

THE OCCURRENCE OF METAPLASIA OF EPITHELIUM IN CANCER.^{1, 2}

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(PLATES XII. AND XIII.)

THE term Metaplasia is applied to such conditions as present evidence of the transformation of cells of a distinct and specific type into others of an equally specific and definite character; it does not include those cases in which a change has taken place merely in the shape of the cell, such as flattening of cubical epithelium in a bronchus or elevation of flat epithelium in an alveolus. Restricted to epithelium, the term requires that cylindrical or cubical epithelium has become squamous, or *vice versa*. As a criterion of the presence of squamous epithelium, one or more of the following conditions must be satisfied: (1) the presence of prickle cells; (2) the presence of keratohyalin; (3) the presence of horn substance.

The following three cases present appearances which suggest that in them a metaplasia of epithelium has taken place.

CASE 1.—Female, æt. 50 years.—*Cancer of the fundus of the gall-bladder, with metastatic infiltrations in the liver and in the head of the pancreas.*—The growth protrudes in the form of a fungating mass into the lumen of the gall-bladder, extending on the other hand directly into the liver substance and the abdominal parietes; the nodules of infiltration in the liver vary in size from a pea to a cherry, and present a mottled appearance. There is no evidence of cancer in any other part of the body. Microscopically, the fungating protuberance is seen to consist of papillæ covered with stratified squamous epithelium, with formation in the outer layers of keratohyalin and horn substance. The papillæ have each a central vessel with a very small amount of connective tissue (Plate XII. Fig. 2). The solid portion of the tumour invading the liver and the abdominal wall is composed for the most part of masses of flat cells with abundant cell-nest formation (Plate XII. Fig. 1). There is comparatively little stroma, and hæmorrhages are present throughout this part of the growth. Among the masses of flat cells, small foci of cylindrical cells arranged in a papillary form are noticed. The nodules of secondary growth in the liver consist of masses of cylindrical cells arranged in a papillary form (Plate XII. Fig. 3); the cylindrical cells showing this perivascular arrangement are in some parts one layer deep, and in other parts two or three layers deep; in these nodules no evidence of squamous epithelium is seen. The small vessels of the papillæ are in parts greatly dilated, and

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² Received July 23, 1908.

hæmorrhages are noticed here also. Examination of the mucous membrane of the gall-bladder shows that at those portions where the malignant growth is active the epithelium is stratified and squamous; but those portions of the wall which are not associated with tumour growth do not show squamous epithelium. The essential feature of the case is that the tumour is a papillary carcinoma, and that the papillæ are covered, in some parts with stratified squamous epithelium and in others with cylindrical epithelium.

CASE 2.—Female, æt. 35 years.—*Cancer of breast*.—There is slight irregular enlargement of the breast. On section a number of small cavities, varying in size from a pea to a walnut, are seen; from these cavities there exudes a creamy fluid composed of epithelial débris and a few polymorph leucocytes. A staphylococcus was isolated from the exudate. The nipple is not affected. The specimen being obtained from an operation, the extent of the metastasis is unknown. Microscopically, the small cavities are seen to be dilated milk ducts, lined at parts with stratified squamous epithelium (Plate XII. Fig. 4), and from this epithelium cancerous proliferation extends into the body of the gland. Keratohyalin and prickly cells are easily demonstrated. The spreading margins of the tumour present the typical appearances of a scirrhus, composed of small spheroidal epithelial cells with varying amounts of connective tissue (Plate XII. Fig. 5). In some parts small masses of from twelve to twenty squamous cells with prickles lie embedded in tissue composed of spheroidal cells in a connective-tissue stroma (Plate XII. Fig. 6). Here also, as in Case 1, the walls of the ducts are squamous only in those parts where there is a direct continuation with the cancerous proliferation. No squamous epithelium is seen in ducts whose walls are otherwise normal.

