The Mode of Origin of Tumors

Solitary Localized Squamous Cell Growths of the Skin*

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INTRODUCTION

The mode of origin of tumors, while clearly a matter of fundamental biological interest as well as of considerable practical importance, has been strangely neglected by most modern pathologists. Many text books fail to mention it, or touch on it but lightly and with no evidence to support the views expressed; and many pathologists appear to have no clear ideas on the subject. The most prevalent view is that each tumor has a simple unicentric origin, arising at a single point in time, from a single small focus of cells, and enlarging only by multiplication of these cells and their descendants. This strict unicentric view is largely a legacy from Cohnheim (5) who, nearly three-quarters of a century ago, raised "the question of the central or peripheral growth of a tumour; understanding by central growth one resulting from the multiplication of the tumour elements themselves, and by peripheral an enlargement of the tumour by a new formation proceeding from the tissues surrounding it." Acceptance of Cohnheim's hypothesis of embryonic rests of course precluded the possibility of peripheral growth. In his own words, "this distinction is meaningless if the tumours do not originate in the fully formed tissues of the part . . . . For if, as we think, tumours develop from embryonic germs, a peripheral growth in the above sense does not take place."

Although Cohnheim's hypothesis of the origin of tumors from superfluous embryonic cells has been abandoned by most modern pathologists, who are now satisfied that, on the contrary, most tumors do "originate in the fully formed tissues of the part," his concept of restricted unicentric origin and purely intrinsic growth has largely persisted. The popularity of this view may be gauged from the following citations from well known works on tumor pathology.

Mallory (11) insisted that "Tumors grow entirely by multiplication of their own cells, not by transformation of normal cells into tumor cells"; and that attempts to trace gradations between normal and neoplastic tissues are "founded on incorrect observation, interpretation and deduction." According to McFarland, (12) "It seems well to think of a tumor as beginning at a minute focus, starting, as it were, from a single cell or group of cells, and increasing in size through multiplication of the particular elements concerned. . . . There seems to be no ground for assuming continuous transformation of normal tissue into tumor—no successive beginnings." Kettle (9) said, "It is generally held that tumours arise from one cell or group of cells, and not as the result of a change affecting a comparatively large area. Whatever may be the size of the tumour, all its cells are the direct descendants of the mother cell or cells." MacCallum (10) does not discuss the general question of the mode of origin of tumors; but, while he observes of carcinoma of the skin that where the cancerous epithelium is in continuity with the surrounding epidermis there is not an abrupt transition, yet he says, "It is not believed that the epidermis is converted into tumor tissue as the tumor spreads, but that all tumor epithelium arises from that which first began to grow"; and he explains the gradual transition from epidermis to tumor as due to "a secondary healing together." Ewing (7), after briefly discussing the possibility that tumors may develop by progressive neoplastic change in a field of tissue, concludes, "yet these instances of lateral extension of tumor processes, if they eventually stand the test of criticism, are rare, and it should be emphasized that the great majority of tumor-cells are isolated in origin and throughout their history." In view of his own immediately preceding comments on the sequences of changes to be seen in the genesis of cancers of the breast, and his depiction in his Fig. 4 of "atypical epithelial hyperplasia on the edge of a beginning carcinoma of the skin," Ewing's retreat to the orthodox unicentric view appears illogical.

A few general pathologists, however, have dissented from the strict unicentric views and have held that at least some tumors arise from more or less extensive fields of tissue and enlarge not only by cellular proliferation but also by progressive neoplastic conversion of tissue within those fields. The following succinct statement by Borst (1) is worth citing at length. "Each tumor is at first locally limited; it starts from a field
that usually is narrowly circumscribed, and at its periphery a histogenetic study is only possible if the tumor-formative field has not yet been totally incorporated in the growth, i.e., in early beginning tumors, or if, as is seldom the case, further similar foci are present in the neighborhood of an already established tumor.” After referring to the deceptive appearances that may be produced at the margins of carcinomas by irritative epithelial hyperplasia and the admixture and fusion of cancerous and noncancerous tissue, Borst goes on to say, “In examining the periphery of a carcinoma, then, one must be very cautious and critical. The view must be adhered to that the predisposition to carcinomatous change is generally restricted to a circumscribed focus; as long as this disposition is not yet wholly exhausted, the transition from normal to cancerous epithelium at the margin of a carcinoma can be traced; if, however, the whole of the predisposed focus has undergone cancerous change, then the established carcinoma grows purely intrinsically, and a continuous cancerous transformation of hitherto normal epithelium at the periphery of the carcinoma no longer occurs. This applies to the so-called unicentric carcinomas, which comprise the majority. Infrequently the formation of a carcinoma appears to be multicentric. Such cases merge into those with primary multiple development of carcinomas in an organ or system. And in yet rarer cases an organ appears to be predisposed throughout to the development of carcinoma, so that this commences simultaneously in very many places—diffuse origin of cancer, e.g., in the stomach, kidney, liver. In the case of multicentric cancer formation in an organ, enlargement of a carcinoma by the peripheral addition of neighboring cancerous foci can take place.”

In his Treatise on Tumors Hertzler (8) stated that evidence had accumulated to substantiate the view that carcinomas may enlarge by appositional growth and by the addition of multicentric foci. In intestinal growths, “the changes in the glands gradually shade off into the normal, as if some stimulus were causing successive glands to undergo abnormal proliferation, the changes being the less marked the further removed the glands are from the source of stimulation. The same is frequently seen in the skin epitheliomas.” Yet Hertzler then falls back to the orthodox unicentric viewpoint.

