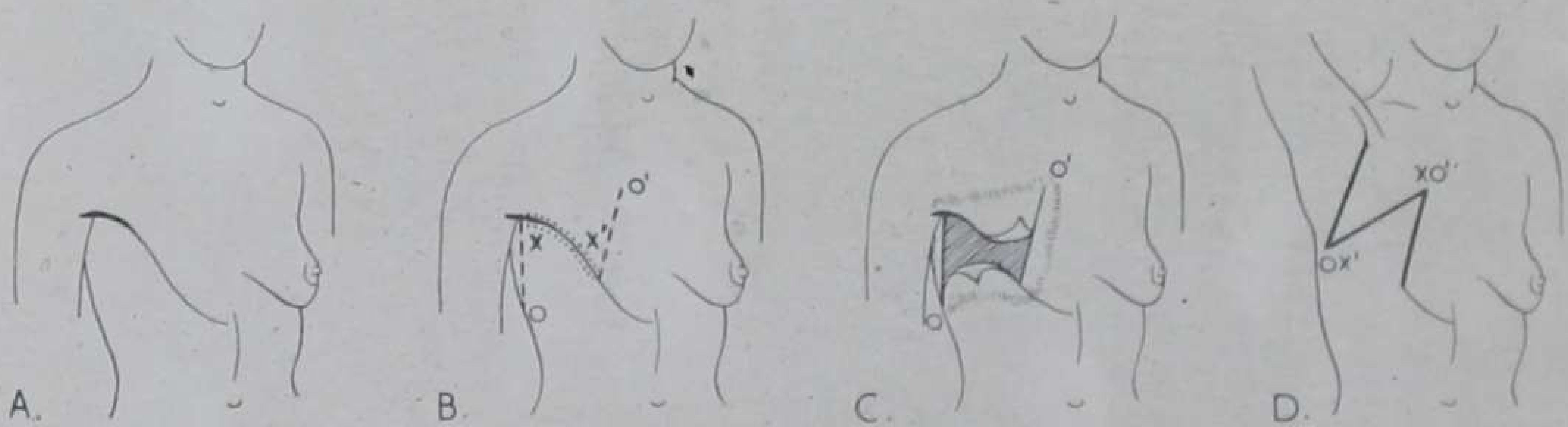


Fig. 184.—" Z " plastic for axillary scar. A, Depicts an anterior axillary scar limiting abduction of the arm ; B, The scar is excised and the Z flaps outlined with apices of about 60° ; C, The Z flaps are elevated ; D, The apices of the flaps have been transposed : X^1 to O and X to O^1.

1–2 weeks after the operation or when healing permits. Irradiation is also of great value when combined with surgery in the correction of hypertrophic and keloidal scars on the breast and chest wall.

At operation the area to be excised is marked out in ink, infiltrated with saline and adrenaline, and excised. The resultant defect may be closed by direct approximation after undermining. This closure is done with fine sutures in layers, using the technique already described. Sutures are removed on the 3rd–6th day. If a defect cannot be easily closed by approximation, or, if it lies along the anterior axillary fold, local flaps should be cut. These may be either rotation flaps or " Z " plastics ; grafts may be necessary for the secondary defects.

" Z " Plastics (*Fig.* 184).—In the reconstruction of the upper part of a mastectomy scar which is anchoring the arm to the side, a " Z " plastic, a most useful procedure, can be employed provided there has been little tissue loss. In a " Z " plastic the scar is lengthened at the expense of the breadth, the vertical pull of the scar is broken so that the interdigitating flaps can be more easily stretched than the original vertical scar. These effects permit an increased abduction at the shoulder.

A

B

Fig. 185.—Radium and diathermy necrosis of right breast. Treated by radical excision of ulcer and transposition of left breast with dermatome graft to secondary defect. A, Shows ulcer with sloughing intercostal and 5th and 6th costochondral junctions in area of dense scar tissue, with telangiectases and pigmentation of skin. A 'delayed' flap of the whole of the skin and subcutaneous tissue of the left breast has been cut. Excision of ulcer and scar tissue and 6 in. of ribs and cartilages left defect 6 in. across which was closed by swinging left breast across and filling secondary defect with dermatome graft from left thigh. B, Condition six months after operation. There was complete relief of pain, and the patient started to eat and sleep well from the time that the scar tissue and necrotic tissue was excised and the defect covered.

Technique.—The scar is excised. Two "V" flaps of skin and subcutaneous tissue are cut—with equal limbs and angles of 60° at the apices—on either side of the excised area. Both flaps containing skin and subcutaneous tissue are raised and rotated through an angle of 90° so as to bring the apex of one to lie at the base of the opposite flap from which it is furthest, and fixed in position by interrupted sutures. The apices are held by sutures passing from side to side of the defect and transfixing the dermis of the apex only.

Rotation Flaps.—If the loss of skin from the floor of the axilla has been considerable—this may be measured by taking patterns of the two sides—viable "Z" plastics cannot be cut sufficiently large. A big rotation flap, or tube pedicle, will be required in such cases. The former can be conveniently swung from above and posteriorly, and should be 'delayed' if of greater dimensions than approximately 10–15 × 10–15 cm.

REPAIR OF X-RAY DERMATITIS AND IRRADIATION ULCERS ON THE BREAST AND THORAX

Irradiated tissue is poor surgical material and cannot be undermined with safety for plastic repair. Furthermore, irradiation ulcers are liable to malignant degeneration. A radical excision of all affected tissues is therefore required, and this may have to include areas of rib if these are exposed and sequestrating, with consequently a very considerable defect.

The very large defects have to be covered by free grafts (*Fig.* 185). The excision and grafting may have to be done at separate stages, depending on the condition of the patient. For smaller defects a local 'delayed' flap, or a tube pedicle from the abdominal wall, can be used.

II. RESTORATION OF THE MAMMARY PROMINENCE. BREAST PROSTHESES. GYNÆCOMASTIA.

RESTORATION OF THE MAMMARY PROMINENCE

The operation described in the case below was introduced by Gillies for the restoration of the mammary prominence when it is absent on one side. By far the most common cause of this is, of course, a mastectomy for disease, but occasionally a congenital absence, or a lack of growth of the breast following radiotherapy for some overlying skin condition, is seen.

Case.—**Restoration of the Mammary Prominence.** (*Sir Harold Gillies' case.*)

Fig. 186 shows the Gillies method for the restoration of the mammary prominence as described in the text. An application of X rays to a capillary nævus of the skin of the breast region had resulted in complete arrest of growth of the left breast. The method used to restore the mammary prominence is demonstrated by the figures. A tube pedicle, comprising

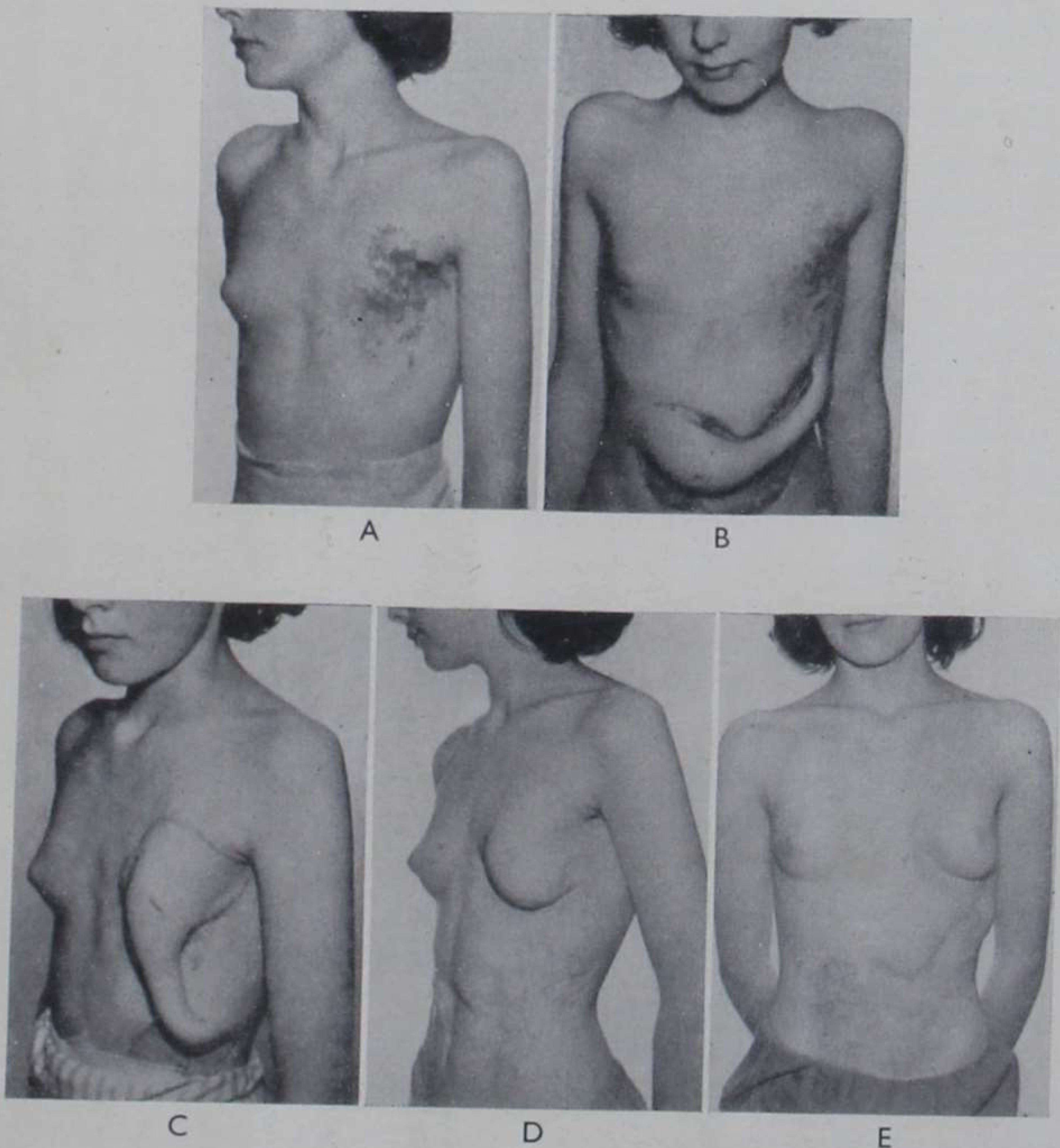


Fig. 186.—Restoration of the mammary prominence. (*Sir Harold Gillies' case.*) A, Mixed nævus of breast treated by radium; B, Design of curved tubed-pedicle flap; C, Suture of pedicle into recipient area; D and E, Early result of replacement of breast by tubed-pedicle flap.