CASE 3.—Male, æt. 53 years.—*Cancer of the pyloric end of the stomach, with metastatic infiltration in the lymphatic glands in the portal fissure and in the head of the pancreas*.—The growth encircling the stomach about half an inch above the pyloric ring is about one inch in breadth and half an inch in depth. There is no ulceration of the mucous membrane. From the cut surface of the tumour there exude droplets of white creamy material consisting of large flat epithelial cells and cellular débris. To the naked eye the mucous membrane appears to be of normal thickness, and its sharp delimitation by the muscularis mucosa is apparent on the cut surface of the tumour mass. Microscopically, the following changes are observed in the mucous membrane:—(1) At parts the epithelial elements have entirely disappeared, and the remaining structure is composed of small round cells composing a granulation tissue. (2) At parts there is an adenomatous proliferation of small darkly stained cubical cells lying in a matrix of small round cells and fibrous tissue (Plate XIII. Fig. 7); these glandular masses may be seen perforating the muscularis mucosa; the lumina are at places lined by a single layer of cells, and at other places they may be lined by a multicellular layer. (3) At other parts the normal framework of the mucous membrane would appear to be present, but the epithelial cells have assumed a flat squamous-like appearance; their nuclei stain faintly, the protoplasm is large in amount and takes on the eosin stain readily (Plate XIII. Fig. 8); here the muscularis mucosa is perforated by masses of large squamous looking cells. Spreading in the muscular coat of the stomach wall the cellular elements are arranged in large masses, suggesting the centripetal proliferation and desquamation of cells from a layer originally lining an adenomatous lumen (Plate XIII. Fig. 9); the basal layer consists of smaller cells with more darkly stained nuclei, and the cells proliferating from this layer show protoplasmic cell bridges (Plate XIII. Fig. 10); the cells on the surface of the layer and next the centre of the lumen are large, with faintly staining nuclei and relatively abundant eosinophile protoplasm. In the loose adenoid tissue beneath the muscularis mucosa the form of growth is distinctly adenomatous, the lumina being lined with one layer of cells. In addition to the frankly glandular and squamous types, a form of

growth, which might be regarded as medullary cancer, is present; this consists of large masses of cells irregularly arranged in a minimal amount of connective-tissue stroma; this medullary type would appear to constitute at parts an intermediary form between the glandular and squamous growths. Examination of the lymphatic glands reveals the presence of these various types. The purely glandular type is seen as in Plate XIII. Fig. 11, while Plate XIII. Fig. 12 shows squamous cells, adenomatous structure, and an intervening mass of medullary cancer. In this case the plastic character of the epithelium concerned in the malignant proliferation is seen in various ways. (1) In the mucous membrane an adenomatous proliferation takes place at one part, and a squamous proliferation at another. (2) The cubical cells lining the acini proliferate into a multicellular layer, and there is evidence that this layer is at parts composed of squamous cells. (3) In the main tumour as well as in the infected glands a medullary form of cancer merges on one side into adenomatous structure, and on the other side into squamous structure.

There is considerable evidence, then, in favour of the view that in these cases a metaplasia of the epithelium accounts for the appearance of double tumour. In the breast, stomach, or gall-bladder the occurrence of a squamous epithelioma is exceedingly rare, if one excludes those cases of breast cancer where the nipple is affected. Squamous epithelium occurs naturally on those surfaces exposed to irritation, *e.g.* the skin, mouth, œsophagus, etc.; it is not uncommon for a surface originally covered with cylindrical epithelium to change its type and become squamous under the influence of some irritation; this is seen in the bronchi and uterus most frequently; in broncho-pneumonia, cases have been described where the larger bronchi showed great proliferation of their cylindrical epithelium, the walls of the smaller bronchi were completely destroyed, while the epithelium of the middle-sized bronchi had assumed a squamous type, thus showing that where the irritation had not been severe enough to cause destruction a specialisation in the form of squamous epithelium had occurred. In the case of the gall-bladder and of the breast there is evidence of irritation; the fungating mass of the former projects into the lumen of the gall-bladder, and is covered with masses of muco-purulent-looking material, while the dilated ducts of the latter are filled with a soft creamy material, the products of cellular destruction and inflammatory reaction; the wall of the gall-bladder and of the milk ducts is covered with stratified squamous epithelium, which is continuous with the spreading cancer; in both cases as the growth recedes from the site of irritation the epithelium assumes a different type, and in neither case is squamous epithelium seen which is not associated with cancer. In the stomach, malignant adenomatous proliferation and squamous epithelium are both seen in the mucous membrane; this squamous epithelium is not of the stratified variety, but rather indicates that the normal glandular cells have undergone a change, the connective tissue framework remaining undisturbed (Plate XIII. Fig. 8). It is to be noted that in this case also the mucous membrane is infiltrated with large numbers of small round cells, indicating probably the presence of some irritation. In all these cases, then, the plastic character of the epithelial elements