That mammary tumors often arise simultaneously or successively from extensive tracts of breast tissue is clear from the work of many pathologists, notably Cheatle (3), Nicholson (16), Cheatle and Cutler (4), and Muir (1941). To Cheatle belongs the credit for first demonstrating this conclusively in sections of whole breasts, and for insisting that “the primary cancer process transforming epithelial into malignant cells may commonly operate on extensive duct surfaces. . . . Having been established at one part of a duct, it may affect other parts of it, or other ducts.” Nicholson, endorsing Cheatle’s conclusions, said, “I have insisted for years that hyperplasia passes insensibly into carcinoma, and that this gradual change can nowhere be better studied than in the breast, and that tumour formation is here multi-, or rather omnicentric.” Muir expresses the same conclusions as regards mammary cancer in the following words, “Malignancy is often not only of multicentric origin but can be seen to occur gradually and to affect groups of cells in a diffuse fashion, all stages of the process being traceable”; the neoplastic change “is regional rather than focal.”

Elsewhere, in his Textbook of Pathology, Muir (15), after stating that, “As a rule, the origin of a malignant growth appears to be from a single focus,” goes on to say, “While the cells of a malignant growth are generally sharply demarcated from those of the surrounding tissues, it may be impossible sometimes to say exactly where the margin of the growth is. This is especially so in the case of epithelioma, where there may be a gradual transition between the cells of the tumour and the adjacent epithelium. Whether this means that the adjacent cells are being stimulated to malignant proliferation by the tumour cells or whether the change in them occurs because they have been exposed to the same irritation, is a difficult question to answer.”

Most notable of recent workers to insist on the field-origin of epidermal carcinomas are Brunschwig and Tschetter (2), who, in a study of early skin tumors, find “that the processes involve a segment of the epithelium and that they are not the result of changes arising in one cell or a small nidus of cells.” They describe and depict the marginal zone of direct continuity between noncancerous epithelium and cancerous epithelium, which they hold is “best explained by the hypothesis of progressive cancerization of the normal epithelium at the margins of the initially altered segment.” In early skin tumors produced in mice by applications of methylcholanthrene, Brunschwig and Tschetter also find and depict similar evidence of field-origin and progressive cancerization within the affected field.

Brunschwig and Tschetter were not the first, however, to reach these conclusions on experimental grounds. In 1923 Deelman (6) had made his careful studies of the mode of inception of tar cancers of the skin of mice; and had shown that these tumors arose in a field of tissue by progressive alteration of the epithelium of that field, commencing with hyperplasia, and passing gradually into papilloma formation, and this into carcinoma; and that the origin of these
Fig. 1.—Case I. Vertical section. Mag. $\times 8$.

Fig. 2.—Case II. EE, downgrowths with perfect epidermal structure. CC, atypical downgrowths. Mag. $\times 10$.

Fig. 3.—Case III. CC, cancerous foci with anaplastic cells. Mag. $\times 9$.

Fig. 4.—Case IV. XY, zone of transition between hyperplastic epidermis and crater lip X. EE, epithelium with perfect epidermal structure. Mag. $\times 8$. 
tumors was multicentric and multicellular. Similar field-origin is evident, though often not explicitly stated, in the observations of many subsequent workers in experimental carcinogenesis. Of these we may instance Orr (17), whose descriptions and figures of the inception of tumors in mouse skin following the application of carcinogenic hydrocarbons show clearly the widespread distribution of both the epidermal and dermal changes leading up to tumor formation. Mottram (13) is, I believe, the only experimentalist who has explicitly interpreted his results as pointing to the origin of experimentally produced tumors from single cells. His conclusion, however, is based on the assumption that excessive cellular multiplication takes place from the very commencement of tarring and produces a steadily increasing colony of proliferating cells from then onwards, an assumption not only opposed to our knowledge of precancerous changes in human tissues, but specifically refuted also by other experimentalists. Thus, of precancerous hyperplasia evoked by carcinogens, Orr says, "This epithelial increase . . . is almost immediate, and attains its full extent within the first week, after which there is but little change until the time, about three months later, when tumours are going to arise."

We are faced, then, on the one hand by a large body of authoritative and widely accepted opinion, from Cohnheim to Ewing, that most tumors are strictly unifocal (and therefore unitemporal) in origin and that their growth is purely intrinsic; and on the other hand, by clear evidence, like that of Cheatle, Muir, Deelman, and Brunschwig and Tschetter, that this assumption not only opposes to our knowledge of precancerous changes in human tissues, but specifically refutes also by other experimentalists. Thus, of precancerous hyperplasia evoked by carcinogens, Orr says, "This epithelial increase . . . is almost immediate, and attains its full extent within the first week, after which there is but little change until the time, about three months later, when tumours are going to arise."

I decided to re-examine carefully my specimens of tumors of the human epidermis and related stratified epithelium: those of the lip, tongue, vulva, and penis. These epithelia were chosen for two reasons. In the first place because, since they are accessible to direct examination, the development of tumors in them is often closely observed from their inception and early tumors are often available for microscopical examination; and in the second place, because such tumors presumably afford a parallel to experimentally produced epidermal papillomas and carcinomas. Of my collection of nearly 500 epidermal tumors, about 150 afforded some relevant information as to their mode of origin, and of these 40 typical specimens were selected for detailed study. The present paper is concerned only with solitary localized squamous cell growths of the skin, of which 10 selected examples are described. Other varieties, namely extensive superficial epidermoid carcinomas, basal cell and allied carcinomas of the skin, and carcinomas of the lip and tongue may be described in a later paper. The selected tumors were sectioned vertically through the center with as much as possible of the surrounding tissues. Paraffin-embedded sections were prepared and stained by hematoxylin and eosin, iron-hematoxylin and Van Gieson's stain, and by Verhoeff's stain for elastic tissue.