the umbilicus and most of the abdominal skin and fat, was raised in stages and then swung into position on the left breast after excision of the hæmangioma. Later remodelling operations and revisions of the scars gave an optimum final result.

The decision to submit to an operation for restoration of a mammary prominence must be an individual concern; it cannot be pressed on purely clinical grounds. Yet there is little doubt that many general symptoms, besides those sometimes associated with a mastectomy scar, are due to a woman's sense of loss of her normal form. In such cases the most complete relief of symptoms is obtained when, in addition to excision of the scar, soft tissues are brought from a distance to restore a mammary prominence.

Technique of Operation.—The skin and fat of the abdomen are used for this repair, which is done in stages.

A tube pedicle, approximately 8×4 in., is elevated. This is based above and laterally over the ribs below the axilla, and below extends downwards and inwards to the border of the rectus at about the level of the umbilicus (*Fig.* 186). A month later it is enlarged 4–6 in. to include the umbilicus ; the incisions are carried laterally from the lower end of this thick tube to enclose a disk of skin together with all fat down to the rectus on the opposite side. This disk measures at least 6 in. in diameter. It is not completely encircled and the two incisions are separated by a distal intact bridge of 4–6 in. A period of three months is now allowed to elapse. This disk is then completely circumcised and elevated with the lower end of the tube pedicle. This large disk of skin and fat, together with the umbilicus and the lower end of the tube pedicle, is swung upwards into the prepared position of the missing breast. The lower attachment of the tube pedicle is not divided for six to eight weeks and is then elevated to join the main mass. One or two further remodelling and scar revision operations may be necessary during the next six to twelve months to obtain the best end-result. The final form of the breast will depend upon the sculptural sense of the surgeon.

The secondary abdominal defects created in the early stages are covered by free grafts.

Nipple Restoration.—In the plan described above, the umbilicus is transported to form the future nipple. Gillies has shown that its appearance can be made a much closer match to the intact side by further adjustments. These include the insertion of a small piece of preserved cartilage to produce eversion, and the use of tattoo to give the colour of the normal areola. When the umbilicus is not present in the restored breast, a good match of the areola can be obtained by excising a properly sited circular area of skin and replacing it with a mucous membrane graft taken from the mouth.

Reduction of the Normal Side.—By the method described a mammary prominence of very normal appearance, and of what may be called average size, can be constructed, but it may not, of course, match the intact side. The best results in these cases are, therefore, only obtained by a late reduction of the intact breast to match the reconstructed side.

BREAST PROSTHESES

Breast prostheses of vultex or of soft acrylics can be of considerable value in restoring normal contour when worn under a dress with a high neckline, but are of little use in outdoor pursuits such as tennis and bathing. In many cancer cases prostheses are the only practical measure for the patient. They are used, too, after a bilateral mastectomy, or when there is bilateral congenital absence of the breasts.

THE INCISION FOR GYNÆCOMASTIA

The incision introduced by Jerome Webster for mastectomy in men suffering from gynæcomastia circumscribes half the areola. A trapdoor flap of areola and nipple is elevated and through this the rest of the breast substance can be removed, if necessary piecemeal. The wound can be closed with subcuticular catgut, and, lying at a line of junction between skin and areola, leaves an almost invisible scar—a great advantage to those who object to a breast scar as much as a female breast form.

III. THE TREATMENT OF PENDULOUS AND HYPERTROPHIC BREASTS

A breast reduction, done for those who want it and with reasonable competence, affords great physical relief, and this is the chief object of operation. A surgeon should choose his cases from those who have definite physical symptoms due to excess breast weight, or whose breast shape is a manifest economic or psychological disability. Few operations give greater satisfaction to the patient.

A number of operations have been designed for the reduction of pendulous and hypertrophic breasts, but the basic principles of the good operation are the same. Enough breast tissue, together with excess of covering skin, must be removed to relieve the weight; the incision through which removal is done should be below the new nipple line; the viability of the nipple must not be imperilled. If it is impossible to excise enough breast tissue without prejudicing the blood-supply of the nipple, then the reduction must be done in two stages. The only exception to this rule is the operation in which the nipple is transported as a free graft in an operation reserved for cases of the most massive hypertrophy and the most extreme dependency. The new breast form obtained after excision of excess tissue must be independent both of stay sutures to the pectoralis and of the skin cover. The object for most patients is a "gently pendant" rather than a pointed virgin breast (Gustave Aufright).

Choice Between One- and Two-stage Reductions.—Choice between a one- and a two-stage reduction, and the plan of operation of one-stage reductions, are based on the need for preserving an adequate blood-supply to the nipple (*Fig.* 187). This comes chiefly from the medial side, from the 2nd to 5th intercostal

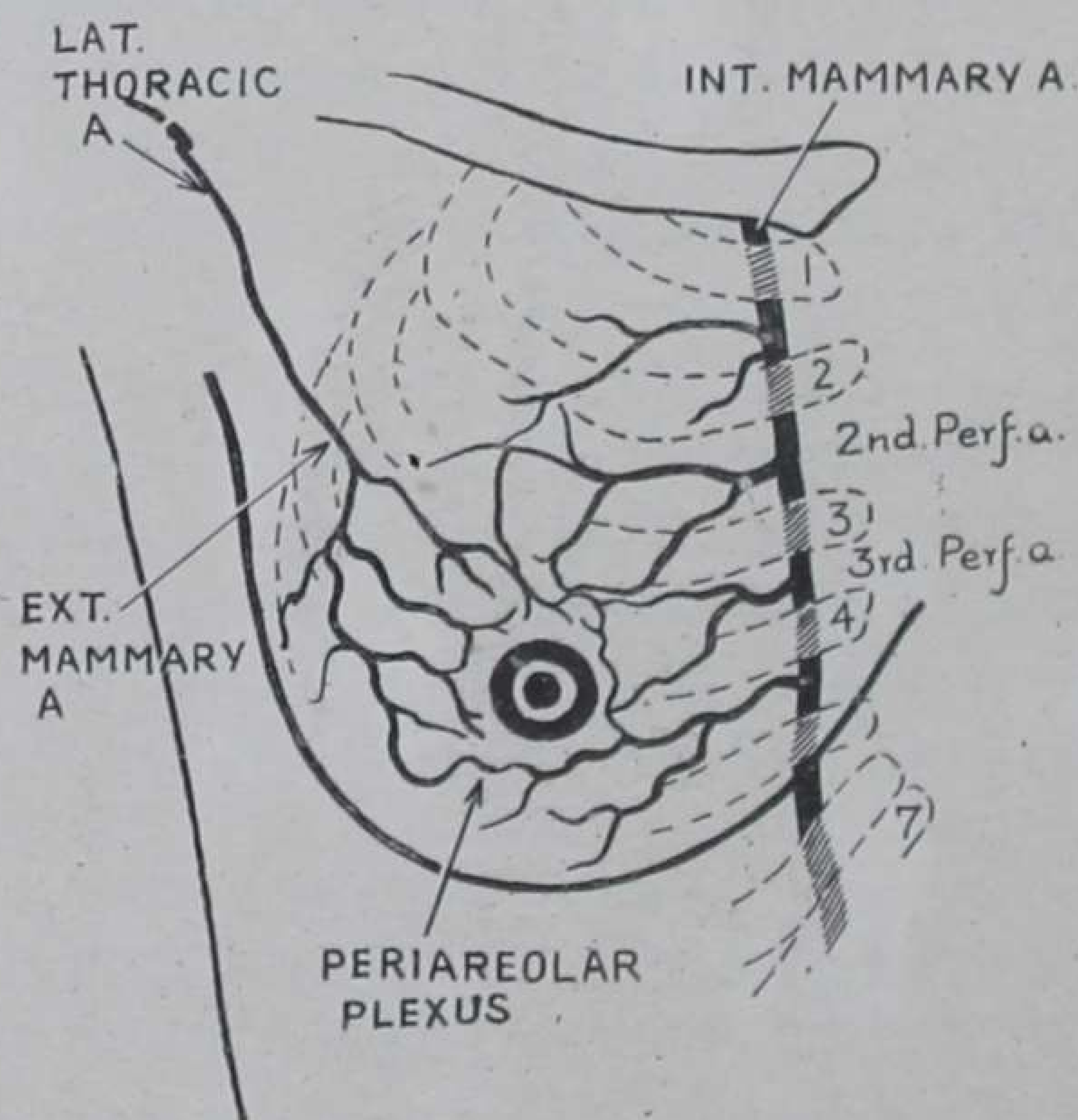


Fig. 187.—Diagram of the arterial supply of the nipple, showing a well-formed periareolar plexus derived from the second, third, and fourth perforating branches of the internal mammary artery and the external mammary branch of the lateral thoracic artery. (*After J. W. Maliniac.*)

branches of the internal mammary. An important part of this supply proceeds close to the deep surface of the dermis on the medial side of the breast to the superficial periareolar plexus which supplies the nipple. The second blood-supply of the nipple is derived from the lateral thoracic artery; usually a subsidiary supply, but in over 10 per cent of cases the chief source. In addition, minor and inconstant branches from intercostals and the pectoral branch of the thoraco-acromial axis run into the periareolar plexus. Sometimes (less than 10 per cent of cases) there is no plexus and the nipple is supplied by branches from one source only—generally the internal mammary. The one-stage Biesenberger operation is designed to preserve intact the main blood-supply of the nipple, while removing the entire lateral supply. The variability of the blood-supply, however, makes the viability of the nipple uncertain when this operation is used routinely.

