ORIGIN OF THE HUMAN BASAL CELL EPITHELIOMA*

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While a voluminous literature relating to the basal cell carcinoma or epithelioma has arisen since Krompecher in 1903 (1) proposed its derivation from the basal layer of the epidermis, there is still lack of general agreement as to its precise histologic origin.

Doubts as to epidermal origin of these tumors were expressed by Mallory (2) and Haythorn (3). Mallory attributed their origin to hair matrices, sebaceous and sweat glands. Haythorn also favored an origin from the hair matrix and sebaceous gland. Wallace and Halpert (4) favored an origin from either the hair matrix or hair follicle anlage, and suggested the term "trichoma" (which actually means tumor of hairs). Lever (5) believed that "basal cell epitheliomas are not carcinomas and are not derived from basal cells but, instead, are nevoid tumors (harmartomas) derived from primary epithelial germ cells." His classification of epidermal tumors is based on this concept. Foot (6) and Swerdlow (7) are in general agreement with this theory.

Support for Krompecher's thesis is found in the work of Montgomery (8), Willis (9), and Teloh and Wheelock (10). These investigators favored multiple points of origin from the basal layer of the epidermis, hair follicles and sebaceous glands. Origin from the sweat glands could not be confirmed. Pinkus (11) defines the basal cell epithelioma as "an aggressive tumor derived from any part of the equi-potential ectoderm of the skin in combination with organized mesodermal stroma."

A number of previous studies have attempted to determine the origin of the basal cell epithelioma by a study of routine pathological sections of clinically obvious lesions. Such attempts, however, are hazardous. By the time a tumor is large enough to be easily recognized, it is usually too far advanced to permit a positive statement as to its anatomical origin. Because the basal cell tumor tends to fuse with any epithelial structure it contacts in its advance, contact with does not necessarily imply origin from such a structure. An opinion as to origin can be safely ventured only when the lesion is a few millimeters or less in size, and preferably in areas such as the trunk or extremities where the hair follicles are relatively far (2.5–4.0 mm.) apart, so that an interfollicular origin, if such does exist, could be established. To be free of connection to sweat ducts the focus would have to be at least less than one mm. in size since over the surface of the body the sweat glands have a distribution of 120–620 per square centimeter, depending on the location (12).

The present report describes the findings in five cases of multiple superficial basal cell epitheliomatosis having lesions less than 2 mm. in size, as well as larger growths. One of the cases also had typical destructive rodent ulcers. I believe that some of the basal cell proliferations presently described are smaller than any previously reported.

METHODS

Tissues were fixed in buffered formalin and paraffin sections were cut at 10 microns. Sections were stained with hematoxylin and eosin, periodic acid-Schiff, toluidine blue, and orcein-Giemsa. Each specimen was studied completely by means of vertical serial sections.

Tri-Dimensional Models

Many of the basal cell growths described in this report were studied by making tracings of serial sections with the Camera Lucida. This device consists of a prism situated over the eyepiece of the microscope and an attached mirror which reflects the image of the section downward onto the table next to the microscope. The sections may then be traced onto white paper or a card placed at the point where the image is reflected onto the table. If such tracings are not made, it becomes very difficult to be certain where one proliferation begins and another ends. From these tracings the tumors can be reconstructed as tri-dimensional models. The Camera Lucida drawings are transferred by tracing over carbon paper onto a firm white cardboard-like material called "process board" (obtainable at art supply stores). The process board used was approximately 1 mm. thick, which was the approximate thickness required to make the models proportionate in three dimensions. The process board tracings were cut out with a razor-blade cutting device, glued to-

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gether, and painted in contrasting colors. It is in the construction of such models that the intricacy of even the smallest growth can be appreciated.

Case 1

A 42-year-old brunette white woman first noted the appearance of small dark papules on the chest and back in 1957. These have progressed in number and size since onset.

The patient is a registered nurse. She was suspected of having pulmonary tuberculosis in 1938, but a positive diagnosis was not made. Nevertheless, she began to sun bathe vigorously in the succeeding summers, at least two hours daily three times a week. The patient tans darkly without much burning. In 1941 pulmonary hemorrhages led to a positive diagnosis of tuberculosis with a cavity in the right apex. She was hospitalized from 1941–43 and received no light therapy. From 1944–47 she resumed sun bathing several times a week during the summer, and since then about once weekly. Because of follow-up visits and pneumothorax treatments, the patient had chest x-rays about three or four times a year from 1938–48 for a total of about 34. Since then, she has had yearly chest x-rays. She had complete gastro-intestinal x-rays in 1953 and 1957, and a course of 12 superficial x-ray treatments to the face for acne in 1951. She consulted a dermatologist in 1959 for the lesions on her trunk. Several of these were excised and proved to be small basal cell epitheliomas. About ten were destroyed by electrodesiccation.

The patient was first seen by me in January 1961. She was of large stature, having brown eyes and a medium brunette complexion. Particularly on the right lateral chest wall, the region about the right axilla, inner aspect of the right arm, and back were numerous tiny and medium sized pigmented papules ranging in size from less than a millimeter to 4 mm. There were also two superficial plaques about 1 cm. in size with a thin elevated border on the back. Also present on the back were about six large comedos. A total of about 30 lesions were counted. The skin was otherwise normal in appearance. There was no evidence of x-ray dermatitis.

The fortunate circumstance of this patient was the pigmented character of the lesions. As a result, barely visible pigmented spots, less than a millimeter in size, were found and excised. A total of 12 specimens were obtained. These included a 1 cm. superficial plaque, three papules 3–4 mm. in size, and nine lesions 2 mm. in size or less of which five were smaller than 1 mm. All the excised papules and plaque were surrounded by normal appearing skin, and proved to be basal cell epitheliomas.

A study of vertical serial sections of these lesions followed from beginning to end revealed that the basal cell growths originated from the epidermis, the upper part of the outer root sheath of the follicles, and from dilated follicular openings. A detailed description follows.

1) Epidermal Origins

The epidermis was the most frequent source of basal cell proliferations. Individual nests as small as 175 x 165 microns (Figs. 1, 2) and larger lesions up to 1.5 mm. (Figs. 3, 4) were found free of connection to hair follicles. Lesions less than 500 μ in size were usually free of connection to sweat ducts as well as to hair follicles.

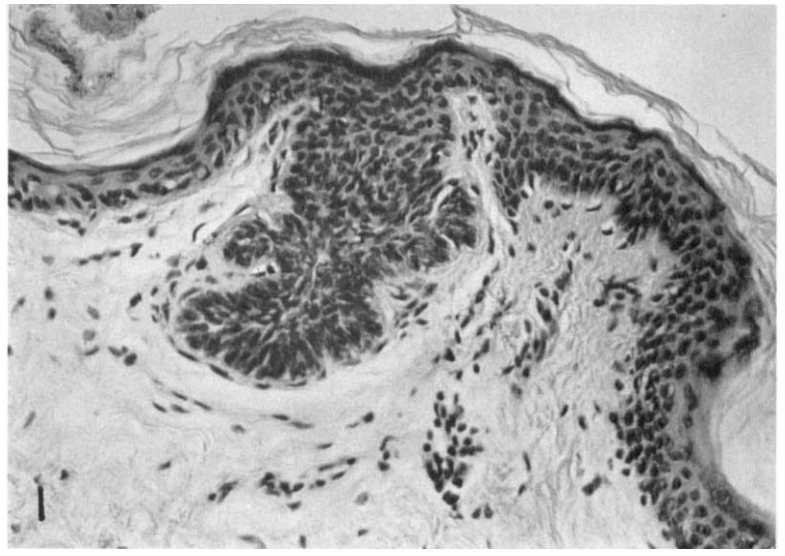


FIG. 1. Small basal cell tumor arising from epidermis. This was unconnected to either hair follicle or sweat gland. Size: 175 x 130μ, and 165μ deep (into the corium). H & E, × 225.