**Case I. (section no. 4440)**

A hemispherical growth 1.5 cm. in diameter, with a heavily keratinized, rough surface, was excised from the forearm of a man of 85. Most of the keratin became detached during preparation of the sections. The epithelium is everywhere perfectly differentiated, with no cytological indications of its neoplastic qualities. That it is neoplastic and cancerous, however, is shown by its invasion and disruption of the dermis. As Fig. 1 shows, the surrounding epidermis undergoes gradual hyperplastic thickening and keratosis as it approaches the growth, and this hyperplastic epidermis passes gradually into papillary neoplastic epidermis, with no visible alterations in the cytology of the epithelium. The epidermis of the growth shows fully differentiated spinous cells, a prominent stratum granulosum, and a sharply demarcated stratum corneum. Mitoses are few, and little if at all more numerous in the neoplastic tissue than in the hyperplastic epidermis. Where hyperplasia ends and neoplasia begins, and where the latter is innocent and where malignant, it is impossible to say.

The dermis beneath the growth and the immediately neighboring epidermis shows an abundant infiltration by lymphocytes and plasma cells. The dermal elastic tissue shows definite increase and degeneration, appearing in hematoxylin-stained sections as a conspicuous pale blue layer measuring up to nearly 2 mm. thick and consisting of almost homogeneous material formed by the fusion of swollen elastic fibers. Except in the immediate proximity of the tumor, this altered elastica is unassociated with round cell infiltration; and it extends with a little diminution in thickness right to the edges of the section, about 1 cm. from the growth margins. It is interrupted by the epithelial downgrowths of the tumor, beneath which there is no sign of elastic overgrowth.

**Case II. (section no. 5414)**

A hemispherical, horny growth of 6 months' duration and 1.5 cm. in diameter was excised from the dorsum of the hand of a man of 56, who was a gasworks employee handling tar.

The epithelium.—The tumor is a highly differentiated, epidermoid carcinoma, with broad downgrowths to a uniform depth in the dermis, and
Fig. 5.—Case V. XY, transition zone. CC, deeply penetrating cancerous downgrowths. Mag. × 5.
Fig. 5A.—Same section as Fig. 5, showing darkly stained, thick layer of subepithelial elastic tissue (Verhoeff's stain). Mag. × 6.
Fig. 6.—Case VI. XX, crater lips. EE, marginal epidermis-like downgrowths. CC, more active carcinoma, sharply delimited from E at the arrows. DD, thick layer of altered elastic tissue visible. Mag. × 8.
Fig. 6A.—Elastic tissue shown in Fig. 6 darkly stained by Verhoeff's stain. Mag. × 6.
covered on the surface by a thick layer of keratin. Some of the downgrowths in the central parts of the tumor (e.g., those marked CC in Fig. 2) show some histological evidences of malignancy, namely widespread incomplete keratinization, large irregular spinous cells, and some nuclear irregularities in the marginal cells. But others of the downgrowths (e.g., those marked EE) show perfect epidermal differentiation of spinous, granular, and horny layers. The surrounding epidermis shows gradual hyperplastic thickening as it approaches the tumor, and there is a gentle transition from nonneoplastic to neoplastic epithelium. In the superficial central parts of the growth, also, no sharp distinction is possible between residual nonneoplastic surface epidermis and the cancerous downgrowths from it.

The dermis.—Beneath both the growth and the hyperplastic epidermis there is an abundant infiltration by plasma cells accompanied by fewer lymphocytes. The dermal elastic tissue shows decided increase, with swelling and partial fusion of its fibers, to form a well-marked, pale blue layer in the hematoxylin eosin-stained tissues. This extends with slight diminution in thickness to the edges of the section, at the extreme periphery of which it is unaccompanied by round cell infiltration. The elastic layer has been invaded and destroyed by the cancerous downgrowths.

CASE III. (SECTION NO. 5734)

A horny "papilloma" 1.5 cm. in diameter was removed from the forearm of a man of 49. A small, scaly nodule had been present for 4 years and had enlarged in the last 3 months.

The epithelium.—The structure of the bulk of the tumor accords with the clinical diagnosis; it is highly differentiated and epidermis-like and consists of large, regular downgrowths between exaggerated dermal papillae. That the tumor is really cancerous, however, is shown by invasive disruption of the dermis by the downgrowths, and especially by the presence of multiple small foci of histologically frank carcinoma at the margins of some of the downgrowths (CC in Fig. 3). These foci, while still epidermoid in structure and continuous with the well-differentiated epithelium without sharp demarcation, show groups of anaplastic cells with irregular or multiple hyperchromatic nuclei and many mitotic figures. These foci clearly possess increased invasive powers, for they have extended into the dermis to a deeper level than that of the general depth of the major downgrowths, and in finer strands of epithelium.

The adjacent epidermis as it nears the growth shows gradual increase in thickness, and this hyperplastic epidermis shows no sharp demarcation from the neo-plastic epithelium. Surface keratinization is abundant.

The dermis beneath the tumor proper and the hyperplastic epidermis immediately contiguous with it shows an abundant infiltration of lymphocytes, plasma cells, and eosinophile cells. Except where it is disrupted by the downgrowths of the tumor, the dermis shows a well marked layer of excessive elastic tissue with swollen fibers. This changed elastic tissue is most prominent and thickest close to the growth, but it extends right to the cut edges of the section, and on one side extends beyond the limits of leukocytic infiltration.

CASE IV. (SECTION NO. 1852)

A wart-like growth of 8 months' duration was excised from the dorsal aspect of the wrist of a man of 46. It was a non-ulcerated projecting mass nearly hemispherical in shape and 1.5 cm. in diameter, with much of its surface presenting a mass of rough keratin. This broke away when the tumor was being sectioned, leaving the symmetrical crater seen in Fig. 4.