The normal position of the nipple in the nulliparous breast of a young woman is about 16–18 cm. from the suprasternal notch, and the distance between the two nipples about 20–22 cm. If the bulkiness of the breast has produced a dependency of the nipple of more than 6–9 cm. below the normal, removal of enough tissue to relieve symptoms and restore shape can only be done in one stage with some risk to the viability of the nipple.

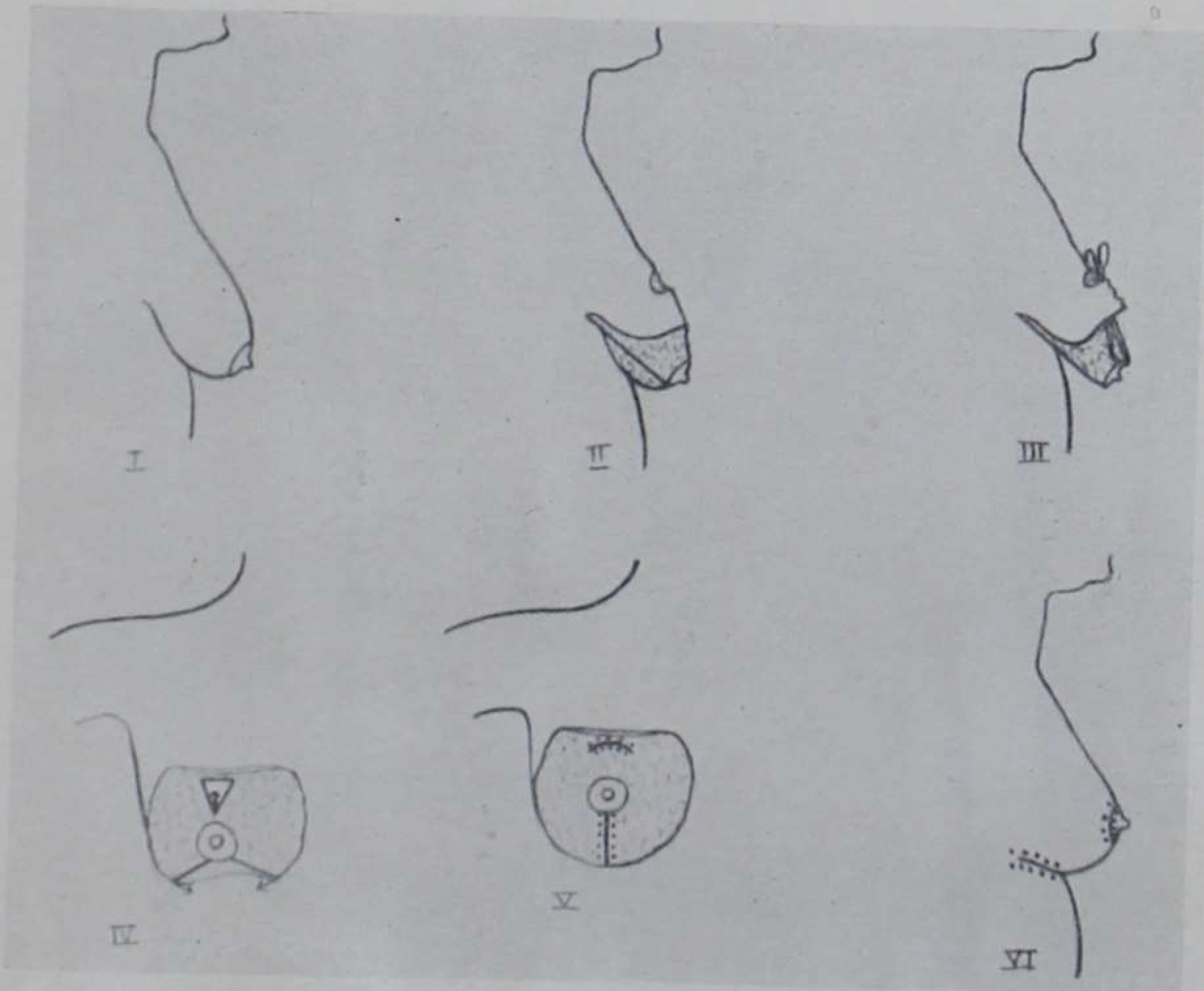


Fig. 188.—Passot type double pedicle reduction. (I) Breast before operation. Elliptical incisions are made from lateral to medial side of breast; one passes just above the nipple and one just above the submammary groove. The breast is dissected from the upper flap. Its lower half and a central upper segment are excised (II and IV). The raw edges are apposed and fixed with sutures (V). The circular area for the new nipple 6 to 7½ in. below the suprasternal notch is excised (III), and the nipple sutured into its new position. The skin incision is closed in the submammary groove (VI).

Two types of one-stage breast reduction are available for the less bulky breasts, the Passot and the Biesenberger.

In the Passot operation (*Figs.* 188, 189) most of the lower half of the breast substance below the nipple, and a central wedge above it, are removed. Viability of the nipple is assured by a double pedicle of medial and lateral breast tissue through which a blood-supply will reach the nipple whatever the vascular pattern. After the excisions the breast substance is displaced upwards by suture of the raw surfaces, and a reasonable form is obtained, but the double pedicles of breast substance can leave somewhat prominent lateral and medial folds on either side of the breast. For this reason the operation is best reserved for well-built people with good breadth of shoulder, in whom such folds are less obvious.

In the Biesenberger operation (*Figs.* 190, 191) the lateral half and most of the lower part of the breast substance are excised by an

