ON THE MINUTE ANATOMY
OF
TWO CASES OF CARCINOMA OF THE BREAST
PRECEDED BY ECZEMA OF THE NIPPLE AND AREOLA.

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IN a paper read during the last session I described the minute anatomy of two breasts which had been the seat of long-standing eczema of the nipple and areola.

The present paper contains a description of the minute anatomy of two cases of hard carcinoma of the breast, which were preceded by eczema of the nipple and areola. For the first of these cases I am indebted to Mr. Savory; for the second to Sir James Paget. My thanks are due both to Sir James Paget and Mr. Savory for the trouble they have taken to further the following research, and for the very kindly interest they have shown in it throughout.

Mr. Savory's patient (Case 1) was a lady, æt. 66, in whose breast a tumour had only been noticed for seven weeks. The appearance of the tumour was preceded by an eczematous condition of the nipple and areola, but only

by a very short interval, about a fortnight. There was no family history of cancer.

In consequence of the rapid growth of the tumour amputation was performed at an early stage of the disease in June, 1876.

When handed over for examination the general characters of the growth were those of a circumscribed hard carcinoma, about the size of a small egg, situated in the upper and inner portion of the breast, and reaching to within about half an inch of the areola. The intervening space between the tumour and the areola was occupied by slightly indurated fatty and fibrous tissue and glanducts. The nipple and areola were considerably thickened. The nipple was hardly so prominent as usual; its surface was ulcerated, and the ulceration was partly covered by a thick scab. The condition of nipple and areola was not nearly so bad as in the first two cases examined.

Sir James Paget's case (Case 2) was that of a lady, æt. 48, who had suffered from eczema of the nipple and areola of about three years' duration. The breast had remained apparently quite healthy until three or four months ago.

Amputation was performed in October, 1876, and the breast was almost immediately handed over for examination. The nipple was retracted, but unequally so, being much more drawn down on one side than on the other. Its surface was here and there rough and eroded. An eczematous patch occupied about one half of the areola, spreading on to the side and up to the free surface of the nipple. This patch was raised, indurated, uneven, and scabbed over. The remainder of the areola appeared thickened, but not ulcerated or scabbed over. The tissues immediately beneath the areola were rather more indurated than normal. About half an inch below the areola commenced marked induration of what had every appearance of infiltrated or disseminated hard carcinoma, very different in character from the form of cancer in Case 1, but quite as typical of another not uncommon

kind of cancer. This condition extended through the whole of a large breast, infiltrating unequally, forming here and there a hard nodule as large as a small nut, but nowhere producing a large circumscribed mass. A dilated duct was traced down for about one inch below the nipple into the cancerous disease.

The breasts were treated in the same manner as those previously examined. Sections were made from all parts of the tumour of the nipple, and of the intermediate tissues; and the order of these sections was carefully preserved, so that there could be no doubt as to the position from which any given section was taken. Some sections were made perpendicularly, some horizontally, in order to trace, as effectually as possible, the connection between diseased tissues, which could not, save by the greatest good fortune, be observed in any single section.

Stated as shortly as possible, the appearances observed were as follows:

Proliferation of the mucous layer of the epidermis of the nipple and areola, and infiltration of the cutis and subcutaneous tissue with small round cells.

Alteration and proliferation of the epithelium of some of the galactophorous ducts and small-cell infiltration of the surrounding tissue. Besides these diseased ducts several ducts were observed in Case 2 (Pl. VII, fig. 1) dilated, but having a tolerably normal lining of epithelium (fig. 2). In both cases, too, a number of normal ducts were discovered.

Enlargement of the acini, which were filled with epithelium.

Infiltration of the surrounding connective tissue with small cells (fig. 2).

All these changes are such as were described as existing in one or both of the two former cases. Further is now to be added:

Dipping down of the epidermis in Case 2 into the cutis, and the presence of a few cell-nests, giving to the

thickened portions of the areola and nipple the characters of epithelioma.