The epithelium.—The tumor is a well differentiated epidermoid carcinoma composed of short, stout downgrowths invading the dermis to an evenly uniform depth. Most of these downgrowths in the central part of the tumor are histologically cancerous, although well differentiated, consisting mainly of large, coarsely spinous cells and showing widespread but incomplete keratinization. Mitotic figures are present in moderate numbers, especially in cells along the margins of the downgrowths; some of them show abnormal, e.g., triad, forms. Others of the downgrowths show complete differentiation, with the formation of normal looking spinous cells, a stratum granulosum, and sharply delimiting keratin pearls. Where these normal looking downgrowths are in continuity with clearly cancerous ones, the epithelium shows a gentle transition. The epidermis peripheral to the crater margins, XX, shows gradual hyperplastic thickening as it approaches the growth, but there is no clearly cancerous epithelium external to the crater. On the other hand, it is not possible to assert that all the epithelium within the crater is cancerous. Indeed, some of the more superficial epithelium in the crater floor, as at EE, has all the appearance of residual noncancerous epidermis, in continuity with, and without clear demarcation from, its cancerous downgrowths. Similarly in the neighborhood of the lips of the crater, XX, there is a gentle transition from noncancerous to cancerous epithelium. Observe, also, how just peripheral to the crater edge the epidermis in the zone XY is thinner than the more peripheral hyperplastic epidermis. Underlying this thinned zone of epidermis is the peripheral part of the growth where it invades the dermis.
Fig. 7.—Case VII. Vertical section of slightly more than one-half of the growth. X, invagination lip. EE, surface zone of epidermis-like growth. CC, more active carcinoma. PP, cartilage. Mag. X 16.

Fig. 8.—Case VIII. X, invagination lip. Y, region of neoplastic transition without invagination. EE, surface epithelium potentially or actually cancerous. C1, 2, 3, 4 and 5, foci of active carcinoma. Mag. X 12.

Fig. 8A.—Structure of actively cancerous foci shown in Fig. 8. Mag. X 160.
The dermis around the clumps of growth and beneath the thickened marginal epidermis is infiltrated by plentiful plasma cells and a few lymphocytes. There is a slight increase in the number and thickness of the dermal elastic fibers around the tumor margins, un-

accompanied in the more peripheral parts by round cell infiltration.

CASE V. (SECTION NO. 3569)

A woman of 75 had noticed an enlarging growth on the dorsum of the wrist for 3 months. She also had multiple hyperkeratoses on the dorsa of the hands and on the face. The projecting hemispherical tumor, which measured 2 cm. in diameter and had a horny summit, was excised along with a wide margin of skin. The horny material was detached during preparation, leaving a crater as shown in Fig. 5.

The epithelium.—As the growth is approached from the periphery of the section, the epidermis shows gradual hyperplastic thickening to about the region of Y, between which and the crater-margin, X, the epithelium becomes thinner again but very irregular. In zone XY it is impossible to decide whether the epithelium is hyperplastic or neoplastic; it is this zone that immediately overlies the most marginal of the carcinomatous clumps invading the dermis. The epithelium in the floor of the crater is complete, thin, perfectly differentiated, and indistinguishable from normal or hyperplastic epidermis. Yet that it is cancerous is shown by its having penetrated into the
dermis, interrupting the dermal elastica (Fig. 5A), and by its having given off the obviously cancerous downgrowths CC. These downgrowths themselves are highly differentiated, showing all the characters of epidermis; namely, normal looking spinous cells, a well-marked stratum granulosum, and sharply limited stratum corneum in the form of concentrically laminated keratin pearls. Extending from their deepest parts, however, lie small clumps of deeply penetrating carcinoma cells with imperfect differentiation and many mitoses.

The dermis.—Abundant lymphocytes along with some plasma cells lie beneath the cancerous area and the adjacent zone of hyperplastic epidermis. The dermal elastic tissue is notably increased, forming a prominent layer up to 1.5 mm. thick extending with gradual diminution of thickness from the neighborhood of Y to the edge of the section (Fig. 5A). Its fibers are enlarged and distinct in most situations, but there are patches of degeneration and hyaline fusion. In the peripheral parts of the section the altered elastica is unaccompanied by round cell infiltration.

**Case VI. (section no. 2126)**

A hemispherical growth 1 cm. in diameter, of unrecorded duration, was excised from the neck of a man aged 70.

The epithelium.—As the surrounding epidermis approaches the growth, it shows steady hyperplastic thickening. At about XX in Fig. 6 this thickened epidermis passes insensibly, and without change of cytological characters, into the bulky downgrowths EE that form the marginal parts of the growth. That these downgrowths are cancerous in spite of their complete epidermal differentiation, is clear from their penetration into the dermis with interruption of the elastica (Fig. 6A). The bulk of the central part of the growth, CC, consists of moderately active, histologically frank carcinoma, composed of closely packed anastomosing strands and masses of imperfectly formed spinous cells with patchy, incomplete keratinization and a moderate number of mitoses. Between the bulky marginal downgrowths, EE, and this frankly carcinomatous tissue there is an abrupt transition, shown by the arrows in Fig. 6.

The dermis.—Plentiful lymphocytes and plasma cells underlie the growth and the hyperplastic epidermis marginal to it. The dermal elastic tissue is greatly increased in amount and shows advanced degeneration, with swelling and fusion of fibers to form an almost homogeneous layer up to 2 mm. thick. In hematoxylin-eosin-stained sections this forms a prominent blue zone, visible at DD in Fig. 6, but more strikingly shown by Verhoeff's stain in Fig. 6A. This altered elastic layer is interrupted by the downgrowing tumor, from which it extends prominently with slight diminution in thickness to both edges of the section. In the more peripheral parts it is unaccompanied by leukocytic infiltration.

**Case VII. (section no. 4582)**

A projecting, rough-surfaced, hemispherical growth 8 mm. in diameter, of unspecified duration, on the outer edge of the pinna of the ear of a man of 57 was diagnosed as a "papilloma" and excised.