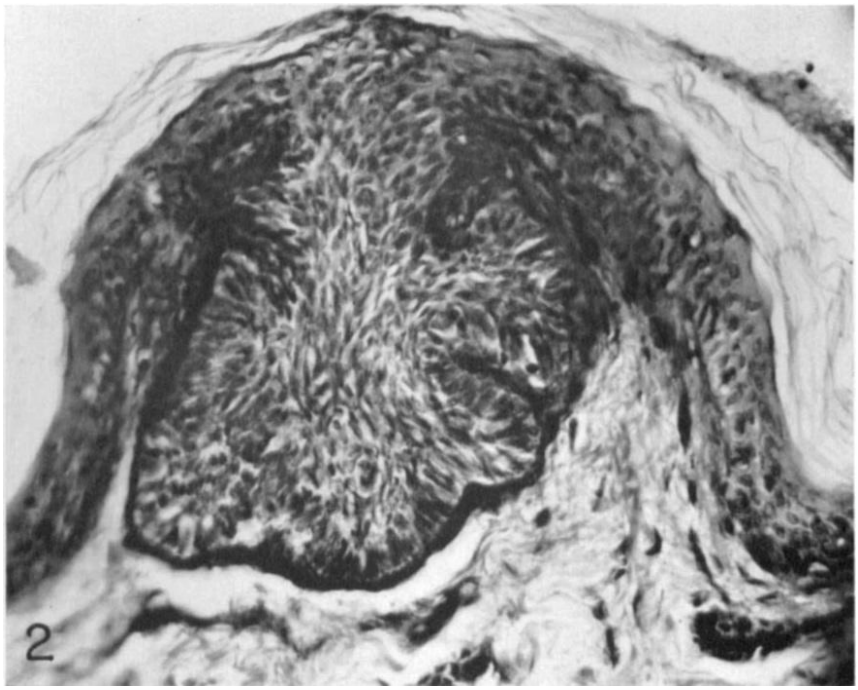


FIG. 2. Epidermal basal cell nest, unconnected to follicle or sweat gland. Size: 240 x 200μ, and 200μ deep. Note thick basement membrane. PAS, × 280.

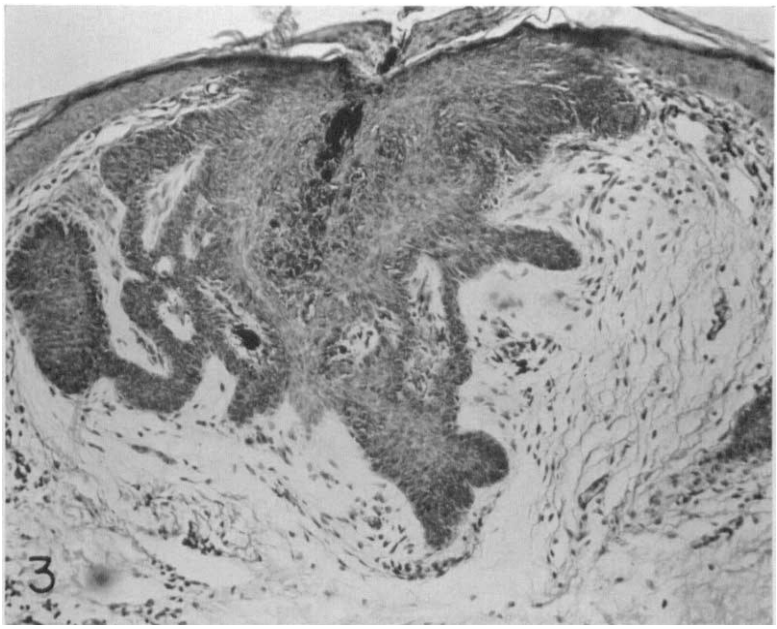


FIG. 3. Epidermal nest (600 x 450μ) containing melanin. Note young connective tissue stroma around the lesion. H & E, × 135.

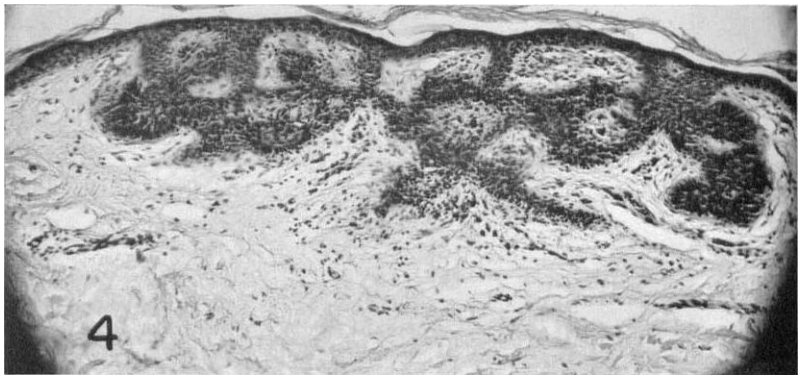


FIG. 4. Epidermal lesion, 1.5 x 0.9 mm. There is a continuous interconnection of the strands and cords comprising this lesion. H & E, × 90.

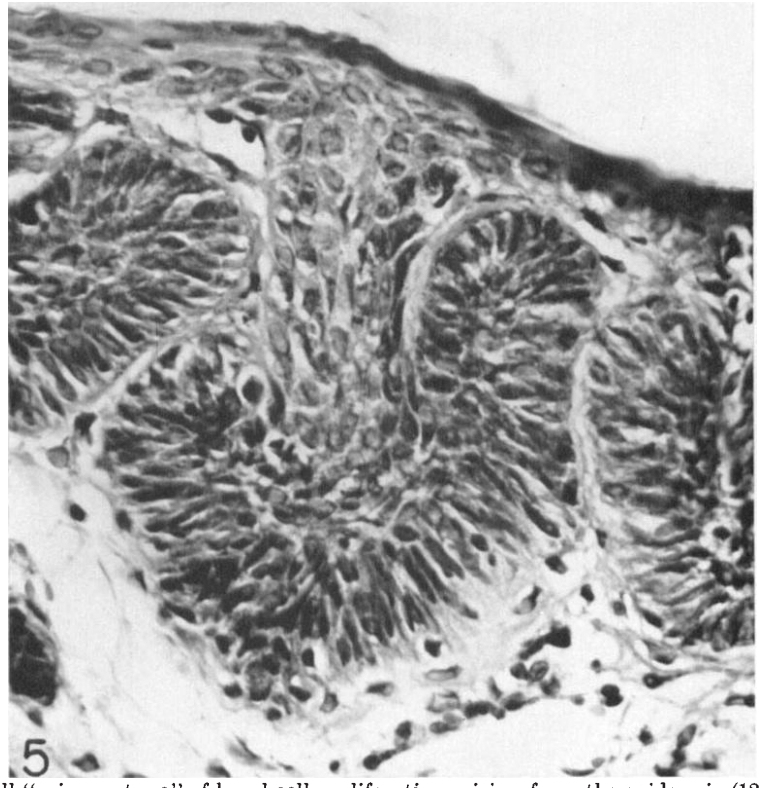


FIG. 5. Small "primary type" of basal cell proliferation arising from the epidermis (120 x 100μ). This is a higher power of Fig. 8. H & E, × 465.

