Remarks ON THE INTRA-EPITHELIAL GROWTH OF CARCINOMA.*

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CARCINOMA is usually regarded as an infiltration of tissue spaces and lymphatics by epithelial cells which have acquired the malignant neoplastic property. The essential neoplastic change, however, occurs first in epithelium which still has normal relationships to connective tissue, and the break through of basement membranes or other normal boundaries follows on the acquisition of malignant properties by the cells. This is well illustrated by the experiments of Murray and Woglom (1921), who showed that autoplasmic transplantation of skin lesions produced by tar might be followed by growth of the transplant and infiltration before local infiltration could be recognized at the primary lesion. The amount of neoplastic proliferation which occurs before actual infiltration of the tissues varies much in different cases, and the factors determining it can in great part be only conjectured; but in the case of the mamma, what can be justifiably described as cancerous proliferation within the ducts may be of an extensive nature before invasion of the surrounding connective tissue occurs. Theoretically a skin epithelioma, for example, might extend and destroy the epidermis without infiltrating the subjacent tissue, but this is rarely seen; the break through into the tissue spaces occurs comparatively early. In other words, the connective tissue route of growth is preferred, we may say, as offering least resistance. In certain conditions, however, free growth of cancer cells occurs within the substance of the epidermis and other epithelia, and this is the subject of the present communication. In discussing the conditions of occurrence, I cannot claim to bring forward anything new, but I think that it may be useful to discuss the phenomenon in its various aspects, especially as it has been little recognized by writers. I shall speak chiefly of the growth and extension of cancer cells in the epidermis, which may occur under three conditions.

1. The cancer cells may reach the normal epidermis by direct spread from an underlying growth, thereafter extending within the epidermis.

2. The cancer cells may reach the epidermis by continuous growth from the duct of a gland opening on the surface. The outstanding example of this is Paget's disease of the nipple occurring secondarily to intraduct carcinoma.

3. The cancer may start in the epidermis itself and spread within it, instead of infiltrating the subjacent tissue as is usually the case. In some apparent instances of this condition the point of origin may be in the skin appendages. I have illustrated these three possibilities by the diagrammatic sketches; the cancer is shown in black.

1. Spread from Underlying Growth.

I have put first direct invasion of the epidermis by an underlying growth because it can be so definitely followed; in this way we get a picture of how the cancer cells spread and what appearances may result. The occurrence

in question is relatively uncommon, and has been described chiefly in connexion with the nipple. In most instances, when a cancer of the substance of the nipple reaches the epidermis, the latter merely becomes destroyed and ulceration follows, but sometimes the cancer cells penetrate the basal layer and gain a foothold in the epidermis, within which they behave like parasites. They flourish especially in the lower part of the rete malpighii, and may extend widely in a lateral direction from the point of entrance. Isolated cells may be detached and carried upwards to the surface by the growing epithelium; they undergo degeneration as they pass upwards, and ultimately only degenerated remains are seen, these being enclosed in capsule-like spaces in the horny layer. The histological changes thus resulting may correspond with those seen in Paget's disease, and cases of the kind we have described are sometimes included under this term. This, however, is unjustifiable, as in the condition of the nipple described by Paget there was no infiltrating cancer in the substance of the nipple, though a cancer often appeared later at some distance in the substance of the breast. The process of intra-epidermal growth of cancer has been described by Jacobaeus (1904)

and others, including myself, but the most striking demonstration of its occurrence is that recently brought forward by Shaw Dunn (1930). In his case, the growth was a mucin-forming (colloid) carcinoma involving the anal orifice, and in sections stained by mucicarmine the cells wandering in the epidermis are brought out in a striking fashion owing to their content of mucin. The distribution of the cells in the epidermis and their extension over a wide area are clearly shown in the illustration given by him. Familiarity with the appearances thus brought about by what we may call infection of the epidermis is essential to the interpretation of similar changes which may be produced in other ways. The study of cases where the

epidermis is directly invaded by an underlying carcinoma demonstrates what may result when the intra-epidermal type of growth becomes established. In cases of skin melanoma one may sometimes see isolated pigmented cells in the epidermis, and this appears to me to be another example of malignant cells wandering in the substance of the epidermis (see also Jacobaeus, op. cit.).