The epithelium.—A vertical section through the middle of the growth (Fig. 7) shows the following structure. At X the epidermis, which shows little or no hyperplastic thickening, undergoes a sharp invagination and becomes continuous with a layer of greatly thickened convoluted epidermis, EE, that clothes and forms the surface zone of the growth. This layer exhibits perfect differentiation of all the characters of epidermis, and shows no cytological signs of its neoplastic quality. That it is cancerous, however, is shown by its great thickening, its irregular downgrowths into the dermal tissues, and the continuity of these downgrowths with a mass of frankly carcinomatous tissue, CC, that constitutes the central part of the growth and extends down to the cartilage of the pinna, PP. This carcinomatous tissue consists of closely aggregated, narrow, epithelial columns devoid of epidermal characters except for occasional small foci of keratin and a few poorly formed spinous cells. The cells show considerable variation in the size of their nuclei, and mitoses are fairly numerous. The zone of junction of this tissue with the overlying epidermis-like zone EE shows rapid, but not abrupt, transition from the one to the other; the columns of the frankly cancerous tissue are but tendril-like continuations of the deeper parts of the downgrowths of EE. This is clearly shown in the figure.

The dermis.—Beneath the infiltrating edge of the growth and the epidermis at its margins there is a plentiful collection of lymphocytes accompanied by a few eosinophile leukocytes. The dermal connective tissues show some fibroblastic thickening and the formation of many small blood vessels. There is no evidence of any great change in the dermal elastica.

**Case VIII. (section no. 5650)**

A slightly raised, circular growth 1.5 cm. in diameter, with a flat, encrusted surface was excised from the neck of a man of 70.

The epithelium.—A vertical section through the center of the growth shows most of its surface to be clothed by a perfectly differentiated but thickened and very irregular epidermis-like layer, EE, which is continuous peripherally with the slightly thickened hyperplastic epidermis around. The transition from the one
to the other, which is gradual and without any change of cytology, takes place in the neighborhood of the points X and Y. At X the transition takes place fairly rapidly and is accompanied by a sharp invagination of the epithelium; at Y the transition is much more gradual and there is no invagination. It is impossible to decide whether the epithelium EE is extravagantly hyperplastic or already neoplastic; but springing from its deep surface there are multiple frankly cancerous downgrowths. There are at least 3 quite separate downgrowths, C1, C2, and C3; while at C4 there is another small carcinomatous patch probably, but not certainly, separate from C1; and at C5 there is a minute probably carcinomatous focus in the epidermis. The carcinoma C1 penetrates the dermis almost to reach the platsma. The characters of the frankly malignant tissue are similar in all the foci, and are shown in Fig. 8A. It consists of epidermoid carcinoma of active type with abundant mitoses, many large, coarsely spiny cells, and patchy, imperfect keratinization. Although this carcinomatous tissue is quite distinct in structure from the well-differentiated surface epithelium, the region of junction of each cancerous area with this epithelium shows a gentle, though rapid, transition from one to the other.

The dermis.—Lymphocytes and plasma cells are plentiful around the carcinomatous areas, but are few elsewhere and are not present in the dermis away from the growth. The dermal elastica shows decided increase and degeneration, appearing in hematoxylin-eosin-stained sections as a prominent, lilac-blue layer up to 1.5 mm. thick. This consists partly of greatly swollen but still separate elastic fibers, and partly of structureless hyaline material formed by fusion of the fibers. The layer of altered elastica is interrupted by the cancerous downgrowths; peripheral to these it is continuous and prominent, with some diminution in thickness, right to the edge of the section.

Case IX. (section no. 4799)

A growth of several months' duration was excised from the neck of a woman of unrecorded age. It was a nonulcerated, projecting, smoothly hemispherical mass 2 cm. in diameter.

The epithelium.—The marginal epidermis, which shows slight thickening as it approaches the tumor, passes insensibly into the thin but complete layer of epithelium that covers the tumor surface. The rest of the tumor consists of irregular, ramifying downgrowths from this layer. These downgrowths, though clearly cancerous, show almost perfect differentiation of all the features of normal epidermis, including perfectly formed spiny cells, a stratum granulosum, and abundant keratinization forming laminated, sharply defined, epithelial pearls. Mitotic figures are few. The thin surface layer of epithelium also shows complete epidermal characters, and it is impossible to decide where marginal noncancerous epidermis ends and cancerous epidermis begins, or even to exclude the possibility that the surface layer may consist only of stretched residual noncancerous epidermis.

The dermis shows general fibrous thickening forming the stroma of the growth, and this is infiltrated by many plasma cells and lymphocytes. Associated with some of the carcinomatous clumps in which degenerating keratin and some calcification are present, there are a few foreign body giant cells and some polymorphonuclear leukocytes. The elastic tissue of the dermis marginal to the tumor shows only slight increase.

Case X. (section no. 7171)

A slightly pedunculated, nearly hemispherical growth, 1 cm. in diameter, of unrecorded duration, was excised from the skin of the dorsal aspect of the neck of a woman aged 35. The summit of the growth was clothed by a rough mass of keratin, which was detached during preparation.

The epithelium.—The tumor is an epidermoid carcinoma of fairly well-differentiated type. Although its downgrowths penetrate into the dermis of the pedicle only slightly below the surface level of the surrounding skin, histologically they are clearly cancerous, being very irregular, tendril-like and anastomosing in places, with patchily imperfect differentiation. In the floor of the crater left in the summit of the growth by detachment of the keratin the epithelium, though irregularly festooned and papillated, is well differentiated and epidermis-like. The epithelium clothing the sides of the growth, from its base to the edges of the crater, XX, is smooth-surfaced, devoid of excessive keratin, and histologically identical with the adjacent normal epidermis except that it shows moderate hyperplastic thickening. The surrounding epidermis appears quite normal.

The dermis.—The exaggerated papillae and connective tissue strands between the tumor downgrowths are heavily infiltrated by lymphocytes together with a few plasma cells and polynuclear cells. Many of the epithelial cords are invaded and partly disorganized by collections of these leukocytes. Slight perivascular collections of leukocytes are present in the dermis peripheral to the growth. No changes are detectable in the dermal elastica either beneath the growth or in the surrounding skin.

Discussion

A. Review of the Specimens

I contend that in none of the specimens described can the structure be plausibly explained in terms of
the hypothesis of simple unifocal, unitemporal origin and purely intrinsic proliferative growth. Let us review the structure of our specimens from this aspect, comparing and contrasting the figures.