The configuration of what appears to be the primary form of the basal cell proliferation is an inverted tree or mushroom like figure consisting of a short stalk which abruptly blossoms out into a broadened free end in which the tumor cells have their long axes directed toward the center of the nest forming the typical palisade pattern (Fig. 5). The cells in the stalk have their long axes directed perpendicularly to the overlying epidermis. The tumor cells appear to arise from the lower portion of the epidermis but examination of even the earliest lesions does not permit a statement as to whether they come strictly from the basal layer, the lower portion of the prickle cell layer or both.

Characteristically even the smallest nests are

surrounded by an edematous zone so that artefactual clefts outside of the tumor mass are usually present (Figs. 1, 2, 3). In slightly larger lesions fusiform pale staining cells, most likely fibroblasts, could be found in the edematous area (Fig. 3). This undoubtedly is the first stage of the fibrous tissue reaction around basal cell tumors which is characteristic of older lesions (11). Periodic acid-Schiff stains reveal a strong condensation of positive material, diastase resistant, immediately surrounding the nests (Fig. 2). This PAS zone is broader and more intense than that underlying the epidermis.

Melanin was found in very small, 175 μ sized, as well as in larger lesions. In small lesions melanin granules appeared to be primarily in

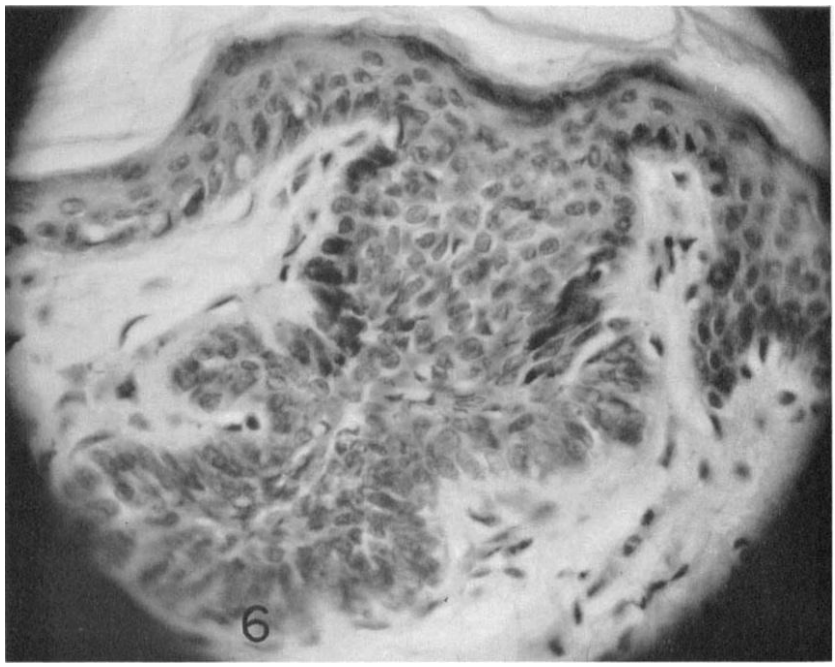


FIG. 6. Filtered higher power of lesion shown in Fig. 1 to show melanin within tumor cells at base of the lesion. H & E, × 400.

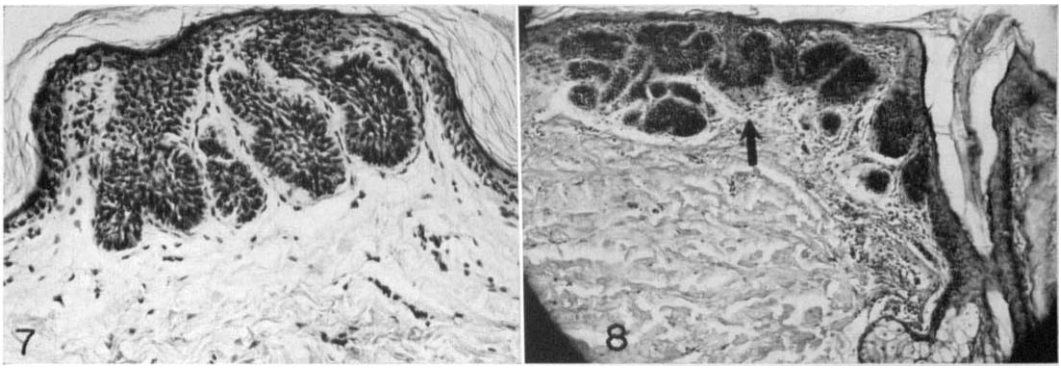


FIG. 7. Epidermal nest measuring 360 x 300μ. This consisted of two branching units which did not fuse. H & E, × 180.

FIG. 8. Basal cell proliferations arising from epidermis and neck of the follicle in 0.9 x 0.7 mm. lesion. Several of the projections from the epidermis maintained their independence throughout the sections. Arrow points to proliferation shown at higher magnification in Fig. 5. H & E, × 90.

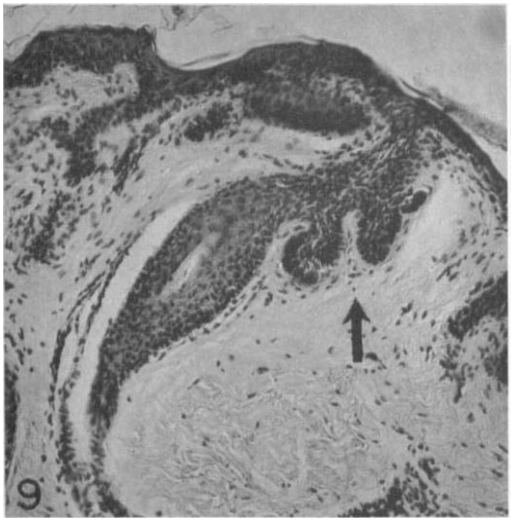
tumor cells in the outer rim of the stalk projecting from the epidermis (Fig. 6). These tumor cells seemed to be a direct continuation of basal layer cells also containing melanin. An occasional melanocyte of the Masson clear cell type was found at the periphery of the stalk. PAS stains revealed that the melanin-containing cells were within, rather than outside of, the PAS positive membrane around the stalk. The melanin tended to thin out in the expanded lower portion of the tumor. In larger lesions, however, large clumps of melanin could be found within the tumor mass (Fig. 3).

Two lesions, 175 x 165 μ, and 200 x 240 μ, presented a simple unbranched structure arising from the epidermis (Figs. 1, 2). A somewhat larger lesion, 360 x 300 μ, consisted of two branching units arising from separate points in the epidermis. These two units maintained their independence throughout the sections (Fig. 7). Lesions 0.5 mm. and larger, with one exception, presented the picture of a continuous network of strands of tumor cells. The structures suggested a fusion of projections arising from various points in the epidermis, but inasmuch as there was a continuous interconnection of the tumor cords in the dermis, the picture may have represented multiple points of secondary fusion with the epidermis. Therefore, a single point of origin from the epidermis could not be ruled out (Fig. 4). However, in one papule, 0.9 x 0.7 mm., having multiple points of origin from both the neck of the follicle and the adjacent epidermis, it was possible to identify independent proliferations within the larger structure arising from the epidermis (Fig. 8).