is associated with the presence of evidence of irritation; whether that irritation is due to a substance of microbic or metabolic origin must be left an open question. In a recent contribution to the experimental side of cancer research Lewin describes changes in the course of transplantation in rat-cancer which, in the light of the cases described above, are of special interest. In the first generation he had to do with an adeno-carcinoma of the mamma; in the second generation the adeno-carcinoma gave place to a cancer of the alveolar type, and to the "massive" type, which he describes as consisting of large masses of cells with relatively little stroma; in the third generation, cornification is seen in parts, and mixtures of the adenomatous and squamous varieties are noticed; in the fifth generation he was able to find the can-croid form only. In the case of the stomach tumour described above, the varieties referred to by Lewin are easily detected, and in Plate XIII. Fig. 12, the adenomatous, massive, and squamous types are all represented.

I have to thank Professor Muir for guidance and advice in the interpretation of this material which he kindly placed at my disposal.

REFERENCE.

LEWIN *Ztschr. f. Krebsforschung*, Berlin, 1908, Bd. vi. SS. 267, 314.

DESCRIPTION OF PLATES XII. AND XIII.

PLATE XII.

- FIG. 1 (Case 1).—Cell nests in the squamous epithelium in that part of the tumour invading the liver and abdominal parietes. ($\times 60$.)
- FIG. 2 (Case 1).—Papilla covered with squamous epithelium, from the fungating mass projecting into the gall-bladder. ($\times 60$.)
- FIG. 3 (Case 1).—Papilla covered with cylindrical epithelium from a secondary nodule in the liver. ($\times 120$.)
- FIG. 4 (Case 2).—Stratified squamous epithelium from the wall of a dilated milk duct. ($\times 60$.)
- FIG. 5 (Case 2).—Spheroidal cell proliferation in the form of a scirrhous at the growing margin of the tumour. ($\times 120$.)
- FIG. 6 (Case 2).—A part of the tumour towards the growing margin, showing in the centre of the field a mass of flat squamous cells (with cell bridges) surrounded by spheroidal cells in a delicate connective-tissue stroma. ($\times 120$.)

PLATE XIII.

- FIG. 7 (Case 3).—Proliferating tubules in the mucous membrane of the stomach, and small round-celled infiltration. ($\times 60$.)
- FIG. 8 (Case 3).—Large squamous cells in the mucous membrane of the stomach, apparently supported by the normal connective tissue framework. ($\times 60$.)
- FIG. 9 (Case 3).—A mass of cells in the muscular layer of the stomach wall. Note the more darkly stained basal layer and the proliferation towards the centre; this represents a tubular formation with proliferation of the epithelial cellular lining. ($\times 60$.)
- FIG. 10 (Case 3).—Protoplasmic cell bridges from the deeper layers of the proliferating cells in Fig. 9. ($\times 500$.)
- FIG. 11 (Case 3).—Adenomatous arrangement of the growth in gland metastasis. ($\times 60$.)
- FIG. 12 (Case 3).—From a section of the same lymphatic gland, showing adenomatous structure, squamous cells, and an intervening mass of cancer cells with little stroma (medullary or massive cancer). ($\times 60$.)