_Tumors I, II, and III_, all from the forearm or hand, closely resemble one another in structure. All 3 consist of highly differentiated, slowly growing epidermis-like tissue of relatively low invasive power. This tissue, together with its overlying keratin, forms in each case a complete nonulcerated hemispherical mass in continuity with the surrounding epidermis, of which it constitutes a symmetrical thickening, with extravagant papillation and keratinization, over a circular field between 1 and 2 cm. in diameter. In each case the surrounding epidermis shows gradually increasing hyperplastic thickening as it approaches the growth, and this hyperplastic epidermis passes gradually into the cancerous epithelium, making it impossible to decide just where the one ends and the other begins.

This structure is incompatible with the view that the tumors arose each from a minute central focus and grew solely by invasive replacement of surrounding epidermis. Even if we supposed the neoplastic cells sprouting out from such a hypothetical focus to spread preferentially within, and to effect cell by cell replacement of, the invaded epidermis (a process for which none of the specimens studied affords any evidence), this would still not suffice to explain the gradual transition from hyperplastic to neoplastic tissue and the absence of any clear, or even approximate, region of demarcation between the two. Each of these growths shows plain evidence of a progressive hyperplastic-neoplastic change, still taking place, in a centrifugal direction over a field of epidermis greater in extent than the present size of the growth. In Borst's words, "the tumor-formative field has not yet been totally incorporated in the growth". The actual size of the potential tumor-formative field in each of these specimens is an area of epidermis clearly at least 1.5 cm. in diameter, and probably much greater than this, since there is a considerable zone of epidermal hyperplasia around each growth, and there is no reason to suppose that we have chanced to examine the tumors just at the time when the neoplastic potentiality of this zone is nearing exhaustion.

_Tumors IV and V_, while showing a general similarity to the previous specimens, present also certain interesting differences. Similar are the high degree of epidermis-like differentiation of the growths, the presence of a peripheral zone of hyperplastic epidermis steadily increasing in thickness as it approaches the growth, and the absence of any clear demarcation between hyperplastic and neoplastic tissue in the zone XY. Different from the previous specimens are the diminished thickness of the epithelium in the hyperplastic-neoplastic zone XY, the relatively small thickness of the cancerous epidermis in the floor of the crater left after removal of the large mass of superjacent keratin, and the sharp invagination of the epithelium at the crater edge, X. It is as if the area of cancerous epidermis, while undergoing great hyperkeratosis but without much proliferative increase in bulk, and while still retaining its marginal continuity with the surrounding hyperplastic epithelium at the invaginating edge, X, had sunk as a whole into the superjacent dermis. In each specimen the most peripheral cancerous downgrowths invading the dermis underlie the thinned but irregular zone of surface epithelium, XY, which is itself in gentle continuity with the more peripheral zone of thick, hyperplastic epidermis.

These very distinct structural characters cannot be dismissed as merely fortuitous, and they are inexplicable on the hypothesis of origin from a tiny central focus and growth by proliferative invasion of surrounding tissue. On the basis of progressive genesis still taking place in a field of tissue, however, these characters at once become intelligible. From the structure of the central parts of these two tumors it is clear that their habit of growth is to produce a relatively thin depth of invading epithelium, surrounded by a large mass of keratin. The thinned, irregular epidermal zone XY is a zone of transition from much thickened but only hyperplastic epidermis on the one hand to clearly cancerous invasive epidermis on the other. As the epithelium of this zone progressively acquires frankly neoplastic properties it invaginates itself at the crater edge, X, and so joins the already invasive neoplastic epithelium in the sides and floor of the crater. It is from these sides and this floor that cancerous downgrowths sprout. Thus the conception of progressive cancerization extending concentrically over a widening area of epidermis affords a clear explanation of the structure of these growths. The diameter of the field that has already become cancerous is 1.5 cm. in Case IV and 2 cm. in Case V; and, especially in Case V, the changes in the surrounding epidermis strongly suggest that the potentially cancerous field is much greater still.

_Tumors VI and VII_. In the interpretation of these two specimens, a minor feature exhibited by III and V deserves further notice. This is the presence in the deepest parts of the growths of small foci of cancerous epithelium of poorer differentiation and greater mitotic activity than the remainder of the tumors. These small anaplastic foci clearly denote an early stage of augmented growth rate and degree of malignancy in parts of these tumors. Such enhanced malignancy with respect to the earlier established, less active parts is seen in a more advanced stage in VI and VII.

In tumor VI, as in the previous specimens, there
is a marginal zone of hyperplastic epidermis that passes insensibly into the epidermis-like downgrowths of the peripheral parts of the tumor. Like specimens IV and V, also, the cancerous epidermis shows invasive invagination, forming sharp crater lips, XX. The bulk of the central parts of the tumor, however, consists of much more active, poorly differentiated carcinoma, and there is an abrupt junction between this and the epidermis-like marginal parts of the tumor. The structure of the tumor thus indicates its development in two stages, namely: (a) a stage of transformation, still in progress, from hyperplastic epidermis to well-differentiated epidermoid carcinoma with invagination and downgrowth of the latter, EE; and (b) a supervening accession of growth rate and malignancy, with corresponding dedifferentiation in the central part of the growth and invasive replacement of the well-differentiated growth, EE, by the more anaplastic component, CC. Incidentally, this specimen affords a good example of the abrupt junction created when a relatively quiescent epidermal tissue suffers proliferative invasion and replacement by active carcinoma. It is this kind of junction that we should regularly see were the strict unicentric view correct, but which, as this study shows, is not observed in early epidermal carcinomas.

A similar two-stage sequence accounts for the structure of growth VII, which, however, shows some further noteworthy features. Here the initial stage of conversion of hyperplastic into neoplastic epidermis appears to be complete, for there is no zone of hyperplastic epidermal thickening peripheral to the invagination lip, X. The whole of the potentially cancerous area has been converted into tumor, the first stage of which is represented by the greatly thickened, irregularly folded layer of epidermis-like growth, EE. The deeper parts of the tumor, CC, which are of much more active and poorly differentiated type, have clearly arisen by a supervening accession of malignancy in the downgrowths of EE; and it seems clear that this has occurred not at a single spot but in a widespread manner.