2) Follicular Origins

Independent origins from the outer root sheath of the hair follicles were also found, though not as commonly as from the epidermis. These were found only from the neck of the follicle, *i.e.*, from that portion of the follicle between the opening of the sebaceous duct and the epidermis (Figs. 8, 9). The basal layer of the upper outer root sheath is, of course, continuous with that of the epidermis. One should, however, point out that in Pinkus' opinion the follicular ostium should be regarded as an integral part of the hair follicle forming an intraepidermal infundibular unit similar to the intraepidermal portion of the sweat duct (13).

Inasmuch as the distance from the opening of the sebaceous gland to the base of the epidermis is usually less than 500 μ for the "sebaceous" type of follicle on the trunk, the basal cell focus would have to be less than 500 μ to be clearly recognized as an independent unit before fusing with the epidermis. A moderate number of such foci were found, but it is possible that a larger number actually arose from the follicular neck



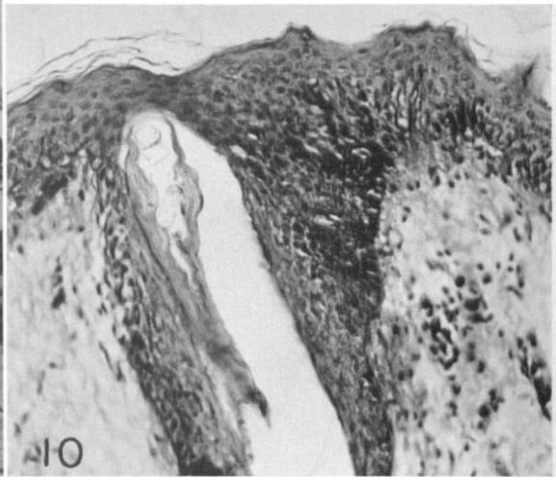


FIG. 9. Basal cell proliferations arising from neck of the hair follicle. H & E, × 135.
FIG. 10. Basal cell growth from region of junction of epidermis and outer root sheath (90 x 80μ, and 180μ deep). PAS, × 225.

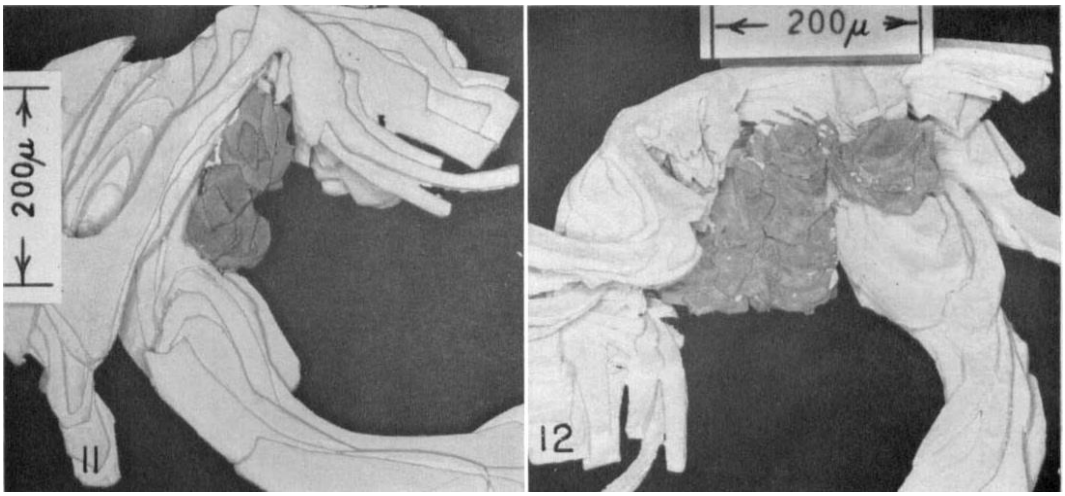


FIG. 11. Tri-dimensional model of follicular proliferation shown in Fig. 9. The basal cell tumor is dark gray.

FIG. 12. Reverse side of model shown in Fig. 11

but could not be so identified because of early fusion with the epidermis.

In some instances, even though the growth was only 100–200 μ, a connection to both epidermis and outer root sheath was maintained in all sections so that it was impossible to be certain of a separate origin from either structure. A number of foci were also found at the point of junction of the outer root sheath and the epidermis (Fig. 10). No foci were found below the sebaceous gland opening.

A tri-dimensional model of the proliferation from the follicular neck shown in Fig. 9 is presented in Figs. 11 and 12.

3) Plugged Follicular Openings

Small proliferations from the walls of dilated follicular openings were found (Fig. 13). This patient also had a moderate number of large dilated pores on the back. One of these was excised and in addition to irregular acanthosis, a tongue-like proliferation of basal cells at one point was found.

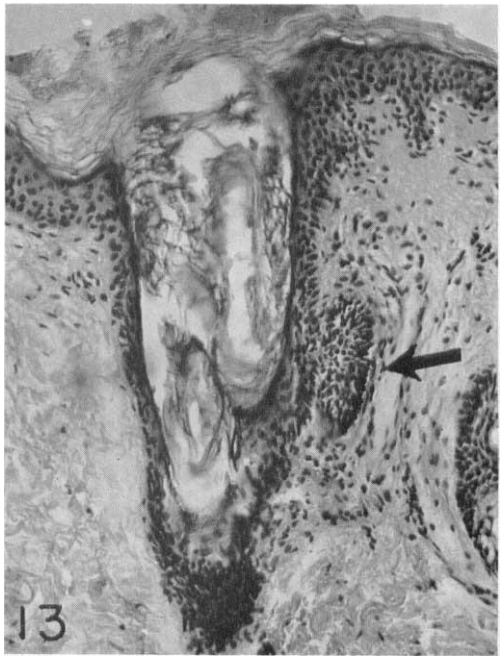


FIG. 13. Basal cell proliferation (arrow) from wall of dilated follicular opening. H&E, × 135.

4) Relation to Sweat Ducts

Eight epidermal basal cell foci 200 to 600 μ in size were found free of connections to the epidermal or dermal portions of the sweat duct (Figs. 1, 2, 7). Lesions larger than 1 mm. were often traversed by the sweat duct but showed no positive indication of arising from this structure.

5) Multiple Foci

Multiple independent basal cell growths in close proximity to each other were often found in the same skin specimen, which was usually about 1 cm. in diameter. In specimen A from the right

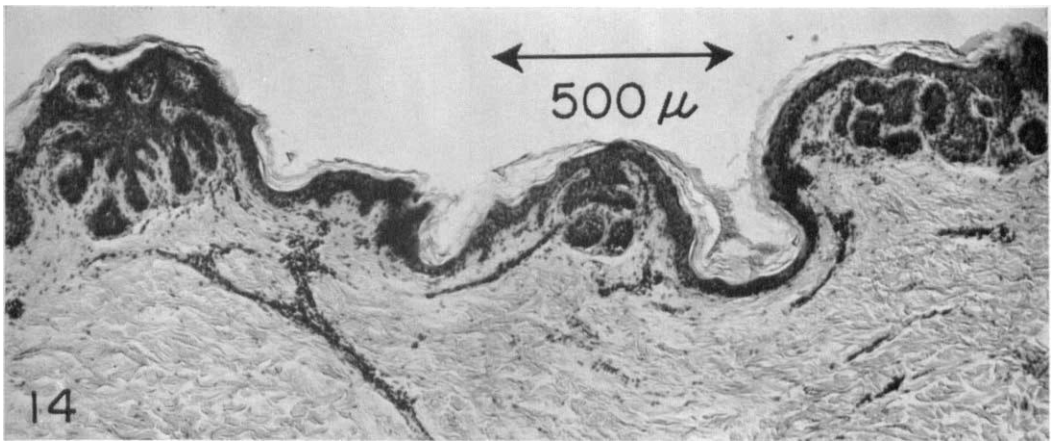


FIG. 14. Three independent epidermal basal cell foci in same section. The intervening and surrounding skin is normal. H & E, × 75.