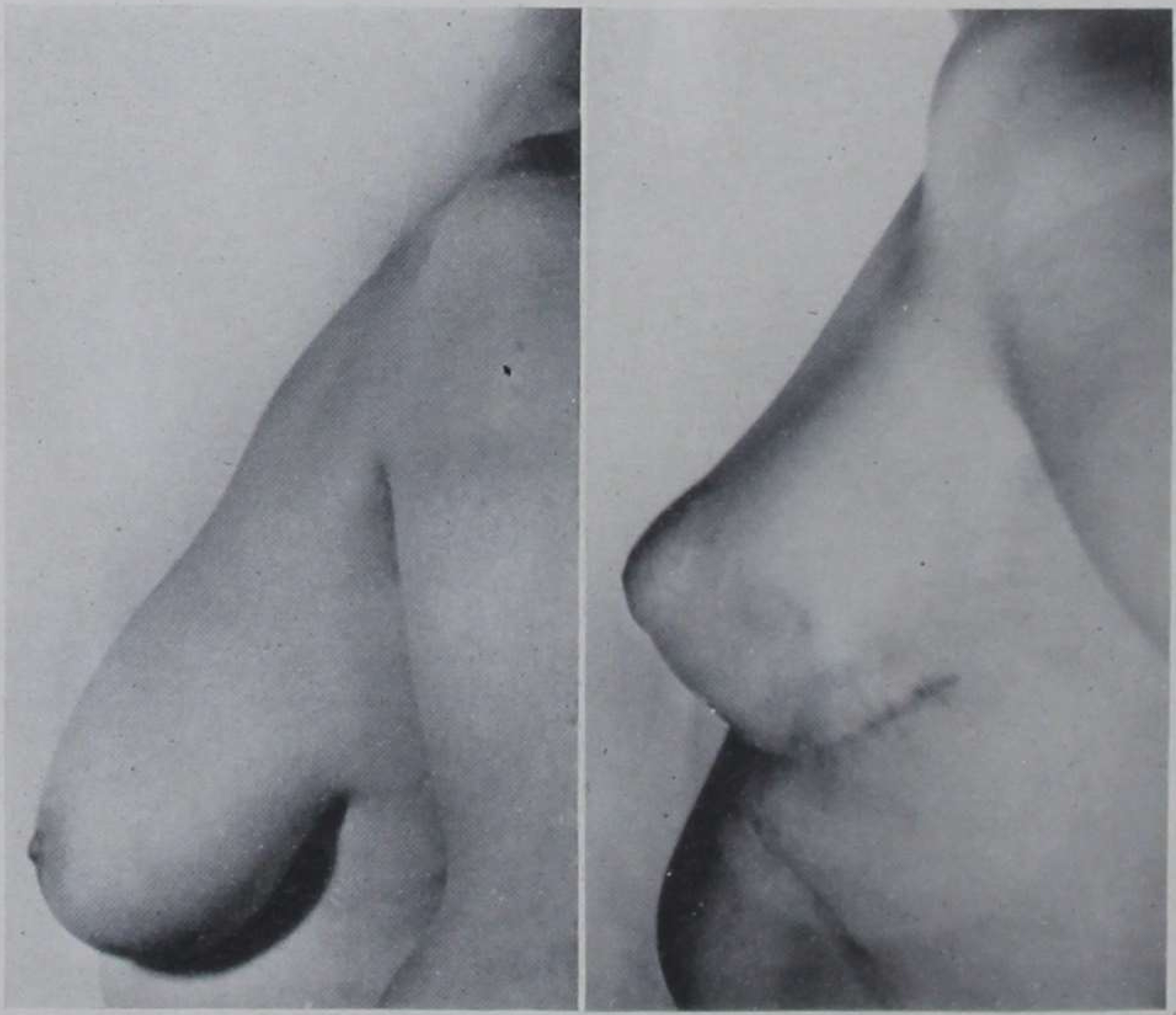


Fig. 189.—Passot type reduction. The photographs show the sort of breast form, with a full forward projection of the nipple, which may be obtained by the Passot operation. In this procedure the nipple is borne on both a lateral and a medial pedicle of breast tissue, after excision of most of the lower half of the breast and of the central upper wedge. Coaptation of the lower raw surfaces displaces the nipple up and forward. It may be necessary at a later stage, as in this case, to thin the medial and lateral pedicles to obtain an optimum result.

S-shaped incision. The lower raw lateral surface is rotated up and apposed to the upper raw surface. The nipple then depends entirely upon the supply reaching it from the medial breast substance, which is sufficient in most cases.

In order to avoid risk some surgeons prefer to excise the axillary tail of the breast together with the lateral thoracic artery as a preliminary step. A month later the operation is completed. The preliminary stage ensures a main blood-supply from the medial side.

When the dependency of the nipple is more than 6–9 cm. below the normal—from the suprasternal notch—the two-stage procedure described by Ragnell is recommended. In the first operation a central wedge of breast tissue is removed from the upper half of the breast above the nipple, when the medial and lateral blood-supply is left intact. Excess skin is excised and the nipple implanted at its

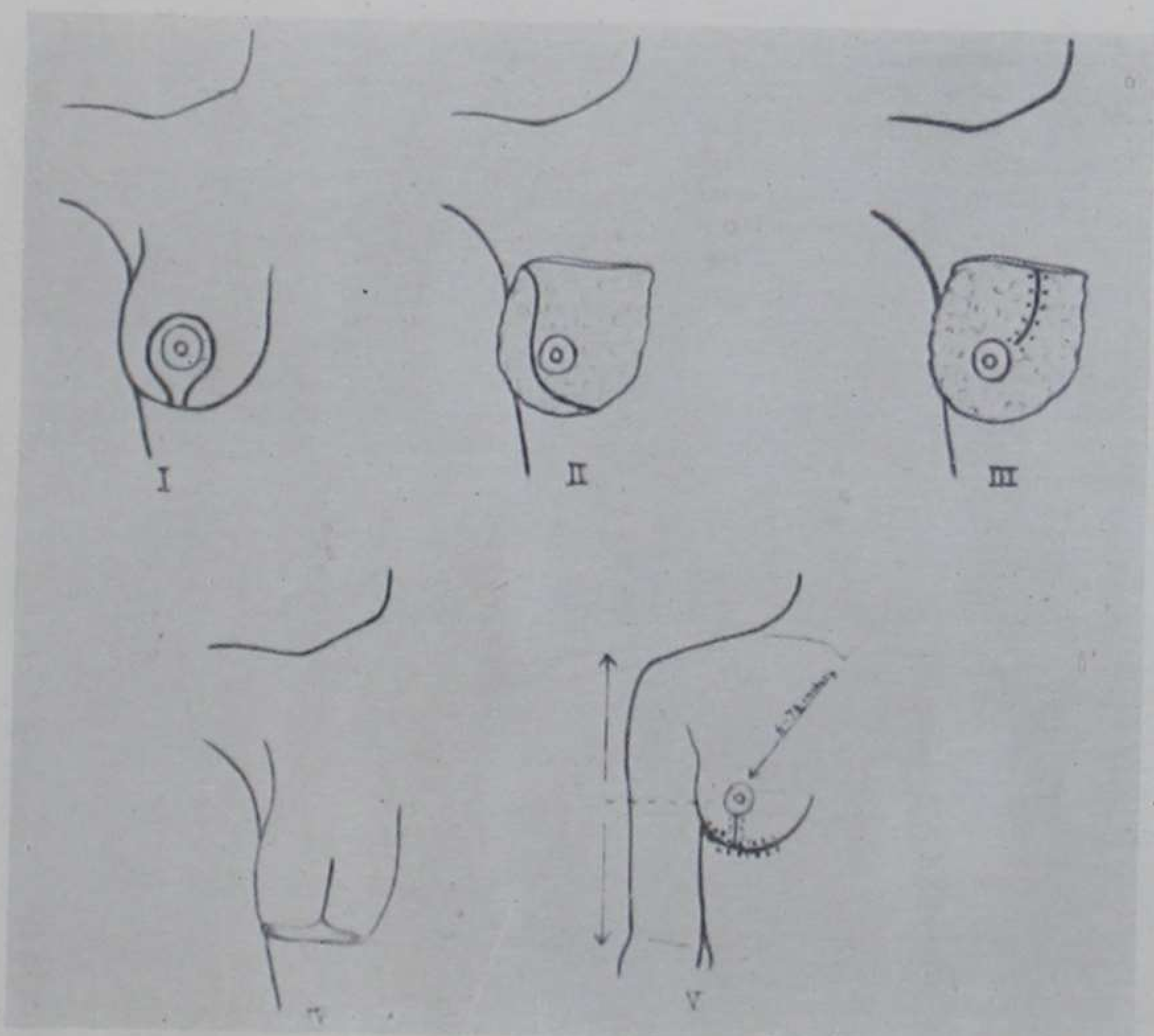


Fig. 190.—Biesenberger type single pedicle reduction. A pear-shaped ellipse of skin is removed from around the nipple and the incisions are carried down to the submammary groove, where they are prolonged on each side (I). The flaps are dissected and the breast presented (II). A wedge of breast, comprising most of the lower and the whole of the outer part, is excised (II). The raw areas are then apposed and sutured by rotating the lower raw surface up to the upper (III). The flaps are drawn over the new breast and excess skin excised (IV). A circular area of skin, 6 to $7\frac{1}{2}$ in. from the suprasternal notch, is excised for the nipple (V), which is sutured in position.

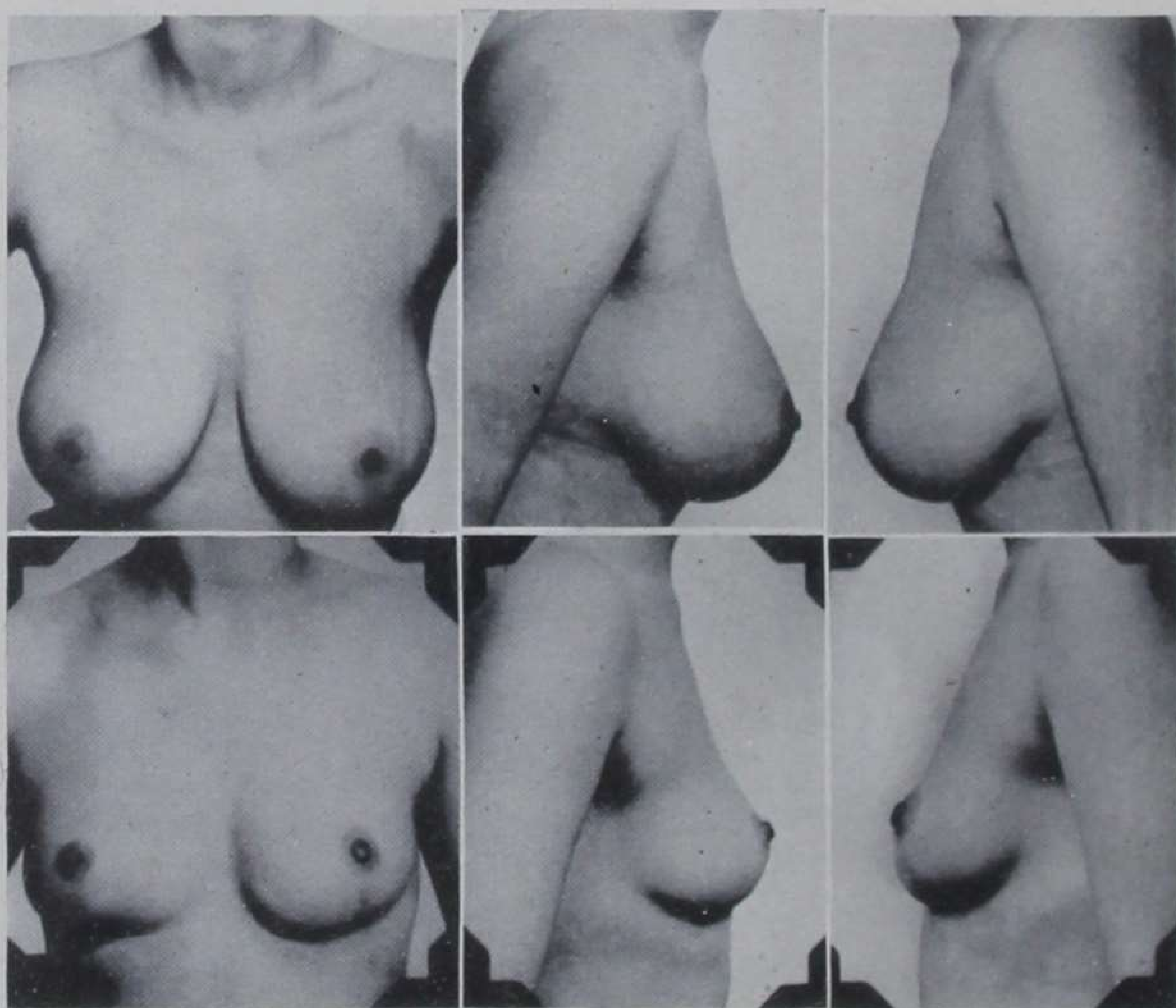
proper level, 16–18 cm. from the suprasternal notch. Two months later the breast is further reduced by the excision of most of its lower half. The raw surfaces are then coapted by suture to produce a normal contour. At this second operation there is no interference with the medial or lateral blood-supply from the level of the nipple upwards.