2. Spread from Duct Epithelium.

The invasion of the epidermis by cancer cells which have reached it by intra-epithelial spread from intraduct carcinoma of the upper ends of the mammary ducts, has already been fully described and discussed by me (1927), and I have little to add. The various stages of hyperplasia of duct epithelium, ultimately culminating in malignant neoplasia, have been described by Cheate (1926) and Charteris (1930), and with their accounts I agree in all essential particulars. One point which I consider of great importance is that in the early stages of the malignant change in the ducts the growth can be seen to be of the intra-epithelial type. The invading cancer cells spread in the epithelium of the ducts, often leading to a layer of new growth of considerable thickness (this is fully illustrated in my paper referred to). Later, the cells break through the surface layer, and there results the more common appearance of masses of cancer cells filling the ducts. Intra-epithelial growth can also be observed in the acini, and in a recent case I have found this occurring on an extensive scale. The intra-epithelial growth within the ducts and the acini is often seen to be widespread, and one must recognize that the disease may start in multiple foci of origin as well as spread directly. But I am of opinion that most of the characteristic features are due to the

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latter factor. Given, then, the fact that intra-epithelial growth of cancer is spreading within the ducts of the nipple, the question naturally arises what course the cancer cells will take when they spread upwards and reach the epidermis, with which the duct epithelium is continuous, and of which it is merely a modification. The answer given by a study of Paget's disease is that the cancer cells continue to spread in the epidermis, and that they may do so over a wide area, there being an extensive lateral growth in the deeper parts of the epidermis. The epidermis, however, offers more resistance to the growth of the cells; they multiply only in the deeper parts of the rete malpighii, and there apparently only with difficulty. Nevertheless, the remarkable fact is that they may remain in the epithelium and show no tendency to pass again to the subjacent connective tissue. The cells wander in the epidermis and many become degenerated, especially in the more superficial layers. Hence the characteristic features of Paget's disease of the nipple result. Such, in my opinion, is the sequence of events in the majority of cases. I am interested to note that in a recent paper on Paget's disease, Simard, working in Masson's laboratory, has arrived at views similar to those which I have expressed. As already stated, a corresponding histological picture arises when a carcinoma in the connective tissue invades the epidermis directly and spreads in it. I also admit the possibility of the occurrence of an intra-epidermal growth from the cells of the epidermis itself, such as is met with in "Paget's disease" in other parts of the body (see below), but I have not met with a case of this.

I may add that since my paper (1927) was written I have had the opportunity of examining seven additional cases of Paget's disease of classical type, there being no carcinoma infiltrating the connective tissue of the nipple in any of them. In all of these cases the characteristic changes are present in the ducts, and in five of them direct spread of the disease from the upper parts of the ducts to the epidermis can be followed. In four of the cases infiltrating carcinoma of ordinary type was present, deep in the substance of the breast. In two other cases there were both intraduct carcinoma and also infiltrating carcinoma in the connective tissue of the nipple. In these two cases it was not possible to state definitely by which of the two routes the cancer cells had reached the epidermis.

In the illustration of one of my cases previously published, the Paget cells in the deepest part of the rete malpighii have assumed a somewhat columnar type, and this is more strikingly seen in one of my recent cases. Not only can the spread of the disease be traced from the ducts to the epidermis, but, at places in the latter, a distinct line of columnar cells is seen resting on the cutis, while on their free surface there is a small collection of fluid which has raised up the epidermal cells. These columnar cells may, in fact, be said to represent a small metastasis from the intraduct carcinoma comparable to what occurs in a lymphatic gland; only, in this case the metastasis has been produced by the wandering of the cancer cells by the intra-epithelial route.

3. Origin in Epidermis.

With regard to the intra-epidermal spread of new growth arising from the skin or its appendages I have comparatively little experience, but there is ample evidence of its occurrence. There is first of all the Paget lesion occurring in extra-mammary sites. This is rare, but a considerable number of cases have been recorded (Susman). I am indebted to Dr. Whitfield for a section from his case of Paget's disease of the vulva (1929), and in it I find a reproduction of the essential features of Paget's disease of the nipple so far as the mode of growth is concerned. The cells are growing in clusters, especially in the deeper part of the epidermis, while isolated cells are scattered through the latter. There is also a striking intra-epithelial invasion of the sweat glands. The cells vary in shape; they are angular or stellate and are loosely arranged as if bathed in an intercellular fluid. Some show a tendency to assume a columnar type. It is not possible to assign definitely the site of origin, but the characters of

the cells suggest to me a glandular structure in the vulva rather than in the epidermis itself. In other cases of similar nature the cells are of more indefinite character, and suggest the possibility of origin from the basal-cell layer. If this were so, such a growth would represent a rodent ulcer (basal-cell epithelioma) spreading intra-epidermally. A corresponding spread of prickle-cell epithelioma is of rare occurrence, but it has been described by Borst (1904), and an account is given also by Borrmann in the case of both epithelioma and rodent ulcer (1904).