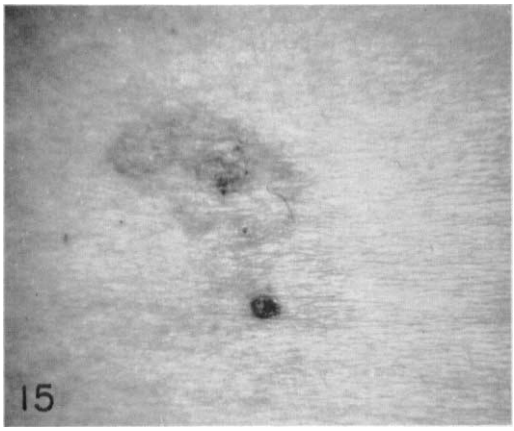


FIG. 15. One cm. sized superficial plaque and 2 mm. pigmented basal cell papule (Case 1).

lateral chest wall near the axilla there was a profusion of small independent growths. At least ten unconnected proliferations ranging in size from 90 x 180 μ to a 0.5 mm. lesion were found (Fig. 14). The borders of some of these lesions were as little as 370 μ apart. In this specimen there was no inflammation, fibrosis or epidermal atrophy. The rete ridges between and around the growths were normal. This specimen contained growths arising from the epidermis, follicular necks, and plugged follicular openings.

Other specimens also contained multiple independent growths though not in such profusion as in specimen A. Of the 12 surgical specimens obtained, seven contained more than one focus. In specimen C, two nests 0.8 and 0.6 mm. in size and 1.5 mm. apart were found. The intervening and surrounding skin was normal.

6) Larger Lesions

That the small basal cell growths found in this patient may eventuate into typical lesions of the superficial basal cell epithelioma is demonstrated by study of the larger lesions from her back. She had three 3–4 mm. sized papules, and two superficial plaques about 1 cm. in diameter having a slightly atrophic center and thread-like elevated border (Fig. 15). Sections through the plaque showed the typical structure of the superficial basal cell epithelioma (Fig. 16).

Case 2.

A 34 year white male had a history of multiple skin cancers appearing since the age of 24. The first lesion, noted in 1952, was a nodule near the right ear. Since that time numerous lesions have appeared on practically all parts of the body, particularly on the head, neck, back and legs. He denied a history of sun bathing, but was outdoors much of the time as a driver for the Air Force from 1951–60. While in the service a diagnosis of basal cell carcinoma was made and many lesions were surgically removed or destroyed by x-ray or electro-desiccation. These included lesions on the upper lip, lower eyelid, and nose. He was also hospitalized and treated at the National Institutes of Health in 1959 and 1961.

The patient is a fair, red-haired, blue-eyed, hirsute, white male of average build presenting numerous papules, nodules, and plaques on most regions of the body excepting the bathing trunk area, dorsa of the hands and forearms, palms and soles. An ulcerated nodule, 1.5 cm. in size, was located below the left inner canthus. Three nod-

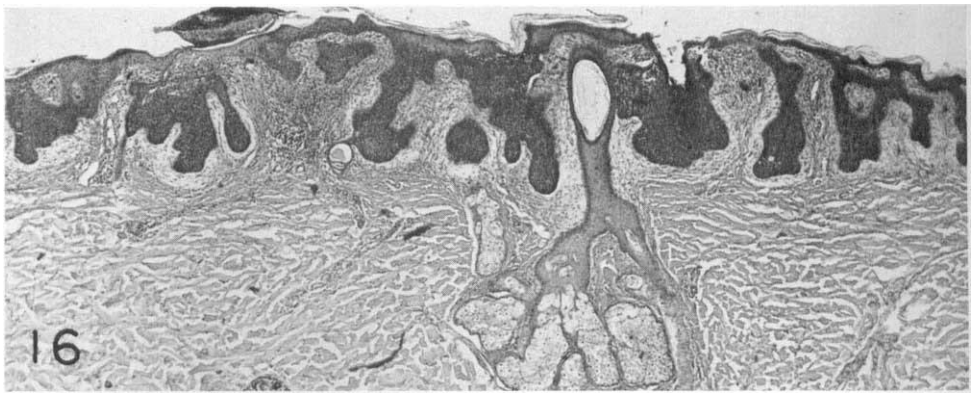


FIG. 16. Section through plaque shown in Fig. 15. An inflammatory infiltrate, mostly lymphocytic, is present. H & E, × 30.

ules, one ulcerated, about 1.5 cm., were found on the neck, and a smaller nodule on the forehead. The distal portion of the nose was involved with superficial ulceration developing in scar tissue. Numerous small and medium sized papules were scattered on the scalp, ears, trunk and extremities. They were particularly numerous on the legs (Fig. 17). About 10 superficial, scaly plaques, 1 to 1.5 cm. in diameter, were present on the trunk and extremities.

He was hospitalized in November, 1962. The ulcerated nodule below the left eye was excised and grafted. The 3 nodules on the neck and one on the forehead were excised. Biopsy reports of these lesions were those of basal cell carcinoma.

Five papules on the lower legs 1 to 3 mm. in size visibly free of connection to hair follicles were excised with about a one cm. margin of normal skin. Study of serial sections revealed 2 of these papules, 2.3 and 1.2 mm. in size, to be free of follicular connection whereas the other 3 were connected to follicles.

Of the 5 approximately one cm. sized specimens, 4 contained a total of 10 smaller independent basal cell proliferations ranging from 120 to 700 μ in size, in addition to the larger papules. In specimen (1) the second focus continued beyond the edge of the specimen. Specimen (2) contained no other foci. Specimen (3) contained a 400 μ and a 280 μ basal cell focus in addition to the 2 mm. papule. Specimen (4) had 4 independent foci ranging from 175 to 700 μ plus the 2 mm. papule (Figs. 18, 19). Specimen (5) contained a one mm. papule and 3 separate basal cell foci 120, 190 and 260 μ separated by 1.0 and 1.1 mm. In all instances these 10 small foci were separated by normal skin and were free of follicular connections. The closest distance between 2 foci was 610 μ.

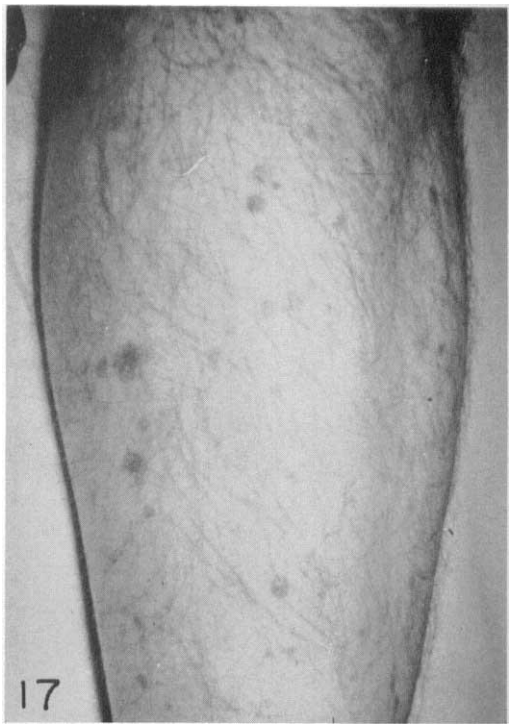


FIG. 17. Small basal cell papules and plaques on leg (Case 2).