Points in Technique in Breast Reductions.—

Pre-operative Plan.—The operation should be done two weeks before a period, and at least six months after lactation.

Whether a one-stage or two-stage is done, a careful pre-operative plan is necessary the day before operation. With the patient sitting in a chair the incisions are marked out in methylene blue on the breast and thorax wall. The new position of the nipple and its size, 16–18 cm. from the suprasternal notch and 20–22 cm. from the opposite side, is similarly drawn with a needle dipped in methylene blue.

1 2 3



4 5 6

Fig. 191.—Two-stage breast reduction. (*Sir Harold Gillies' case.*) Photographs 1 to 3 show the pre-operative condition, a moderate degree of hypertrophy and dependency of the breast in a patient of slim build. At the first operation a Biesenberger type reduction was performed. The bulk of the breast was reduced by removal of its lateral half. At a second stage the scars were revised and a further revision of the form of the breast done to produce the optimum possible effect. Photographs 4, 5, and 6 show the final result.

Circumcision of the Nipple and Undermining of Adjacent Skin.—Saline and adrenaline are injected along the incision lines. The table is tilted so as to place the patient in a semi-sitting position. The first step is the circumcision of the nipple, which is best done with a No. 15 B.P. blade. In many cases it will be necessary to reduce the areola, excising a peripheral ring of areola and reducing the transverse diameter of the new nipple and areola to about 5 cm.

In both the Passot and Biesenberger operations special care is taken to undermine the flaps very close to the dermis near the nipple, especially on the medial side. The blade of the knife is therefore guided by a finger on the overlying skin so that virtually no fat is left on the skin lying medial to the nipple. Towards the periphery—5–6 cm. from the areola—the undermining is at a deeper plane, just superficial to breast parenchyma, and is done chiefly by blunt gauze dissection.

Maliniac's method of nipple reconstruction is shown in *Fig.* 192.

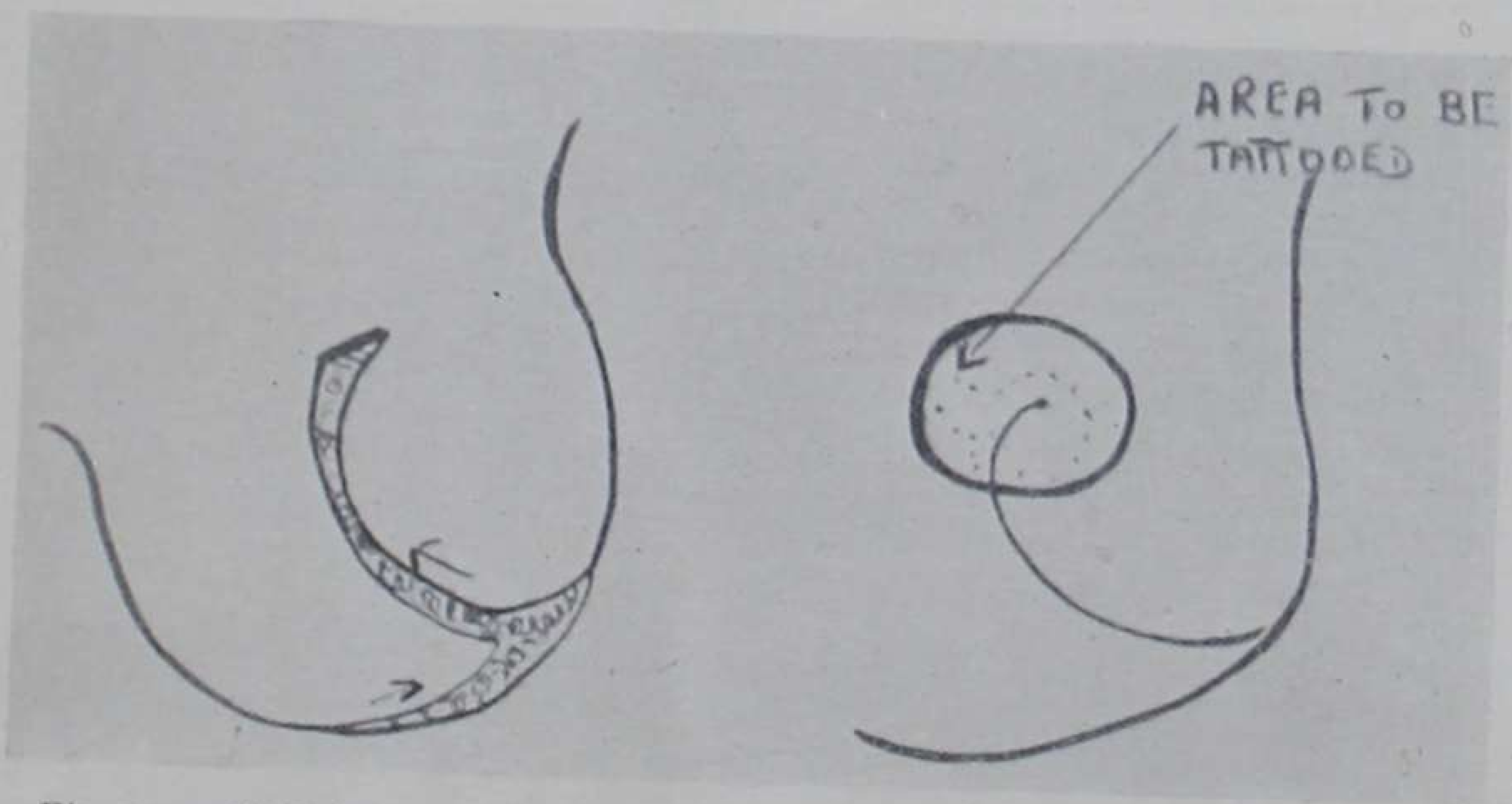


Fig. 192.—Maliniac's method of nipple reconstruction. This method is used for restoration of the nipple when it has sloughed following faultily planned reduction operations. The nipple prominence is provided by a rotation flap. The secondary defect is filled by an advancement from the opposite side. Tattoo provides the areola.

ONE-STAGE BREAST REDUCTIONS: THE PASSOT AND BIESENBERGER OPERATIONS

Skin Incisions.—

Passot Operation.—In the Passot type of operation the nipple is circumcised and adjacent skin undermined. A horizontal ellipse of skin—the upper limb of this runs just above the nipple and the lower limb just above the retromammary groove—is removed. The upper incision is undermined by blunt dissection and the breast substance dislocated into the hand of the operator. Almost the whole of the breast below the nipple is now removed with the knife. A central triangular wedge may also be removed above the nipple. The raw surfaces of the lower cut edge are approximated. The nipple is displaced upwards and forwards and the raw surfaces of the upper central defect are also approximated and sutured. The suturing should be done in such a way and with such adjustments as to produce a proper breast form. Chromicized 0 catgut is used. Additional fixation to the pectoralis is provided by chromic catgut sutures, but the form of the breast should be independent of these temporary sutures.

Biesenberger Operation.—In the Biesenberger operation, after circumcision of the nipple, a pear-shaped incision is extended and carried downwards into the retromammary groove. Here the incision is extended medially and laterally. The two flaps are dissected upwards and inwards and upwards and outwards respectively. At the completion of this dissection, which is usually done bluntly by finger and gauze, the breast parenchyma, with the nipple centrally, is dislocated into the hand of the operator.

A large lateral excision, which comprises most of the breast below and lateral to the nipple is done by a giant S incision. The lower half of this raw surface is then rotated upwards and outwards into apposition with the other half. The effect is again to raise and to push forward the nipple. Sutures are inserted after such adjustments as are necessary to produce the best form.

The Nipple.—At this stage in both Biesenberger and Passot operations (with excisions complete, raw surfaces coapted, and the new breast form obtained) the previously marked-in area for the new nipple is excised. This marked-in area should lie over the nipple without tension when the upper skin-flap is drawn across the new breast. The nipple is sutured to the margins of the defect by subcuticular four o catgut. Keloid formation may occur in this region in the stitch marks of even the finest interrupted silk sutures.