Much greater enlargement of the acini and ducts in the centre of the carcinoma than in the previous cases, so that they had frequently become confluent (the partition-walls being broken down), and their contents had made their way out into the surrounding tissues.

The cancerous change had, however, nowhere advanced so far in Case 1 (fig. 4), but that the rough structure of the breast could still be distinguished, although considerably altered.

This constitutes the rough description of the microscopical appearances. But, whereas formerly I was obliged to be contented with a mere description of appearances, I am now driven to express some opinion as to the origin of the carcinoma, and as to the connection which may exist between it and the eczematous condition of the nipple and areola.

With regard to the various views respecting the origin of carcinoma, the most important of them may be thus expressed—(i) That carcinoma is derived from the connective-tissue elements, (ii) that carcinoma is derived from the endothelium of the lymphatics, (iii) that carcinoma is derived from epithelial elements, (iv) that it is derived from the colourless blood-corpuscles.

In the present case I shall, I think, be able to prove that the carcinomata were derived from the epithelial elements of the mammary gland and its ducts; but, before attempting this, will endeavour to show that it could not have arisen from any of the other elements.

For such negative proofs Case 1 is particularly well adapted, as the various structures in the younger portions of the tumour are very distinct and well defined.

Looking very closely at the cell elements lying within the ducts and acini, and at those lying in the surrounding connective tissue anywhere, except in the most advanced portions of the carcinoma, so great a difference exists that it would be impossible to mistake them or to con-

found them together (figs. 2, 3, 5—9). The cells in the ducts and acini are of larger size, many of them of very much larger size than those lying outside. Their nuclei are also large, with well-marked outlines, having one, two, or more nuclei, not colouring very deeply with hæmatoxylin, showing generally a very granular appearance. With the exception of the borders of the cells or remains of the old cells, nothing in the ducts and acini has coloured deeply. Sometimes there is seen only a nucleated protoplasm (fig. 3), not differentiated into cells, like granulation tissue, but with large nuclei like those just described. Although there are great differences in size and shape, not only between the cells of different acini and ducts, but even between those of the same duct and acinus, such differences are easily reconcilable, and the gradual steps may be traced which connect the most distant forms. The cellular elements of the connective tissue are all easily classed under two forms—(1) small bodies, rather nuclei than cells, well-defined, equal in size, generally round or spherical, but often irregular in shape, not nucleolated, colouring *very* deeply, sometimes but not very often surrounded by a small quantity of protoplasm; (2) oval bodies of larger size, but not nearly so large as most of the nuclei of the cancer cells, not very vigorously defined, generally containing one, sometimes two nucleoli, colouring very faintly, and not shewing a granular appearance. These bodies were not nearly so numerous as the first.

For the purposes of discussion, the cells lying in the connective tissue, may be supposed to be derived from the connective-tissue elements, or from the blood-vessels. If the cells in the ducts and acini are formed from them, it must be by considerable changes. Traces of such changes ought to be discoverable either in the connective tissue, or in the ducts and acini, or in the walls of such ducts and acini. No one could for an instant imagine that these cells, wandering into the ducts and acini, became there suddenly transformed into the cells with which these

cavities are filled. I have looked most carefully in all three of these situations, but have totally failed to discover any such transitional forms. Occasionally one or two of the small dark corpuscles can be found in the midst of the larger cells in the acini, but quite unchanged, and apparently in no way affected by the neighbourhood of these cells. The presence of such a cell in the cavities only makes the difference in the characters of the cells more striking. Again, the position of the corpuscles in the connective tissue is not at all suggestive of continual influx into the ducts and acini, for they frequently lie at some distance from these cavities; and even where they lie in tolerably close proximity, the walls are almost always quite free from corpuscles. Against these facts, I know of nothing of equal value which could be set forth in favour of the connective-tissue or blood-corpuscle origin of the carcinoma. It might of course be argued, that in the earliest stages of the disease the cells within the ducts and acini are formed from the connective tissue or blood elements, and that transitional forms exist during that period. If that ground be taken, it must then be admitted that such a mode of formation has ceased, and is replaced by another totally different mode, so that either theory would thereby lose almost all its value. Against it, on the other hand, I have to set the same appearances as those described in the two breasts examined last year, in which the difference between the two sets of corpuscles was just as marked as in these breasts.