All foci were studied for possible connection with the sweat ducts. Nine basal cell foci, 175 to 600 μ in size, were found free of connection to the intra-epidermal or dermal portions of the eccrine sweat ducts as well as hair follicles (Fig. 18).

Case 3.

A 40 year white male had a history of progressive appearance of superficial plaques since age 21.

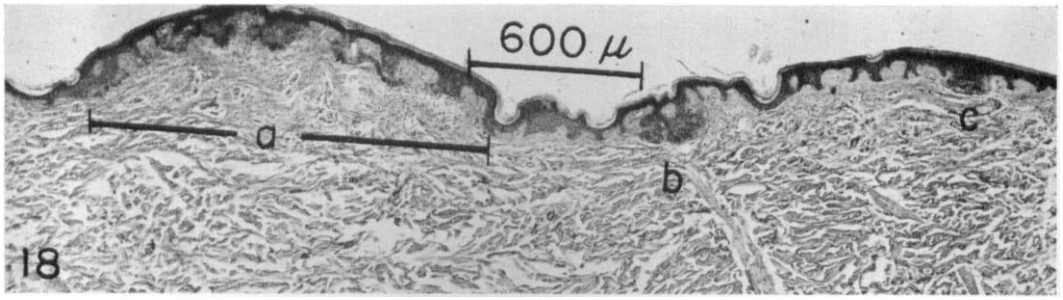


FIG. 18. Section of basal cell papule (a) and adjacent grossly normal looking skin which contained other microscopic basal cell foci (b) and (c). Papule (a), 2 mm. in size, was free of follicular connection. Foci (b), 440 x 280μ, and (c), 175 x 120μ, were also unconnected to sweat glands. H & E, × 45.

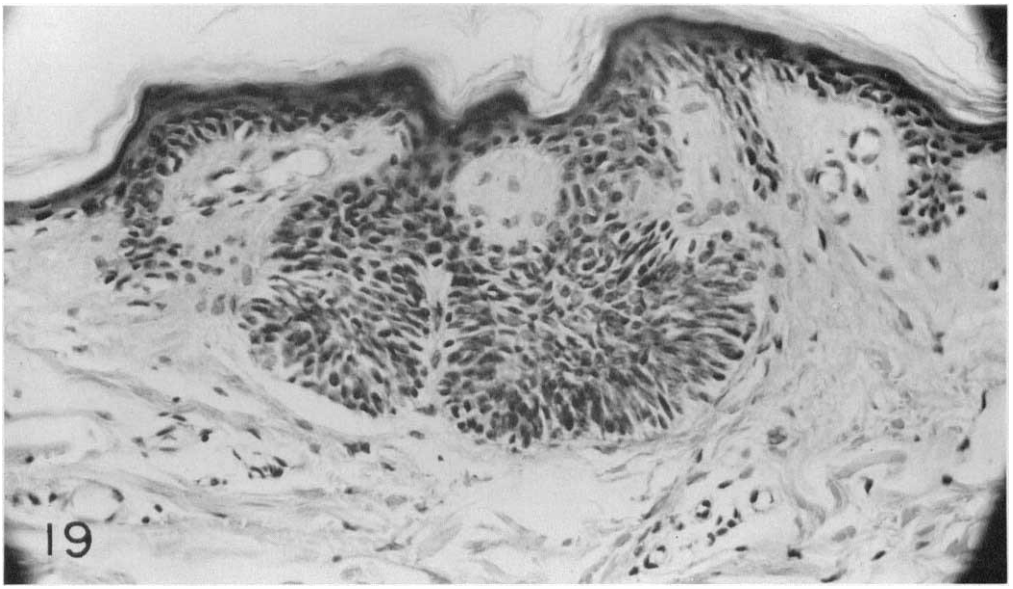


FIG. 19. Higher power of focus (b) in Fig. 18. H & E, × 280.

The first lesion was noted on the upper abdomen in 1943. Since then other plaques gradually appeared on the neck, trunk, and extremities. He was treated in 1943 for venereal disease with injections for two weeks but was vague as to details. Subsequent serologic and spinal fluid exams have been negative. His condition was not diagnosed as skin cancer until 1958 at which time two lesions on the trunk were treated with x-ray. There was no history of arsenic ingestion.

The patient is a fair-complexioned white male of average build, with blue eyes and reddish-brown hair. He denied excessive exposure to sunlight and tans moderately. Examination revealed about 20 sharply defined superficial plaques from 1 to 5 cm. in size on the neck, chest, abdomen, back and extremities including the forearms. These were usually scaly or slightly crusted with a thin elevated border. Some showed slight central depression. Papular lesions, 2–5 mm. in size, were scattered on the body and were numerous on the legs. In addition, discrete keratotic papules were found on the palms and soles. Patches of seborrheic dermatitis involved the scalp and sternum. X-rays revealed no jaw bone cysts or bifid ribs as have been found in basal cell nevi.

Biopsy specimens were taken from 10 of the superficial plaques which were later destroyed by curettage and desiccation. Two of these showed the picture of Bowen's disease. The others were typical superficial basal cell epitheliomas. Biopsy of a keratotic papule from the sole showed only acanthosis and hyperkeratosis without precancerous changes.

Three papules on the legs, 1 to 3 mm. in size, grossly free of connection to hair follicles were excised. Serial section of two of these papules revealed basal cell growths, 1.6 and 1.1 mm. in size, which were not connected to follicles (Fig. 20). The third papule, showed only acanthosis and hyperkeratosis without basal cell proliferation.

Case 4.

A moderately obese 61-year-old white woman with fair complexion, blue eyes and blond hair, sustains burns, but never tans, on exposure to the sun. From about 1955 on she began to sun bathe intensively. In 1957 small papules appeared on the neck and scalp. A diagnosis of cutaneous malignancy was apparently made, and several of the lesions were destroyed. In 1958 more papules appeared on the neck, shoulders, back and arms. She was treated for "psoriasis" with ultraviolet light to the chest and back in 1960. In early 1961 she was seen by a dermatologist who made a clinical diagnosis of superficial epitheliomatosis. At this time there were about 40 papules and small superficial plaques on the scalp, neck, shoulders, upper back, breasts, legs and dorsum of the left hand. A biopsy specimen of a shoulder lesion revealed a superficial basal cell epithelioma. Many of the lesions were then destroyed by electrodesiccation. There was no evidence of psoriasis.

She was first seen in 1961. Five skin specimens, about 1 cm. in size, were surgically removed from the posterior shoulders and upper back. Scarred areas were avoided. Two of the specimens contained a 4 and a 5 mm. papule which showed the typical structure of basal cell epitheliomas. The other three were clinically "normal" skin. Two specimens showed no basal cell growths. The fifth specimen (E) contained four separate basal cell growths measuring 1.8 x 1.0 mm., 0.9 x 0.6 mm., 0.6 x 0.4 mm., and 0.2 x 0.15 mm. The two smallest foci in (E) arose from the epidermis and showed no connection to hair follicles (Fig. 21). The smallest focus was also unconnected to a sweat duct. The two larger growths showed apparent origin from both the epidermis and upper outer root sheaths. However, because in the larger growths there was a confluence of the nests, it was difficult to be certain of precise origins. In this specimen there was a moderate degree of inflammatory infiltrate, mostly lymphocytic. While there was some spotty flattening of the rete ridges in the areas of inflammation, they were otherwise well preserved. There was no fibrosis or epidermal atrophy. Clinically, there was nothing to suggest a superficial plaque or pre-existing lesion. It can be seen in Fig. 21 that the rete ridges between the epidermal nests are normal.