On the hypothesis of simple unicentric origin and purely intrinsic proliferative growth, neither the general structure nor the dual character of the neoplastic tissue in tumors VI and VII is intelligible. The conception of cancerization of a field of epidermis, with supervening augmented growth rate in the same field, however, readily accords with the structure observed.

Tumor VIII is of great interest in that it shows multiple, separate foci of histologically frank carcinoma springing from the deep surface of a considerable area of hyperplastic (or possibly neoplastic) epidermis. These little separate carcinomas all consist of similar, rather active, tissue; and all show a similar relation to the surface epithelium, with a rapid but not abrupt transition from one to the other. The nature of the surface epithelium itself, whether only hyperplastic or already neoplastic, is not certain for the same reason that in previous specimens it has been impossible to say precisely where hyperplasia ends and neoplasia begins, save by the invasive powers displayed by the epithelium. However, that the surface epithelium in the present specimen is potentially, if not actually, cancerous is shown by its having given origin to multiple clearly carcinomatous downgrowths, while the presence of an invaginating lip at X points strongly to genuinely carcinomatous properties. In the light of the two previous specimens we may strongly suspect that here, too, we are witnessing a two-stage transformation comprising: (a) a hyperplastic-neoplastic change in the entire field of surface epithelium, accompanied at X by invasive downgrowth; and (b) the supervention of enhanced growth-rate, with invasive powers at multiple spots in the deep parts of the already unstable epidermis. It can scarcely be doubted that, had this lesion not been excised, more and more of this unstable epidermal field would have passed into frank carcinoma.

Tumor IX shows characters rather different from those of the previous specimens. The marginal epidermis shows only a little hyperplastic thickening, but as it is traced onto the surface of the growth it is impossible to decide even approximately where non-cancerous epithelium ends and cancerous begins. The ramifying cancerous downgrowths themselves show perfect histological differentiation, and are connected with the surface epithelium at many points and in a uniform manner over the whole extent of the growth. It is difficult to picture how this tumor could have developed by purely proliferative growth from a single minute focus, but easy to understand how it could have arisen progressively from a field of epidermis coextensive with it, i.e., a circular area 2 cm. in diameter.

Tumor X is unlike any of the other specimens in that, while its tissue histologically is clearly cancerous, it has failed to effect invasion of the dermis; its growth has been almost wholly outwards and it has attained a pedunculated form. Hyperplastic epidermis clothes the sides of the projecting growth, but the surrounding epidermis shows no alteration. In other respects the structure resembles that of IV and V, with a similar continuity of hyperplastic epidermis with cancerous epithelium at sharp crater edges XX. The growth is to be interpreted as arising from a field of epidermis coextensive with it; much of this field has already become cancerous, but the residual hyperplastic epidermis on the sides of the tumor has yet to become so. In spite of the invasive invagination dis-
played by the cancerous epithelium, it has failed to penetrate the dermis but has suffered instead a kind of partial extrusion on the surface as it grew. We shall return to this feature presently in considering the dermal changes.

B. CHANGES IN THE EPIDERMIS

A striking feature of many of these early growths is the retention of almost perfect epidermis-like structure by the cancerous epithelium. This may show distinctly the various strata of the epidermis, as well as cell details such as spines, keratohyalin granules, and nuclear characters identical with those of normal cells. Mitotic figures are often little or no more numerous than in the adjacent normal or hyperplastic epidermis. Indeed, the histology of the epithelium alone, without reference to its position, often gives no indication of its neoplastic qualities. This nearly perfect epidermal structure is retained because the tumor actually consists of a field of cancerized epidermis. In this field cellular structure, arrangement, and rate of multiplication may have undergone but little change; most of the tissue of the growth represents the pre-existing tissue transformed, and not a proliferated colony of descendants of a single cancerous mother cell.

Of course it is not denied that an established tumor grows in bulk by cell proliferation in excess of that of the normal epidermis, or that proliferating tumor tissue also may attain a high degree of epidermoid differentiation. What is to be insisted on, however, as clearly revealed by the specimens described, is that a skin cancer in its early formative stage arises more by a gradual transformation of pre-existing epidermis than by cellular multiplication, and that only after the formative field has all suffered neoplastic change does the tumor grow solely by multiplication. The two processes, neoplastic transformation and increased cellular multiplication, overlap, the former predominating during the early genesis of the tumor, the latter often being initially negligible but gradually taking an increasing and finally exclusive part in the growth of the tumor. As specimens III, V, VI, VII, and VIII show, an established growth may exhibit acceleration of its rate of proliferation, with corresponding structural anaplasia and, no doubt, enhanced malignancy.

It is relevant to refer here to the distinction between "benign" and "malignant" neoplasia. Such tumors as I, II, and III are superficial, clinically innocuous lesions with no risk of metastasis, and are looked upon by the surgeon as benign. Yet to the histopathologist they are cancerous, because the epithelium has penetrated into and disrupted the dermis. Are they "papillomas with early malignant changes," or are they lowly malignant carcinomas ab initio? The distinction is merely verbal; "innocent" and "malignant" are only relative terms, clinically useful in prognosis but not denoting sharply separable classes of tumors. An epidermal "papilloma" differs from a carcinoma only in that the invasive power of the neoplastic epithelium is slight or for the time being in abeyance; the non-invasive growth of today may display its invasiveness tomorrow, and this display does not mean that the cells of the growth have suddenly acquired new properties. It is futile, then, to try to decide how much of the neoplastic tissue in growths like those described is "papillomatous" and how much is "carcinomatous." The epithelium shows a steady progressive change, commencing with preneoplastic hyperplasia and culminating in invasive carcinoma.

