Whether carcinoma ever extends by the transformation of normal epithelial cells into cancer cells at the advancing tumor margin has been a much debated question. The principal evidence in favor of spread in this manner is found in the histological pictures showing all stages of apparent gradual transformation of normal epithelial cells into malignant cells, seen notably in epitheliomata and in cancers of the intestine and duct cancers of the breast. If these are true pictures, their bearing upon the nature of cancer is of the first importance, indicating that the properties of malignancy may be conferred upon normal cells by an influence outside themselves, and that tumors need not necessarily grow exclusively from their own cells.

Borrmann (1), writing of epithelioma and arguing for the origin of tumors from foci of misplaced embryonic tissue, considers that the apparent transitions are to be explained as secondary union of the cancer with the normal epithelium. Ribbert (2), in a discussion of Paget's disease of the nipple, has expressed the same opinion: "Cancer here (of the breast) as elsewhere and like all other tumors, after it is once fully established, grows only from itself. This is a fundamental consideration. . . ."

Janeway (3) has summarized and endorsed the opposite view, that the pictures observed are true transformations. Writing of

1 This work was done during the tenure of a fellowship of the China Medical Board, Rockefeller Foundation.
epithelioma, he says, "The new growth increases in size by a transforming influence upon the adjacent healthy epithelial cells with which it is in direct connection." More recently Ewing (4) has definitely expressed this view. In the breast, for instance, "some acinar and many duct carcinomas arising at one focus, gradually extend over adjoining areas by a gradual transformation of duct and acinar epithelium into neoplastic cells." A similar conception of the spread of carcinoma of the large intestine is mentioned (5). The question has not, therefore, been answered with finality and any evidence bearing on it is worthy of record.

The researches above referred to have been made by histological study of the relation of tumors to surrounding normal epithelium in which they have arisen. The tumor cells, especially in epitheliomata, still bear a more or less close resemblance to the surrounding normal cells and are of necessity in contact with them (unless the normal epithelium has been destroyed well in advance of the cancer), so that every opportunity is offered for the production of deceptive appearances of transition. It is reasonable to expect some light to be thrown on the question by a study of contact between malignant and non-malignant epithelia of different histological type. The problem has been approached experimentally from this point of view by Rous (6) who demonstrated that a transplantable adenocarcinoma (the Flexner-Jobling tumor) would unite directly with normal regenerating skin epithelium of a granulating wound to produce histological pictures of simple union and of apparent gradual transition, without evidence which could be interpreted as showing that the skin cells were actually changed into tumor cells. Previous work with simultaneous grafting of embryo tissues and tumor (7) had shown that the cells of an adenocarcinoma may unite secondarily with normal epithelial cells of quite different histological type and intermingle with them.

We are approaching the problem on experimental animals from a somewhat different point of view. But in the meantime it has seemed worth while to study the experiment, carried out by nature in the human subject, of allowing cancer to grow into contact with normal epithelium, which may be observed when-
ever cancer of the breast involves the overlying skin. The conditions are ideal, inasmuch as the tumor is one arising from the individual's own cells rather than from transplanted material, and, furthermore, the mammary epithelium from which the tumor arises is intimately related embryologically with the skin epithelium, while it is yet sufficiently different in histological appearance to be readily differentiated.

The object of this paper, therefore, is to report a study of the histological pictures seen when skin epithelium has been "exposed" to approaching mammary carcinoma and to show that in the cases studied, no pictures of transformation occurred, but that appearances of histological union were seen which, except for the well-marked difference in morphology between the cells of the two types of epithelium, might be mistaken for true transformations.

The processes which go on when deep carcinoma of the breast approaches the skin have been summarized by Ribbert (2):

"When a cancer approaches the epidermis either it destroys it as a whole by compression, or its alveoli press on the basal layer, blend with it and break through it here and there, or they grow inside the epidermis, building in it epithelial nests and columns."

Each of these processes has been observed in the material studied for this paper. The variation in the general relation of advancing carcinoma to overlying skin has been striking. In some instances a single column of cancer cells has approached and penetrated the entire thickness of the epidermis well in advance of the main tumor mass (fig. 1). In a number of cases, especially at the margins of ulcers, islands of cancer cells have been found immediately against the skin epithelium without the interposition of basement membrane. The arrangement of the groups of cancer and of epithelial cells, however, has not been such as to suggest a true union but only a very close apposition (fig. 2).

In another type of approach a large area of cancer has been circumscribed against the epidermis with a narrow margin of connective tissue intervening (fig. 3). In still other cases, extraordinary pictures of hypertrophy of the epithelium downward in fine processes interlacing with equally fine strands of cancer have presented themselves (fig. 4).
Fig. 1. Path. No. 23931
a. A single column of cancer cells penetrating the epidermis

Fig. 2. Path. No. 25111
At an ulcer margin.  

a, An island of cancer cells in close apposition to skin epithelium which surrounds it on three sides. No basement membrane is seen, but there is no interdigitation of the two types of cells, the arrangement indicating only close apposition and not secondary union.  
b, Point of contact of another island of cancer with skin epithelium; basement membrane not yet destroyed.
A second type of approach of carcinoma to skin. Broad area of cancer circumscribed against flattened epithelium with narrow zone of intervening connective tissue. No hyperplasia of skin epithelium. No secondary union.