Case 5.

A 49-year-old white male had been developing multiple basal cell epitheliomas since 1943. The first lesion appeared on the left lower eyelid. Numerous others subsequently appeared on the trunk, arms and legs. From 1956–61, 15 such lesions primarily on the back and arms were removed either surgically or destroyed by electrodesiccation. He is of fair complexion and sustains burns, never tans, on exposure to sunlight.

He was first seen in March 1960. Four biopsy specimens, each approximately 1 cm. in size, were taken from the upper back in the general area where epitheliomas had developed. Treated areas were avoided. Three of the specimens contained no epitheliomas. The fourth contained a papule

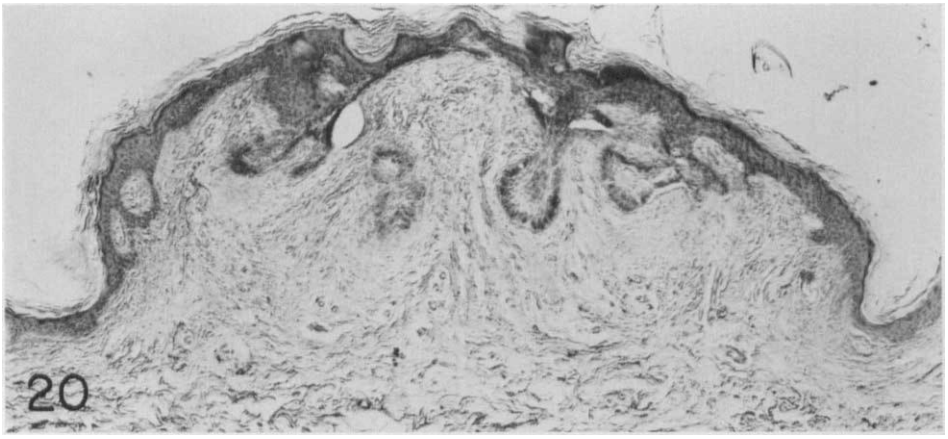


FIG. 20. Section through 2 mm. basal cell papule on leg (Case 3). This was free of follicular connection. Note abundant connective tissue stroma. H & E, × 75.

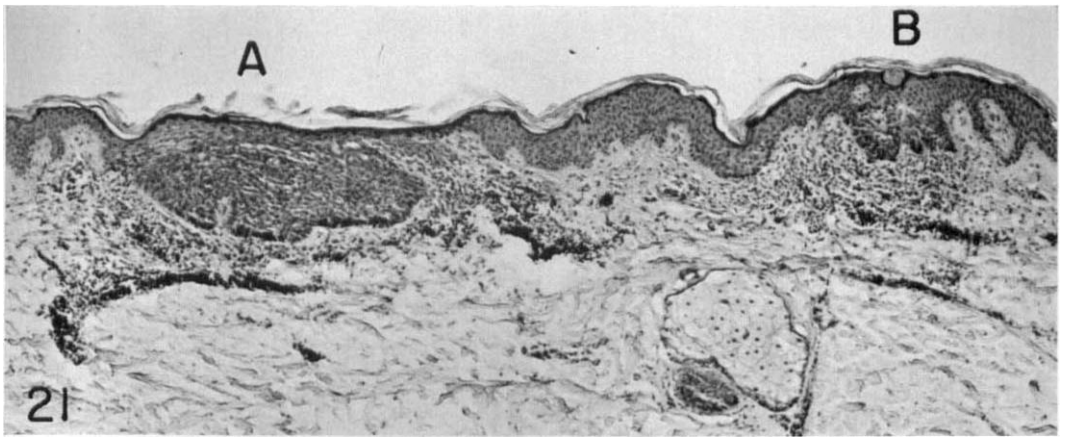


FIG. 21. Case 4. Section through apparently normal skin. Two basal cell foci are separated by normal epidermis. There is an inflammatory infiltrate, but no fibrosis or atrophy. Focus A is 600 x 400μ, B is 200 x 150μ in size. H & E, × 75.

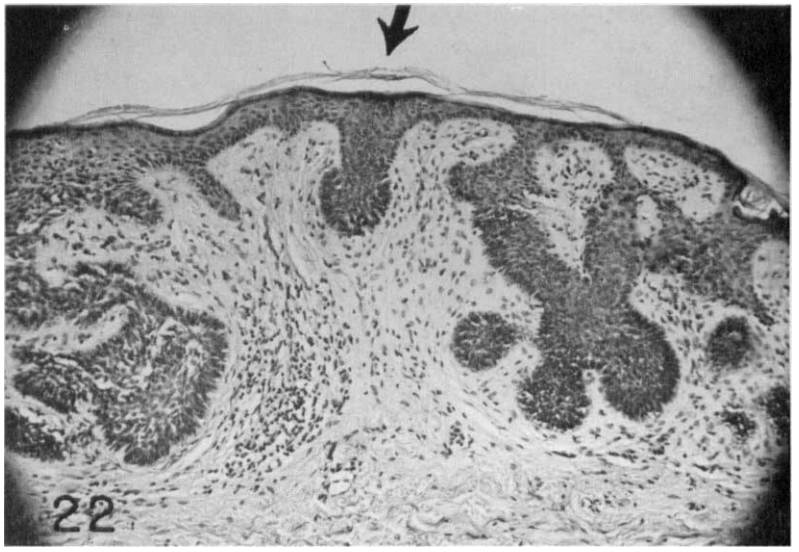


FIG. 22. Case 5. Section through a 1.5 mm. papule. Arrow points to a small "primary type" basal cell proliferation which did not connect to the rest of the lesion (100 x 130μ). H & E, × 90.

about 1.5 mm. in size which proved to be a basal cell tumor.

Serial sections of this lesion revealed a basal cell growth 1.5 x 1.3 mm. having multiple points of origin from the epidermis. While the epithelial nests tended to fuse, at least two small epidermal proliferations within the lesion could be traced from beginning to end without showing connection to the rest of the tumor (Fig. 22). One portion of the tumor was connected to the outer root sheath of a vellus follicle but appeared to arise from the epidermis rather than from the follicle. As in Case 1, the smallest projections from the epidermis produced an inverted mushroom-like figure.

DISCUSSION

1) Epidermal Origins of the Basal Cell Epithelioma.

In the preceding review of the literature, work of others supporting an epidermal non-follicular origin of this tumor has been cited. Additional

supporting evidence for this concept are: 1) case reports of basal cell epitheliomas arising from the palm and soles (14, 15), although some cases so reported were apparently eccrine poromas (16); 2) Madsen, in his painstaking studies, found two incipient basal cell epitheliomas 0.5 and 1.5 mm. in size unconnected to either hair follicles or sweat ducts (17, 18); 3) in Jablonska's report (19) of a 35-year-old woman having numerous widespread basal cell papules, a group of such papules was found between the great and second toes where no hair follicles or sebaceous glands exist. The sections showed the typical structure of a basal cell epithelioma; 4) Pinkus (20) has recently studied the biopsy specimen from the dorsum of the distal phalanx of the fifth finger of a 48-year-old woman who had received much x-ray therapy for hand eczema. The pathology was that of a basal cell epithelioma. The dorsal distal phalanx has no hair follicles or sebaceous glands.