Fig. 1.

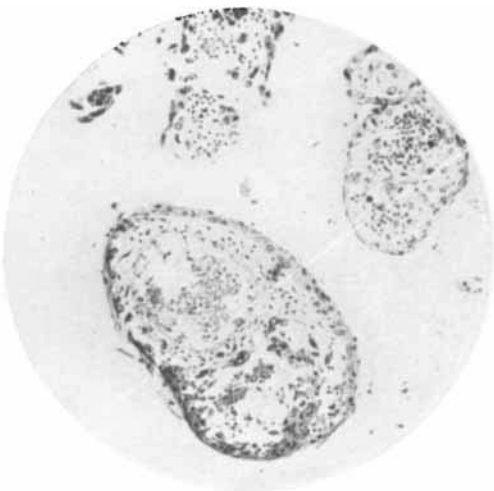


Fig. 2.

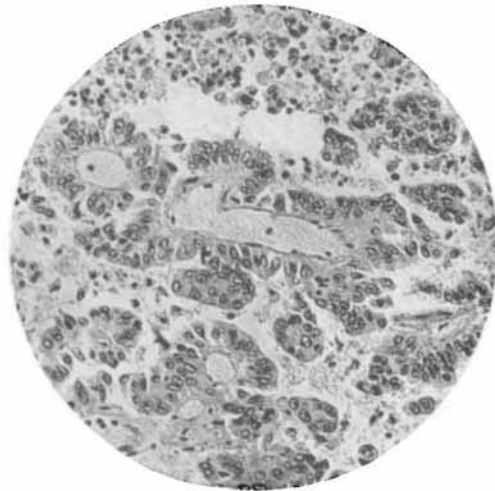


Fig. 3.

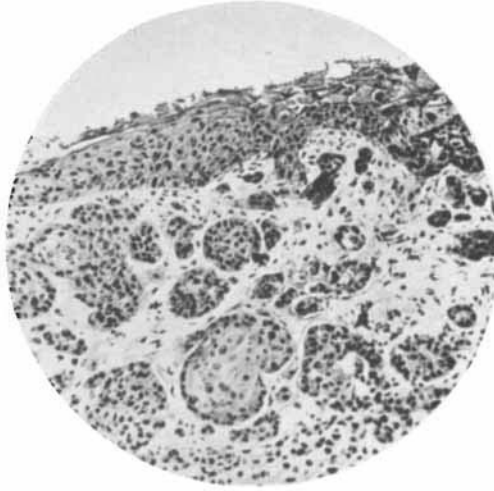


Fig. 4.

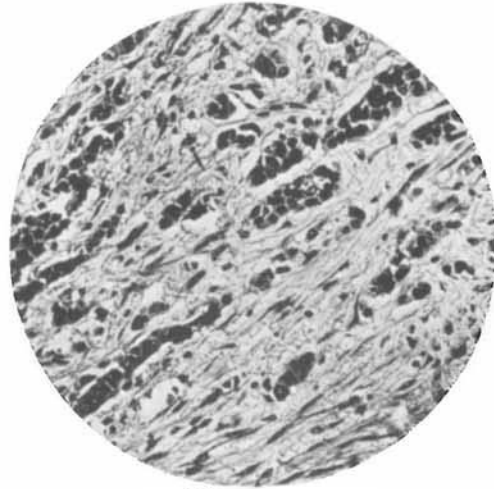


Fig. 5.