Suture of Flaps.—In both operations excess skin is now excised. This comprises, in the Passot operation, the excess in the upper flap after it is drawn down across the breast. The suture line lies in the retromammary fold. It is sometimes necessary to excise triangles or wedges of excess skin at either end of this line to avoid unsightly ‘ dog ears ’ there.

In the Biesenberger operation there is vertical extension from the nipple to this groove. Excess skin and fat are removed with straight scissors from the medial and lateral flaps on either side of this vertical incision and from their lower borders above the groove. The final closure must not be under tension or necrosis of the flaps at the T junction will occur.

Post-operative Care.—Drainage is provided for 48–72 hours at each end of the preliminary incisions. Sutures are removed at the 4th–6th and 8th days. The post-operative dressing should be bulky and provide light compression. Gauze–wool–gamgee packs and crêpe bandages fixed by overlying strips of elastoplast answer this purpose. These dressings should be so applied that the nipples are readily available for examination. The prompt evacuation of a hæmatoma from the areola region may preserve the viability of the nipple.

TWO-STAGE BREAST REDUCTIONS: THE RAGNELL OPERATION

First Stage.—This operation leaves both medial and lateral vascular pedicles of the nipple intact.

The nipple is circumcised and Passot type elliptical incisions are then made above and below the nipple. The upper flap is dissected and the breast mobilized into the hand of the operator. An upper central wedge of breast is cut from above the nipple. In very depleted breasts a vertical incision only is made here.

A circular skin defect is cut for the nipple at the appropriate site (6 in. below the suprasternal notch and 9 in. from the other nipple). The nipple is sutured into place. The two edges of the elliptical defect are sutured along the new retromammary fold.

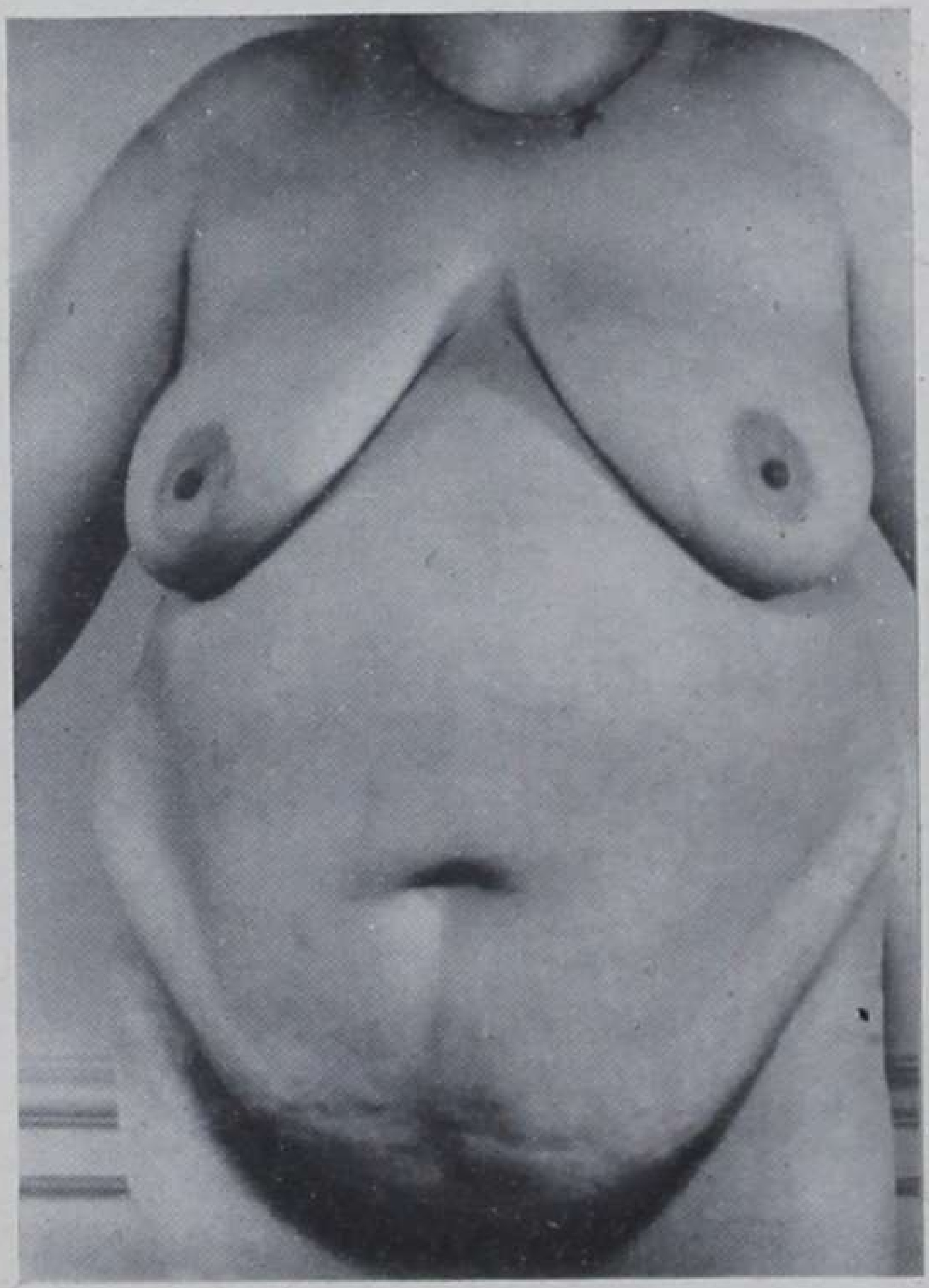
Second Stage.—This stage is done three months after the first stage.

The retromammary incision is excised, generously at each extremity. Skin with subcutaneous tissue is undermined up to the areola border. The necessary reduction of breast substance is done by removing a crescentic wedge from the exposed lower half of breast. The two sides of the raw breast surface are approximated and the skin-flaps adjusted to lie neatly in the retromammary groove by means of sutures. Drainage is instituted at either end.

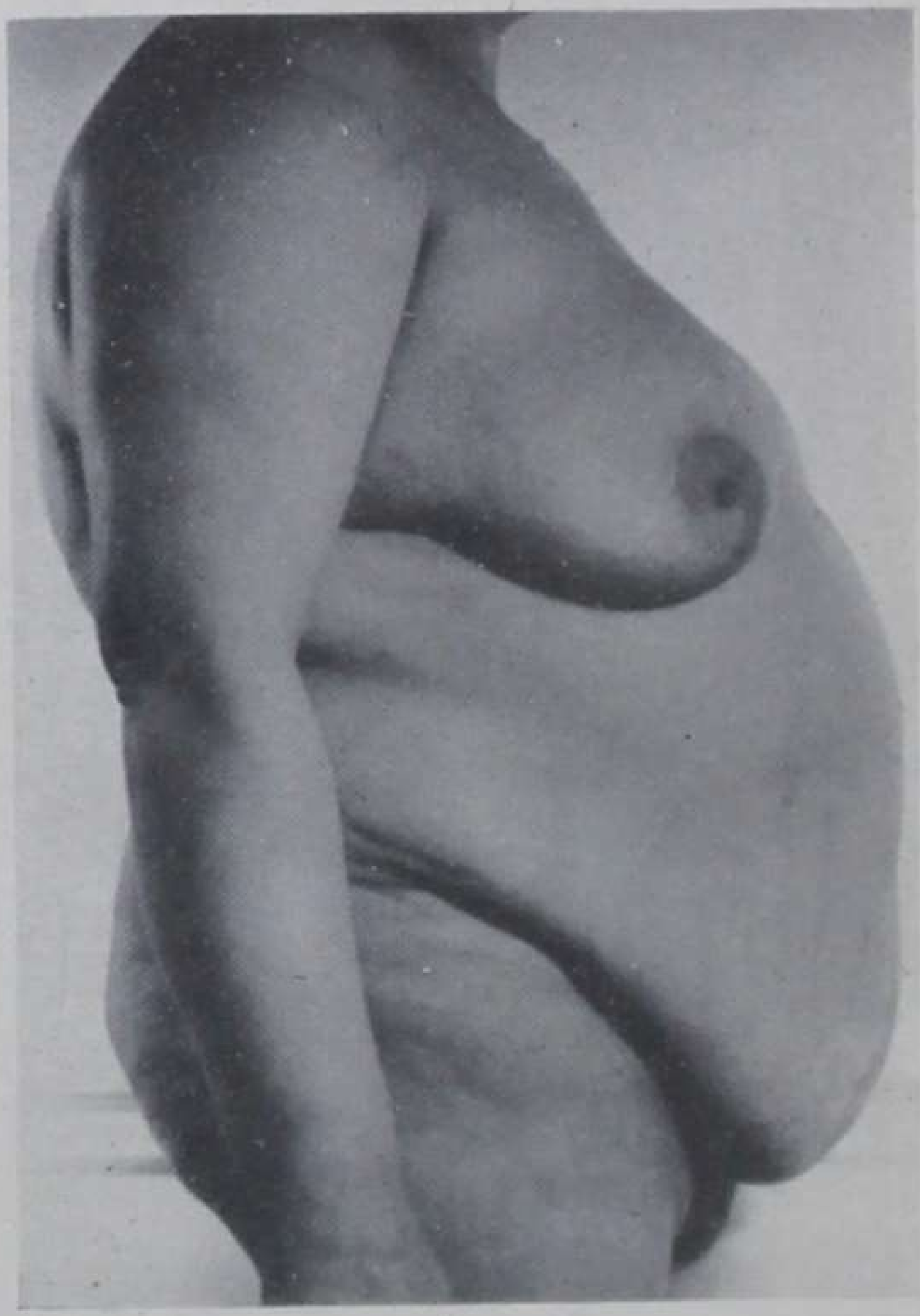
REDUCTIONS USING A FREE GRAFT OF NIPPLE

This operation is reserved for very pendulous and hypertrophic breasts; when, for instance, the breasts reach to the level of the umbilicus or even the groins.