It is in the last-mentioned type of picture that the main interest of the study has centered, for in the relation of the fine strands of cancer and the fine hypertrophic processes of skin epithelium have been found the appearances of secondary union, the interpretation of which is in question. Figure 5 shows a process of downgrowing skin epithelium which has preserved its basement membrane against the cancer strands at its side, but shows apparent union with the cancer cells at its tip. The connection between the two, evident under the microscope, is shown but faintly in the photomicrograph, and for this reason the picture is perhaps not as convincing as that shown in figure 6, from another part of the same specimen, in which a strand of cancer cells lies parallel to, and in intimate contact with, a process of epithelium and the highest cancer cell has definitely interdigitated with the skin cells. The change in its shape is obviously due to
this interdigitation, and it cannot be regarded as a transitional form between normal and cancer cells. The non-malignant skin epithelium is readily distinguished by its fusiform or oval, small, deep-staining nuclei, its spindle-shaped cells with rather dark-staining protoplasm, arranged in a more or less orderly manner in the processes; the cancer cells by their large, irregular, more vesicular nuclei, their scant, ill-defined, and lightly-stained protoplasm, and the irregularity of their arrangement in strands and small islets. There are no intermediate types to be seen. If, however, the carcinoma were of the prickle-cell variety, confusion might easily arise in attempting to designate the last malignant and the first non-malignant cell.

In figure 7 a cell belonging to a small island of cancer has interdigitated with the cells of a process of skin epithelium, approaching in this instance from the side. In spite of the apparent actual histological union it is possible, on account of the marked difference in morphology between the two types of cells, to designate with certainty the last mammary cancer cell and the first epidermal cells, and again no intermediate forms are to be seen.
The material on which this study has been made consists of 475 specimens of cancer of the breast of fully developed scirrhous or medullary type which have been received in the Surgical Pathology Laboratory of the Johns Hopkins Hospital during the past ten years. Of this number 74 showed histological involvement, either of the nipple or of the skin overlying the breast. In 24 of these, however, the cancer had reached only to the lower layers of the derma and showed close approach only to the hair follicles or skin glands—incidentally without showing any appearances of histological union with these structures. It has been considered, therefore, that true “exposure” of the epidermal epithelium to carcinoma has occurred 50 times in the 475 breast cancers observed. Of these 50 exposures 16 showed intimate approximation of cancer to skin cells, but in only 7 of these were seen pictures of apparent histological union such as is illustrated.
in figures 5, 6, and 7. In none of these 7 cases of secondary union was seen any suggestion of transformation of non-malignant into malignant cells. Study of serial sections in a number of specimens has not changed the interpretation of the appearances at any given point.

It is of interest that all the pictures of apparent secondary union found in these cases occurred only where the skin epithelium was definitely hyperplastic, i.e., in those cases in which the skin over the cancer showed the type of reaction illustrated in figure 4. In the experimental work mentioned above, Rous also obtained secondary union between tumor cells and epithelium in hyperplastic activity, either regenerating epithelium on a granulating wound (6) or transplanted embryonic epithelium (7). Active growth of both of two tissues is therefore favorable, if not essential, for secondary union. If the uniting epithelia are dissimilar the cells of each retain their identifying characteristics.

These considerations suggest a reasonable explanation of the apparently perfect transition pictures seen between cancer and surrounding normal epithelium. Certainly hyperplasia of non-malignant epithelium is commonly seen at the margins of cancer, the effect of which is to alter the general morphology of the normal cells in many respects toward that of the tumor cells. Cancer cells, on the other hand, vary from marked distortion to forms nearly, if not quite, normal in morphology. Gradual transition may easily be simulated by this variation of each type toward the other, the line of demarcation between cancer and normal epithelium being obscured by their secondary union.

**SUMMARY**

It is not the purpose of this paper to assert that cancer never extends by transformation at the periphery of normal epithelial into malignant cells, but an attempt has been made to show that, in a considerable number of cases in which conditions for

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1 This reaction of normal epithelium is by no means specific for cancer. Exactly similar hyperplasia is characteristically observed in epithelium at the margins of benign epitheliomata and of ulcers due to tuberculosis, syphilis, or chronic inflammation. Vide, Councilman: Bull. Johns Hopkins Hosp. 1890, No. 2.
the occurrence of this transformation were theoretically very favorable, it has not been observed. Conclusions may be summarized as follows:

1. In 50 instances of “exposure” of epidermal epithelium to cancer approaching from below seen in 475 mammary carcinomas, no picture was observed which could be interpreted as transformation of normal into malignant cells.

2. In 7 cases, however, secondary histological union apparently occurred, which, but for the distinctive morphological appearance of the cancer and the skin epithelial cells, might be mistaken for transformation.

3. In so far as this evidence weighs, it is against the transformation of normal epithelial cells into cancer at the advancing margin of tumor.

4. The pictures of secondary union observed in these cases have occurred only in the presence of hyperplasia of the normal epithelium, and with this in mind a reasonable explanation is suggested of the apparent transitions seen at the margins of tumors, the cells of which are more nearly like those of the surrounding epithelium.

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REFERENCES