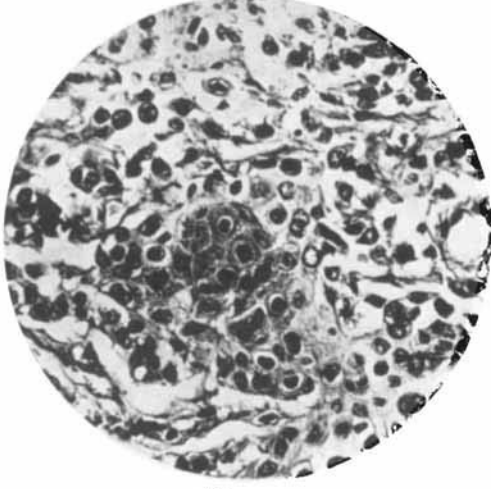


Fig. 6.

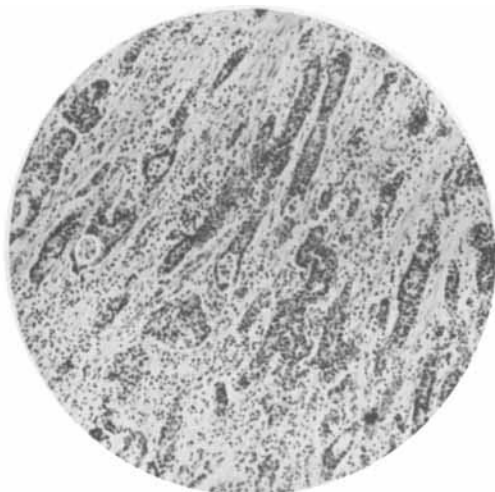


Fig. 7.



Fig. 8.

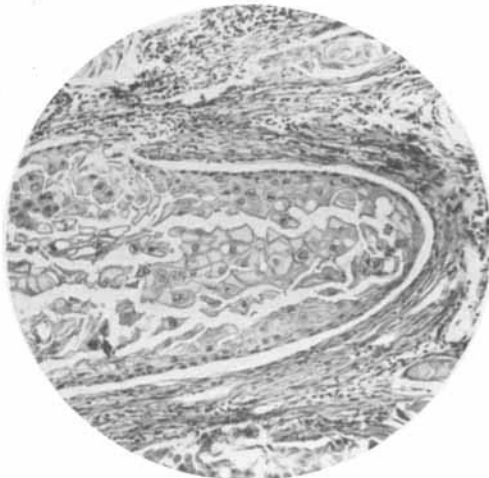


Fig. 9.



Fig. 10.

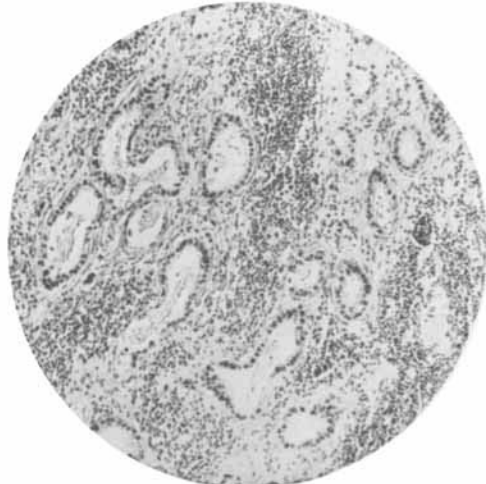


Fig. 11.

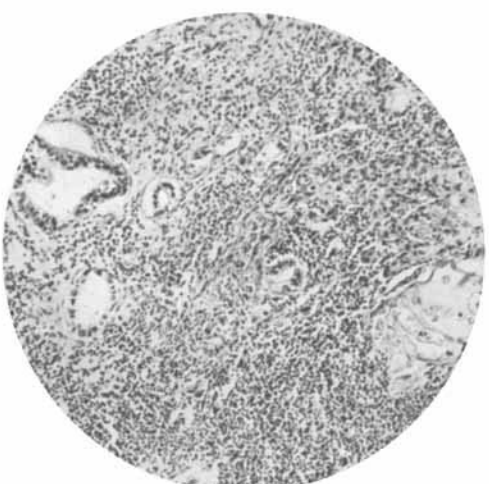


Fig. 12.