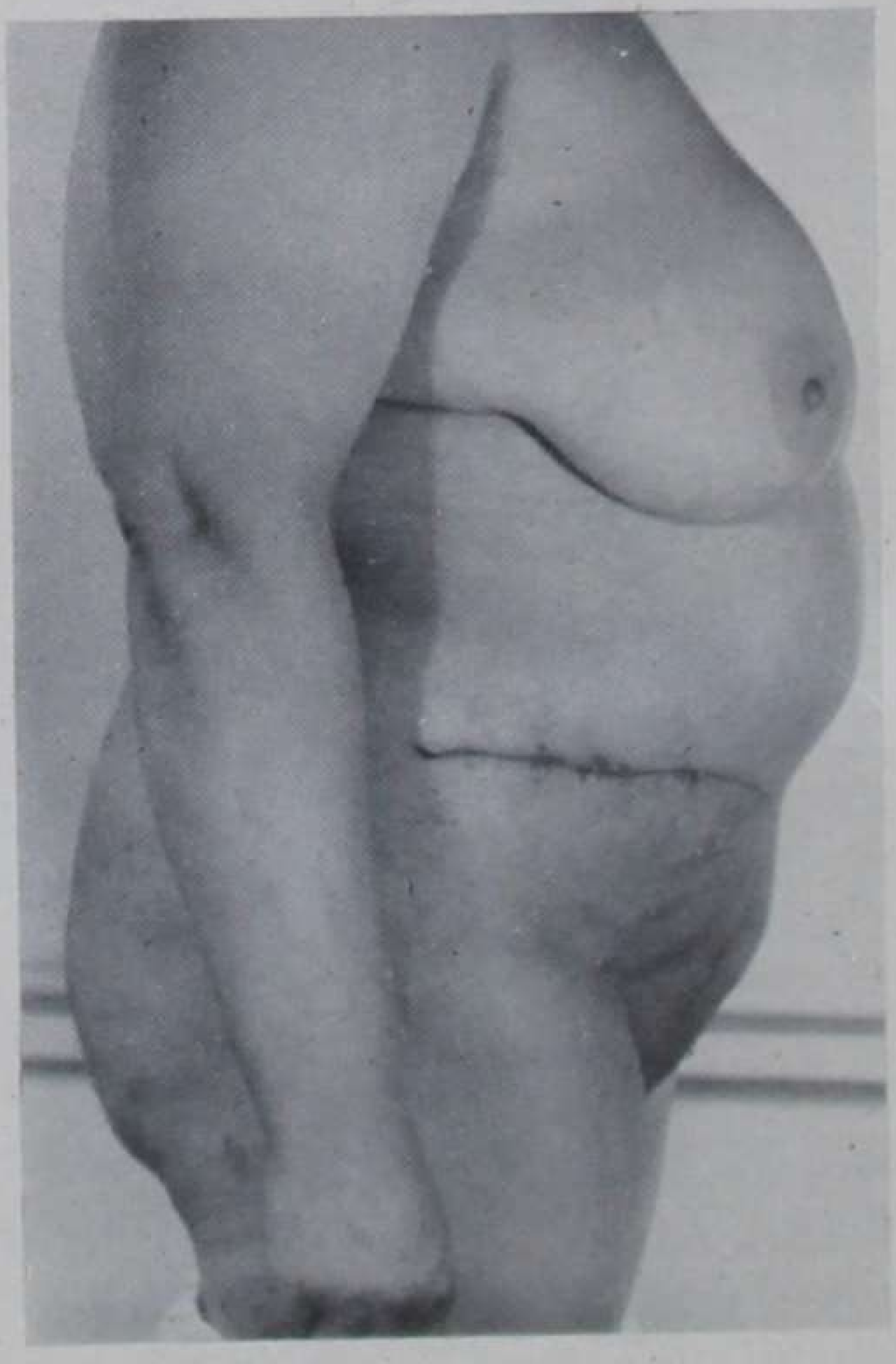
The nipple and areola are excised, together with some erectile musculature. The breast is amputated, using elliptical incisions and leaving enough skin and subcutaneous fat to form small, rounded mammary prominences. The incision is closed along the new sub-mammary line. A circular area of epidermis on the site of and the same size as the new nipple, is now removed. This dissection should be carried out superficially to the deep layer of the dermis, so as to leave a vascular dermal recipient bed for the nipple graft. The nipple graft is now sutured in position. Two or three basting sutures are passed through the areola near the centre into the dermal bed. Pressure is applied to the graft through pressure wool by elastoplast and crêpe. The dressing is taken down and sutures removed on the 6th–10th day. (*Fig.* 193.)



A 1.—Pre-operative. Front view.

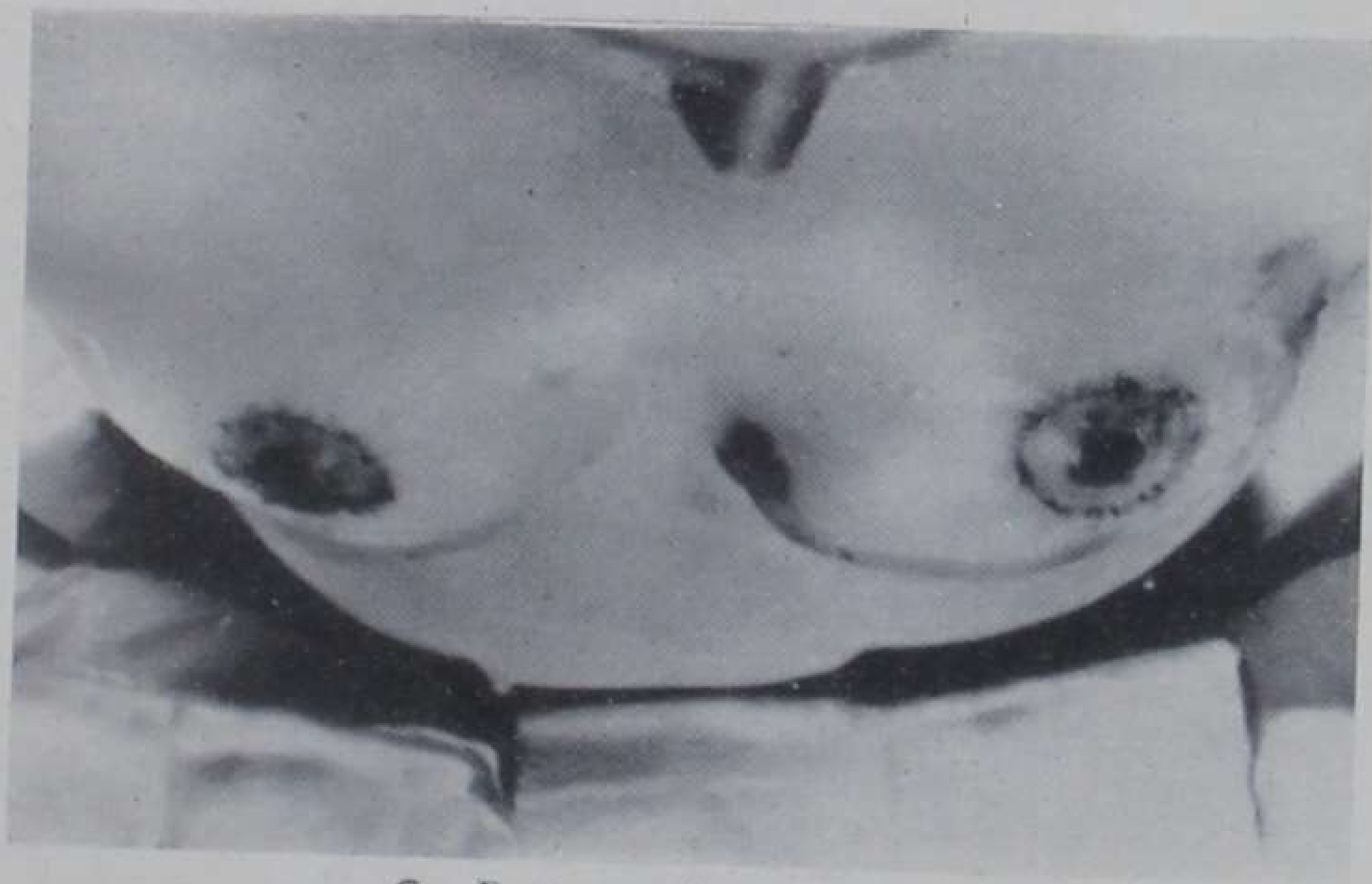


A 2.—Pre-operative. Side view.



B.—Post-operative. Abdomen only.

(For legend, see opposite page.)



C.—Post-operative. Breast.