C. CHANGES IN THE DERMIS

Increase and degeneration of the dermal elastic tissue were prominent in most of my specimens. In assessing the possible significance of these, it was first necessary to ascertain their frequency and degree in noncancerous skin. Various surgically removed skin lesions were examined, and also pieces of skin removed postmortem from the neck, forearm, hand, and leg of 20 middle-aged or old subjects. The skin of the dorsum of the hand and forearm in the elderly often showed pronounced changes in the elastic tissue, resembling those seen in association with carcinomas; the skin of the neck showed such changes less frequently; the skin of the leg seldom showed prominent changes.

Although nearly all my tumors were from the hand, forearm, or neck, regions where senile changes in the elastic tissue are commonly present, there are two strong reasons for believing the dermal changes in the tumor specimens to be at least in part related to the tumors and not wholly coincidental: (a) In several cases, I, V, VI, and VIII, the thickness of the altered elastica near the growth was greater than in any of the noncancerous control specimens examined; and (b) in most cases its thickness was greatest close to the growth and diminished towards the edges of the sections.

There are two possible ways in which these dermal changes might be related to the tumors; either they might be secondary, part of the stromal reaction to their presence, or they might have preceded the formation of the tumors, being part of the precancerous state in the fields in which the tumors later developed. While the first possibility cannot be excluded, I lean to the second for the following reasons: (a) Changes in the dermal elastica, clearly related to the growth because showing diminution in a centrifugal direction around it, are often present at considerable distances.
from it, 1 cm. or more in several cases, and often beyond the zone of leukocytic reaction to the tumor.
(b) There are no comparable changes in the perivascular and interstitial elastic tissue of the deep dermal and subcutaneous tissues beneath the invading tumors, contrary to what might have been expected if the dermal changes were only a stromal reaction to the tumors. The tumor downgrowths make complete breaches in the layer of altered elastica, as if the latter had already been present prior to invasive disruption by the former. (c) Orr (17) has shown that the precancerous changes following the experimental application of carcinogenic hydrocarbons include prominent, and apparently specific, alterations in the dermal connective tissues, including the elastic, and that "when tumours appear, they are frequently related to fibrous scars in the subcutis, to gaps in the elastic tissue of the dermis, or to both." Allowing for the structural differences between mouse and human skin, there is a close parallelism between Orr's experimental results and my own observations, especially as regards the elastic tissue changes. The experimental findings strongly support the view, reached from the purely structural evidence given above, that the changes in a potentially cancerous field of skin include alterations of the dermis and that these play a part in the inception of tumors.

It may well be that carcinogenesis involves not only augmented epithelial growth but also, as Ribbert long ago supposed, diminished connective tissue restraints. Perhaps the peculiar structure of my specimen X was determined by an unusual retention of the restraining capacity of the dermis, so that invasion was deferred and the cancerous epithelium could only grow outwards as it multiplied. Certainly this specimen was also unusual in the absence of any visible changes in the dermal elastic tissue.

D. Conclusion

I believe that the evidence advanced justifies the view that squamous cell carcinomas of the human skin are comparable with those produced experimentally, and are the products of the following sequence of events:

(a) A skin field more or less extensive has been subjected to a succession of carcinogenic stimuli (still often unspecifiable in human beings), which have induced slow progressive changes in both the epidermis and dermis of that field. With the passage of time the epidermal changes become structurally apparent as precancerous hyperplasia, which may persist innocuously as such for long or brief periods. The dermal changes include gradual increase, followed by degeneration, of elastic tissue just below the epidermis. In this precancerous field there is often a visible gradient of both epidermal and dermal changes, usually from a single central focus to the periphery, but sometimes with more than one focus of high cancer potential.

(b) At the central focus (or at several high potential foci) of the field, hyperplasia passes into irreversible neoplasia, with or without immediate invasion of the dermis by the epithelium. Invasion probably commences at points of maximum damage of the dermal elastic tissue.

(c) As cancerous proliferation and invasion progress at the central part of the field, cancerous change of the surrounding unstable epidermis takes place in a steadily enlarging area around the centre. It is at this stage that early carcinomas of the human skin, like those described, become available for study.

(d) After the entire field of the predisposed epithelium has become cancerous the tumor enlarges solely by proliferation of the cancerous cells, and structural evidence of its mode of origin is soon lost.

One final point requires clarification. Some pathologists (e. g., Welch, 18), while properly recognizing that tumors often arise by spreading cancerization of a more or less extensive field of tissue, have assumed this to be brought about by "the passage of a malignant influence from cancer cells to adjacent noncancerous epithelial cells, whereby the latter are induced to become cancerous in situ." However, there is no need to create a stumbling block by supposing any such "malignant influence." In human as in experimental carcinogenesis the effective stimuli are applied, not to one cell or one small group of cells, but to a more or less extensive area of epithelial tissue. All the epithelium in that area is acted upon similarly, though of course usually not equally. Neoplasia will commence where the stimuli have been maximal, but the neoplastic response will later be manifested by neighboring tissue that was subjected to the same original stimuli. The timing and distribution of this progressive response will depend on the distribution and intensity gradients of the causative stimuli.

SUMMARY

1. The structure of a series of early, localized squamous cell carcinomas of human skin is described, including the dermal as well as the epidermal changes.
2. The structure of these growths is incompatible with a strict unicentric view regarding their origin, but shows instead that each has arisen by spreading cancerization of a field of epithelium. Such cancerization usually commences from a single central focus, but several initial foci may be present.
3. The precancerous state of an area of skin includes significant dermal changes, especially in the subepithelial elastic tissue, and invasion of the dermis...
by the cancerous epithelium probably commences at points of greatest damage of the dermal elastica.

4. Progressive neoplasia in a field of tissue does not imply the passage of any carcinogenic stimulus from cell to cell, but is merely the progressive response of an area of epithelium to the same original stimuli, a response graded according to the gradients of the effective stimulation.

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