2) The Outer Root Sheath.

Although Foot (6) subscribed to the primitive germ cell theory, he, nevertheless, emphasized the follicular neck as a source of basal cell proliferations. Montgomery (8), Teloh and Wheelock (10) also believed they found origins from the upper outer root sheath.

3) The Sebaceous Glands.

In this study, no origins were found from the sebaceous glands. However, it is likely that basal cell epitheliomas arise from the germinative layer of the sebaceous glands as well as from that of the epidermis. Sebaceous glands were found to be a frequent source of experimentally produced basal cell epitheliomas in the rat (21).

4) The Sweat Glands.

Little evidence for a sweat gland origin of the basal cell tumor has been presented by previous investigators. In cases 1, 2 and 4 of this report basal cell foci, usually less than 500 μ, were found free of connection to sweat glands. It might also be mentioned that basal cell tumors are produced by carcinogens in abundance on the hairy surface of the rat which has eccrine sweat glands only on the digital paws (21).

5) Multicentricity.

In his studies of the origins of the basal cell epithelioma, Madsen (17, 18) has argued against a multicentric origin of such tumors. He pointed out that in its early stages the tumor destroys the rete ridges. It then enlarges by centrifugal spread and as it does, there is patchy death of tumor cells in the central portion and these are replaced by fibrous tissue. Hence, study of an older plaque shows central atrophy of the epidermis with destruction of the rete ridges, fibrosis, an inflammatory infiltrate, primarily lymphocytic, and scattered basal cell nests within the atrophic area. These changes can readily be seen by studying the cross section of an older superficial plaque. It is likely, as Madsen contends, that the basal cell nests in the central portions of the plaque represent remnants of the original tumor, which has extended peripherally, rather than new independent proliferations.

Nevertheless, in the material studied for this report the evidence points to the probability that a basal cell tumor may originate from multiple closely placed foci which fuse to form a larger structure.

As previously described, in Cases 1, 2, and 4 multiple small foci were found in close proximity to each other. These were separated by normal skin and were as little as 370 μ apart. It would seem then just a question of time before the closely placed nests would enlarge and fuse to form a larger structure. The lesion thus formed could then enlarge centrifugally in the manner described by Madsen, and might also engulf other nearby foci in the process of spreading. This, of course, does not exclude the possibility that any given tumor may arise from the division of one malignant cell. But it does point to the likelihood that a field effect is produced by the carcinogenic effect of ultraviolet light or other factors leading to the development of multiple basal cell foci within a small area.

It was also somewhat surprising to find that even within individual lesions, separate points of origin could occasionally be demonstrated. These were found, as previously described, in a 0.3 and a 0.9 mm. papule in Case 1, and in a 1.5 mm. papule in Case 5. In other lesions in Case 1 larger than 0.3 mm., the structure suggested origins from closely set points, but since there was complete fusion of the projections, individual components could not be isolated.

6) Superficial and Deep Epitheliomas.

While over 90 per cent of basal cell epitheliomas occur on the face (22), it would be extremely diffi-

cult to be certain of the histologic origin of tumors taken from this region because of the closeness of the hair follicles (less than 1 mm. apart). On the trunk and extremities where the follicles are farther (2–4 mm.) apart, an independent epidermal origin, if such did exist, could be established.

The question might then arise as to whether conclusions drawn from the superficial growths on the trunk and extremities are applicable to the deeper, destructive basal cell carcinomas. Willis (9) expressed the opinion that there is no real histogenetic difference between the superficial and deeper forms of the basal cell tumor. There is no essential difference between the two types as regards character of the invasive growths, surrounding connective tissue stroma, and inflammatory infiltrate. Case 2 in this report had destructive ulcers on the head and neck as well as superficial plaques and small papules on the trunk and extremities. Nevertheless, some explanation is necessary for the relative lack of invasiveness of the trunk lesions. The following factors may be of importance: 1) continued exposure to the carcinogenic action of ultraviolet light on exposed areas may enhance the malignancy of the tumor, 2) degenerated (basophilic) collagen, more commonly found on the face, may be more easily invaded than normal collagen or may contribute to this invasion, 3) the thicker dermis of the back may act as a mechanical barrier to invasion, 4) inasmuch as hair follicles are a source of these growths, their greater concentration on the face could mean more possible foci and earlier fusion of such foci.

7) Comparison with Basal Cell Epitheliomas in the Rat.

In a previous study (21) the microscopic origins of experimentally produced basal cell epitheliomas in the rat were found to be the epithelium of the follicular openings, the sebaceous glands, and the walls of the follicular canals (outer root sheath). Possibly due to the closeness of the follicles in the rat, a purely interfollicular epidermal origin could not be positively established. Also, the mechanical tendency of the carcinogens to concentrate in the ostia, follicular canals, and sebaceous glands could have been responsible for this localization. In both the rats and humans small basal cell proliferations were found arising from the walls of plugged follicular openings.

8) Do Basal Cell Epitheliomas Arise from the Basal Layer?

Close examination of even the smallest proliferations does not permit a statement as to whether the tumor cells arise from the basal layer, the lower portions of the prickle cell layer or both. This point may be of questionable significance in view of current concepts regarding the biology of the epidermis. It is now generally accepted that the prickle cell, granular cell and keratin flake are progressive stages in the evolution of the basal cell (23). A tumor arising from the epidermis would have to come from cells still capable of mitosis, which are primarily the basal cells and cells in the lower portion of the prickle cell layer (23, 24). Nevertheless, the unanswered question remains as to how two epitheliomas or carcinomas the basal and squamous types, having such marked behavioral differences, can arise from the same structure, the epidermis.

While the basal cell tumor cells resemble cells of the basal layer, they nevertheless show distinct differences from these cells even in routine hematoxylin and eosin sections. The tumor cells stain more deeply with hematoxylin, are more elongated, and the striking palisade arrangement is not present in the normal epidermis. The cells of the basal cell epithelioma are mutant cells having their distinctive morphologic and physiologic properties.

SUMMARY

A study has been made of the microscopic origins of the basal cell epithelioma in 5 patients with multiple superficial lesions, including one with destructive ulcers on the head and neck.

Numerous small basal cell foci were found arising from the epidermis independent of connections to either hair follicles or sweat glands. The upper outer follicular root sheath was also a source of these foci. Independent small basal cell proliferations were found in close proximity to each other. The opinion is expressed that basal cell tumors develop from the fusion of closely set multiple foci.

ADDENDUM

Since this report was submitted, opportunity was afforded to study the histologic orgins of a case of nevoid basal cell epitheliomas (basal cell nevus). A 14 year old white girl, who exhibited lesions at the age of 18 months, was reported at

age 10 as Case No. 3 in the article by Howell and Caro, "The Basal-Cell Nevus" (A.M.A. Arch. Dermat. 79:67–80, 1959). At that time she had innumerable small basal cell papules primarily on the chest and back, with scattered lesions on the face, abdomen and elsewhere. She also had dentigerous cysts of the mandible and maxilla. Since that report her skin lesions have remained relatively stationary but she has continued to develop troublesome jaw bone cysts. Study of a biopsy specimen from the back revealed small epidermal basal cell proliferations free of connection to either hair follicles or sweat glands.

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