Bowen's disease is another lesion which comes up for discussion in this relationship. I have not myself had an opportunity of examining a case, but from the accounts given and from the illustrations it has seemed to me possible that it represents a carcinoma spreading laterally in the epidermis without infiltrating the tissues underneath. I am interested to find that this view has been adopted by several recent writers—for example, Fraser (1928), Wise (1929), Efler and Anderson (1930). The lesion usually remains indefinitely in the epidermis, but occasionally an infiltrating carcinoma develops. However, I do not wish nor, in fact, am I qualified to discuss in detail the nature of such skin lesions. I wish rather to emphasize the general principle—namely, that malignant growths arising from the epidermis or its appendages may spread in a lateral direction within the epidermis instead of passing into and infiltrating the subjacent connective tissue. Such intra-epidermal growth, meeting with resistance as it does, is usually of very slow progress, and the disease clinically is of a very chronic nature. In the case of the epidermis, just as has been stated above with regard to the ducts of the mamma, the possibility of multiple foci of origin must be recognized as well as extension from a particular focus.

Conclusions.

When we consider the features of intra-epithelial growth of carcinoma and its results in the three conditions which have been discussed, we find that they present various points in common. In the first place, as has been stated, the growth of the cancer cells in the epidermis apparently meets with considerable difficulty, and is accordingly relatively slow; in fact, it would appear that it is only in the deeper parts of the epidermis that active proliferation can occur at all. The malignant cells are carried up in the process of normal growth of the epidermis and soon show signs of degeneration. Further, even in the deeper part of the epidermis the growth is not always continuous, and it is not uncommon to find the cells scattered in the rete malpighii and sometimes spreading widely into the sebaceous or sweat glands. The appearances, in my opinion, can only be explained by the view that the malignant cells wander in the epidermis, and this holds in all three conditions discussed above. I convinced myself of the occurrence of the wandering of the cells several years ago from the study of Paget's disease of the nipple of the ordinary type, and it is still more convincingly demonstrated in cases of secondary invasion of the epidermis by an underlying carcinoma, as in Shaw Dunn's case. When, as sometimes happens, resistance to growth is great, the cancer cells may be found only singly or in small clumps, and nearly all in a more or less degenerated condition. Such cases are unsuitable for histological study and interpretation, and this fact is partly responsible for the great variety of opinions which have been expressed with regard to Paget's disease of the nipple. In certain cases, however, all intermediate stages can be found between such degenerated cells and masses of cells which present the features of cancer cells and are undergoing active mitotic division.

I have already indicated that the cells in the epidermis always appear to be growing in somewhat unfavourable surroundings, and another striking fact is that they are restrained in some way from breaking through the limits of the epidermis and infiltrating the cutis. I have never, in fact, seen a clear example of re-passage from the epidermis to the connective tissue, although, of course, the possibility of its occurrence cannot be excluded. But we can at least say that once the intra-epidermal extension of the growth has been established, the cells tend to be restricted to the epidermis.

The presence of cancer cells growing in the epidermis leads to a definite reaction in the cutis. There occurs new formation of capillaries, and this is accompanied by extensive infiltration of leucocytes and plasma cells; I have also met with eosinophils in large numbers. When the growth within the epidermis is discontinuous, a definite relationship between the affection of the epidermis and the underlying cellular reaction can often be recognized. Owing to the new formation of blood vessels and their congested state, and to a certain amount of exudate which soaks through the epidermis, the characteristic features of such lesions are produced. Of course, at a later stage the affected epidermis may become destroyed, and then there is a red surface formed by granulation tissue.