The same arguments serve equally well against the lymphatic origin of the disease, whilst to them may be added, that the first formations of new cells of the layer types are not observed in or near the positions assigned to the lymphatics of the breast.

To turn to proofs of the epithelial origin of the disease, I would point to the change in the characters of the epithelial cells lining the ducts, the transformation of cylindrical into spheroidal or squamous cells, the widening out of the ducts and complete filling up with these

cells; the dilatation of the withered acini or new development of acini now filled with the same kind of cells as fill the ducts; the complete absence of all other cells save the epithelium from which these new cells could be formed; the continuous dilatation until the cavities are fused together, their contents burst forth into the surrounding tissue, and cancer is fully formed; the evident youth of numbers of the cells, and the presence in some of the cavities of nucleated protoplasm. As to the manner in which the new cells are formed it appears to be sometimes by multiplication of nuclei and division, falling short of which the nucleated protoplasm is produced; or by endogenous multiplication (figs. 5—9), of which there are many evidences in most of the ducts and acini (fig. 2). The exact manner of this endogenous multiplication I have not been able satisfactorily to discover from these specimens.

If it be asked what is the relation which the cell elements in the connective tissue bear to those in the ducts and acini (which I should regard as essentially the cancer cells), I should say that they are the result of irritation, the product either of blood-corpuscles or connective corpuscles, or perhaps both. They have all the characters of such cells; they are found in great abundance in the close vicinity of the blood-vessels; similar cells can be seen in the blood-vessels. Such cell tissue is the natural result of irritation and inflammation. With respect to the theory lately put forward by Dr. Creighton, of the relation between these small bodies and the cells in the cavities, there does not appear to me any sufficient proof that they are the remains of old vacuolated cells on their way to or within the lymphatic channels. The only point in which the two things resemble one another is the depth to which they both colour. In other respects they are most different. The remains of the vacuolated cells vary very much in shape and size, are much more frequently triangular or quadrilateral with incurved sides than round or spherical, are generally

larger than the corpuscles in the connective tissue, and have an incomplete appearance when separated from the thin outlines with which they are usually in connection. Nor are there any transitional forms to be found between the two, although they were just as carefully searched for as the transitional forms between the cells outside and inside the cavities.

From these and the two former cases the following conclusions may, I think, fairly be drawn :

(i) That a certain relation existed between the eczema of the nipple and areola and the carcinoma of the breast.

(ii) That one of the first effects of the eczema was to produce proliferation of the mucous layer of the epidermis of the parts affected.

(iii) That in time the epithelium lining the galactophorous ducts became affected in like manner.

(iv) That the disease travelling along the large ducts reached the smaller ducts and acini, which became dilated and filled with proliferating epithelium, which was at length, so to speak, discharged into the surrounding tissues.

(v) That the carcinoma thus formed was therefore essentially a disease of epithelium.

DESCRIPTION OF PLATE VII.

Eczema and Carcinoma.

Fig. 1. Horizontal section below nipple, showing disease in ducts. (B. 4 in.)

Fig. 2. Portion of duct with proliferating epithelium wall, and surrounding tissue containing corpuscles of two kinds. (Oc. 3, obj. 7, tube drawn out, $\times 260$.)

Fig. 3. To show duct or acini filled with epithelium (a good example of nucleated protoplasm). (Oc. 3, obj. 7, t. d. o. $\times 260$.)

Fig. 4. Sketches of portions of breast affected with carcinoma, showing structure of mammary gland remaining, but altered. (B. 1 in.)

Figs. 5 to 9. To show endogenous formation of epithelial cells. ($\times 260$.)