Fig. 193.—Breast reduction in treatment of obesity: use of nipples as free grafts. A1, A2, Show a patient of middle age suffering from gross obesity, chiefly concentrated in pendulous breasts and pendulous abdomen. Such cases are particularly suitable for the method of breast reduction with free graft of the nipples. The excess breast tissue is cut off through an elliptical incision. The nipples are excised and freed completely of their subcutaneous fat except for the very centre. They are then sutured on to circular dermal defects situated 6 in. from the suprasternal notch and 4–4½ in. from the midline. B, Shows the effect of the preliminary reduction of the abdomen (*by Sir Harold Gillies*). C, Post-operative view of the breast after reduction and free graft of the nipple. Taken at the first dressing, a week after operation. The grafts were a complete edge-to-edge take, and the patient was out of hospital in ten days free of dressings. 17 oz. of tissue was removed from each breast.

POST-OPERATIVE EFFECTS AND EVALUATION OF RESULTS

Post-operative Effects.—Early complications of breast reduction include hæmatomata and necrosis of nipples and flaps. All except the smallest hæmatomata should be evacuated promptly. This generally necessitates an anæsthetic, removal of sutures, and gentle digital exploration. Necrosis of the nipples is very uncommon in two-stage operations, but an incidence of over 1 in 20 is reported from many sources in one-stage procedures. Major necrosis in flaps is treated by excision of ischæmic tissue, a free skin-graft to the defect, and a late plastic repair.

Fat necrosis occurring in the first two weeks after operation has been reported, and is said to have led to break-down of the wound, delay in healing, and the need for secondary repair to get the optimum shape.

Few patients are known to have lactated and fed a baby properly after a breast operation. The general result is a short period of scanty milk production. This effect may not be entirely due to operations, as many hypertrophic breasts have scant breast parenchyma with little power of milk production.

Cysts are perhaps more common in breasts that have been reduced than in normal breasts, but there is no evidence that the operation predisposes to any other disease.

Evaluation of Results.—It must again be emphasized that a breast reduction "is chiefly an operation of commodity" and if done for a definite disability and symptoms, gives almost invariable satisfaction in their relief. Judged, however, from the æsthetic point of view the results are not always of the same standard, but when the main reduction has been done, attention can then be concentrated on modelling without risk to the viability of the nipple. It is well, therefore, to warn most patients that two operations will probably be necessary to get the best possible result.

Of the operations described, the Biesenberger type of reduction gives most consistently the forward-standing nipple and most comely appearance; but it carries the greatest risk of nipple necrosis. The better the appearance at one stage the greater is the risk. Gillies' aphorism concerning the constant struggle in plastic surgery between blood-supply and beauty applies very aptly to breast reductions.

APPENDIX

STATISTICAL DATA ON BREAST CANCER

By Anthony Green

Statistical data, although in some respects misleading, provide the only means of making a comparison between different lines of treatment. The following figures have been chosen to exemplify certain points.

I. Incidence of Breast Cancer Giving Age and Sex, 1911–1945, Great Britain

Period	Males					Females					
	35–44	45–54	55–64	65–74	75 and over	25–34	35–44	45–54	55–64	65–74	75 and over
1911–20	1	3	6	12	25	22	176	474	696	946	1503
1921–30	1	3	8	14	27	24	187	508	782	1052	1740
1931–35	1	3	9	17	33	26	189	529	839	1098	1849
1936–39	1	4	8	16	35	27	184	516	830	1132	1889
1940–44	1	4	8	19	28	30	201	533	823	1114	1612
1945	1	3	6	17	46	31	198	500	784	1067	1590

For women the rates at ages under 55 were higher in 1940–44 than in any previous period, the slight improvement noted in 1936–39 being reversed; at 55–74 a decline has occurred in recent years following the continuous rise in rates up to about 1935, and at ages over 75 a considerable fall occurred in 1940–44 with a further decline in 1945. In the view of our Chief Medical Statistician, the decrease in child-bearing has probably tended to enhance the rates at ages under 55, whereas earlier and effective treatment amongst the older women has contributed to the decline shown at ages over 75.

From the General Register Office, London, 1948

II. Proportion of Right- and Left-Sided Breast Cancers

Sex	Right	Left	Bilateral	Unspecified
Males	30	33	—	7
Females	2623	2995	643	269

Registrar-General's Report, 1935.

III. Life Expectancy with Untreated Cancer of the Breast

Seven authors, 777 cases, the mean survival of which is 38·5 months.

Influence of age on survival (8 authors, 756 cases):—

Age	No. of Cases	Mean Survival in Months
25–34	44	33
35–44	120	43
45–54	196	38
55–64	188	40
65–74	157	41·5
75 and over	51	32·4

Wade, *Brit. J. Radiol.*, 1946, July.

IV. Comparative Frequency of First Symptoms Observed by Patients

First Symptoms Noticed by Patient	Luff	Lane-Claypon	Cade	Percentage of Total
Lump in the breast	740	196	434	68·6
Lump and pain	81	140	70	68·0
Pain	48	89	31	8·4
Discharge from nipple	35	37	12	4·2
Retraction of nipple	23	11	8	2·6
Hardness of breast	2	12	2	0·8
Axillary swelling	2	—	6	—
Other symptoms	—	18	—	—
Total	931	503	563	—

Cade, *Malignant Disease and its Treatment by Radium.*

V. Influence of Duration of Disease on Survival Rate (5 Years)

Duration	Cases	Stage I	Stage II
		per cent	per cent
Under 6 months	86	75	42
6–12 months	52	59	33
Over 12 months	16	77	28

Peters, *Canad. med. Ass. J.*, 1944, Oct., 335.

VI. Results of Treatment for Cancer of the Breast

a. American surgical results before radiotherapy was widely used :—

Author	Cases	5-year Cures	
		per cent	
Greenough and Simmons	69	32	About 35 per cent (all operable cases)
Lee and Cornell	75	15	
Sistrunk and MacCarty	278	36	
Moschchowitz et al.	89	34	
White	157	36	
Axillary glands not invaded			
Greenough and Simmons	16	56	About 65 per cent (Stage I)
Sistrunk and MacCarty	86	63	
White	55	70	

White, *Cancer of the Breast*, 1930. Harpers.

b. Some recent results. All operable cases :—

Method of Treatment	Author	Clinic	Selection	5-year Survival
				per cent
Surgery alone	Harrington	Mayo	Treated cases	47·6
Surgery alone	Gordon-Taylor	Middlesex Hospital	Treated cases	51·9
Local amputation and post-operative X rays	McWhirter	Edinburgh	All operable cases	56
Surgery and post-operative X rays	Peters	Toronto	Stages I and II	54

c. Comparison of surgery and surgery with added radiotherapy in the same clinic by the same operators :—

Method of Treatment	5-year Survival: All Operable Cases	5-year Survival: Inoperable Cases
	per cent	per cent
Radical surgery alone	36	0
Radical surgery and post-operative X rays	44	2·5
Local mastectomy and post-operative X rays	56	14

McWhirter, Edinburgh.

d. Further results showing the 5-year survival rate in each stage :—

Method of Treatment	Stage I	Stage II	Stage III
	per cent	per cent	per cent
Surgery alone			
Gordon Taylor (personal cases)	86	40	10
B.M.A. Collected cases (Luff)	33	25	3
Radium alone			
Keynes	71	29	23

e. Results of pre-operative X rays and radical amputation in Stages II and III :—

Five-year survivals — 44 per cent

Peters, *Canad. med. Ass. J.*, 1944, Oct., 335.

VII. Sites of Secondary Deposits from Breast Cancer : Clinical Findings

Site	Percentage
Opposite breast	47·6
Skin	18·6
Mediastinum	20·2
Lungs	63·7
Pleura	50
Liver	25
Skeleton	75
Brain	8·9

Howes and Bernstein, *Radiology*, 1942, **38**, 564.

VIII. Sites of Post-operative Secondary Deposits

Site		Number
Local		252
Nodes	Axillary	110
	Supraclavicular	156
	Others	16
Other metastases		40

8th Report of Radium Commission.

IX. Involvement of Sternal (Internal Mammary) Nodes

(*See* Chapter IX, p. 202)

X. Distribution of Post-operative Recurrences

Site	Number
Skin-flaps and scar	82
Supraclavicular glands	37
Sternum	14
Opposite axilla and breast	13
Axilla	9
Distant metastases	9
Total	164

Cade, *Malignant Disease and its Treatment by Radium.*

XI. Interval between Operation and Treatment for Secondary Deposits in 708 Cases

Interval	Percentage
Under 6 months	15
6 months	15
1 year	25
2 years	15
3 years	11
5 years	12·5
10 years	4
15 years	2
20 years and over	1

8th Report of Radium Commission.

XII. Effect of Radiotherapy

Method of Treatment	Recurrences	
	1st year	1–5 years
	per cent	per cent
Surgery alone	20	40
Surgery and post-operative X rays	3	14

McWhirter, *Proc. R. Soc. Med.*, 1948, Feb., 122.

XIII. Effect of X-ray Dosage on the Tumour, as shown by the Histological Picture. (Treatment Time, 3–6 Weeks)

Dose	Histology of Breast on Removal
Over 3000 r	Mitosis suppressed or absent, tumour in scar tissue or destroyed
Over 2000 r	Intermediate effect
Under 2000 r	Tumour well preserved but mitosis inhibited

Lenz, *Radiology*, 1942, June, 689.

XIV. Effect of Tumour Regression on Prognosis. (Pre-operative radiation and radical mastectomy)

Tumour Regression	Cases	Average Survival in Months
Slight	Operable 7	36
	Inoperable 22	10
Marked	Operable 31	60
	Inoperable 22	37

Lenz, *Radiology*, 1942, June, 689.

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