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EFFECTS OF HYPERTONIC SALINE IN THE TOXAEMIAS OF LATER PREGNANCY.*

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Four years ago the authors, in a paper entitled "Diet in the treatment of pre-eclampsia," advocated the use of salt-free diet.¹ Such diets contained about 3 grams of chloride reckoned as sodium chloride, and are more usually nowadays, and more legitimately, called salt-poor. At the time the authors were particularly concerned in making clear that diets high in protein or in fat were quite innocuous to pre-eclampsia. As a practical corollary it followed that ordinary mixed diets of protein, carbohydrate, and fat could be utilized, provided they were salt-free or salt-poor. Not only were such diets innocuous to the pathological condition, but the patients showed marked clinical improvement. In view of the number of factors concerned, however, we did not consider it legitimate to ascribe the improvement to the protein or fat in the diet. Rest in bed and general attention to hygiene are such powerful factors in general clinical improvement that it required much stronger evidence than we possessed to conclude that high protein feeding or high fat feeding was beneficial.

We were also interested in the effect of our observations upon theories of etiology. Protein *per se*—if our observations were correct—could not play a part in the production of eclampsia. Those authors who had ascribed the reduction in the incidence of eclampsia in Germany² during the war as due to a reduction of dietary protein could not, in our opinion, have been correct. That a dietary factor exists appears certain. That the dietary factor is protein, or even fat, is uncertain, despite the popularity of the

former supposition. We may state in further support of our contention that since our previous publication we have given high protein diets, not to pre-eclampsia, in whom there might be a doubt that actual convulsions would occur, but to eclampsia, who, having responded to treatment with sedatives, were admitted to the ward for further observations. We noticed no aggravation of symptoms; indeed, as previously, we found an improvement.

The use of salt-free or salt-poor diets in the treatment of nephritis of the parenchymatous type is well known. The influence of sodium chloride or sodium bicarbonate in definitely aggravating the symptoms of albuminuria and oedema in that condition is a matter of well-known clinical and laboratory demonstration. The observations of our previous paper may have been open to the criticism that we were dealing with patients in whom the kidney lesions were of the parenchymatous type. De Wesselow³ has emphasized the occurrence of this type in the toxæmias of pregnancy.

Since then, however, we have been able to reinforce our conclusions on the part played by sodium chloride by a series of further observations—namely, by the use of sodium chloride intravenously. The use of hypertonic saline solutions has become very general in some centres for the treatment of post-operative paralytic ileus, either actual or threatened. It is also a powerful dehydrating agent and diuretic. In the treatment of eclampsia or threatened eclampsia one notices, too, a tendency towards the use of intravenously administered dehydrating agents. Lazard⁴ has enthusiastically advocated the use of intravenous magnesium sulphate. Titus⁵ uses 50 per cent. glucose solution, though with a confessedly different object. Mussey⁶ recommends ammonium chloride by the mouth. A brief review of many of the older methods of treatment shows that some of the therapeutic agents removed water—for example, purging, venesection, hot packs. These were used frequently and often with success. Their object was to remove toxin, but at the same time they removed body fluid. Thus the use of hypertonic saline solutions might prove beneficial. True it might produce or aggravate oedema in a case complicated by parenchymatous nephritis, but the symptom of subcutaneous oedema has never been considered as the dangerous one in an eclamptic or pre-eclamptic patient. To relieve the symptoms of convulsions and high blood pressure, with its attendant dangers of haemorrhage, would be well worth the cost of a little oedema.

These latter arguments, valid as they may sound, are fallacious. The use of hypertonic saline solutions in toxæmias of later pregnancy is harmful. We present four cases, one normal acting as a control, the other three being varying degrees of toxæmias, though we feel some doubt as to the diagnosis in Case II.

CASE I.—Normal Pregnancy. 0 Para. 8 Months Pregnant.
Aged 19.

Date.	Flood Pressure (mm.).	Urine Albumin (mg. per 100 c.cm.).	Notes.
1929 June 6	128/64	0	Full diet.
" 7			"
" 8	120/58	0	"
" 9			
" 10	124/68	0	300 c.cm. of 10% saline intravenous.
" 11	124/53	0	" "
" 12	117/50	0	Full diet.

The patient had been observed carefully in the clinic, and was normal. The intravenous saline was given on June 10th at 2 p.m. after the noon meal. She complained of thirst, and was given chipped ice; she took an ordinary supper. On June 11th the intravenous saline was given at 11 a.m., and the patient fed on orange juice the remainder of the day. Later in the day two fluid bowel movements occurred, but otherwise no effects were observed.

* A paper read in opening a discussion in the Section of Obstetrics at the Annual Meeting of the British Medical Association, Winnipeg, 1930.