Pigmented Precancerous and Cancerous Changes in the Skin

V. R. Khanolkar, M.D.

(From the Tata Memorial Hospital, Bombay, India)

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The changes to be described here concern pigmented Bowen’s disease, squamous-cell carcinoma and basal-cell carcinoma of skin. They do not include the group of melanoma, melano-epithelioma or melano-carcinoma, nor the pigmentation in conditions sometimes leading to cancer, such as, senile keratosis, keratosis resulting from arsenic, tar or radiation and xeroderma pigmentosum. The changes described in this paper have not attracted enough attention of dermatologists, and Eller and Anderson (8) have stated that pigmented basal cell carcinomas were “quite uncommon.” At a recent symposium on “Malignant Melanomata” in Leeds, England (4) the opinion was expressed that, “It was surprising but true, that these (pigmented tumors of epidermal origin) are not recognised by the majority of pathologists, and there is very little in the literature about them. But it is very important that they should be recognised, for the prognosis and treatment in these cases is exactly similar to that of the non-pigmented tumors of the same series and quite different from that of the melanomata. The important point is for the pathologists to recognise that pigment formation is a function of a group of tumors other than the true melanomata”. It has been suggested that many melanotic tumors reported to have been cured by local excision or radiation were probably tumors belonging to this group. It is known that some of these tumors originate from pigmented nevi and without a histological examination are not easily distinguished from true melanomas.

Case No. | Nationality | Age | Sex | Site | Duration | Diagnosis
---|---|---|---|---|---|---
1 | Muslim | 45 | M | Chin | 1 year | Basal sq. cell ca
2 | Parsee | 60 | M | Scalp | 5 years | Basal cell ca
3 | Hindu (Deccani) | 38 | M | Leg | Mole since childhood, recent growth 3 weeks | Basal cell ca
4 | Hindu (Gujarati) | 54 | M | Forehead | 8 years | Basal cell ca
5 | Parsee | 73 | M | Nasolabial fold | 4 years | Basal sq. cell ca
6 | Parsee | 59 | F | Arm | 6 months pigmented mole started bleeding | Basal cell ca
7 | European | 50 | F | Forehead | 2 years | Basal sq. cell ca

REPORT OF CASES

Case 8. #13052.—A 64 year old lean Parsee saw a skin specialist for a fungus infection of his feet and one finger. He also casually referred to an “eruption” on the chest which was diagnosed as a “precancerous condition.” The patient was therefore referred to the Tata Memorial Hospital. On examination a roughly oval skin lesion was seen over the right lower ribs in the nipple line. It had started as a small dark spot several years back and had gradually increased in a circular spreading manner. There was neither pain nor itching but a slight oozing of clear fluid from the surface. The lesion was about 5 cm. in diameter. Its edge was raised, about 1 mm. wide, wavy and dark purple in color. It was clearly demarcated from the adjacent normal skin. The central portion was smooth, glazed and pale pink. A cluster of few raised pigmented spots was seen in the center. A biopsy from the edge showed the characters de-
FIG. 1.—Case 8.: A camera lucida drawing of a section of the entire tissue removed by biopsy. The oval bud in the center is over the spreading edge of the lesion; and the healed atrophic skin is seen towards its right. Masson's trichrome stain. Mag. × 65.

FIG. 2.—Case 8.: Photomicrograph showing a network of fine argentophil fibers formed by the numerous dendritic processes of proliferated melanoblasts in epithelial buds. Silver impregnation. Mag. × 100.

FIG. 3.—Case 9.: Photomicrograph showing cords of proliferating epithelial cells pushing into the dermis. The central bud shows an area of degeneration and necrosis in the middle with a debris of pigment granules and desquamated cells. Hematoxylin and eosin stain. Mag. × 100.

The lesion regressed rapidly and completely with four exposures of 600 r units daily (85 kv; 1 A1; T. S. D. 15 cms. and a total radiation of 2400 r).

Histological examination.—The biopsy piece (Fig. 1) consisted of stratified squamous epithelium clothing a fibrovascular layer of dermis. The epidermis was thinner than the normal for that region and showed towards the middle of the section a small oval bud of proliferated basal cells pushing downwards in the dermis. The peripheral cells were columnar, contained large oval nuclei and a small amount of pale basophilic cytoplasm. These cells were arranged in a palisade. The more loosely arranged central cells were smaller with round or oval nuclei containing sparse granules of chromatin material. There was a minute area of surface ulceration over the epithelial bud. The epidermis of the normal skin showed widely separated short rete cones. The basal layer of cells was darkly pigmented with fine brown particles. In the healed area, towards the center of the lesion, there was a complete obliteration of rete cones and the epithelium was flat and thin. The basal cells were without pigment. In this area the pars papillaris of the dermis showed a loose, irregular texture of collagen fibrils, interspersed with arcades of newly formed blood capillaries and foci of mononuclear cellular exudate. The pilosebaceous structures were distorted and atrophic. The downgrowing bud was lying in a bed of concentrically arranged lax, edematous collagen...
fibrils. Focal accumulations of lymphocytes and histiocytes were lying outside this zone. In sections impregnated with silver the epithelial bud showed the proliferating basal cells interwoven with a large number of melanoblasts connected with a meshwork of fine argentophile fibers (Fig. 2) formed by the numerous dendritic processes of these cells. The elastic tissue net was absent in the superficial zone of the dermis except along the few hair sheaths and ducts of sweat glands. There were few macrophage cells loaded with coarse brown pigment in the dermis. The section gave an impression of healing at the center and a spreading neoplastic edge at the periphery, consisting of proliferated basal cells and melanoblasts. In the healed area the epidermis and the surface zone of the dermis were morphologically altered, but no trace had been left of the neoplastic epidermal cells.

Case 9. #14275. -- A fair complexioned Parsee, 47 years old, had two small pigmented moles on his body “ever since he could remember.” One was situated over the middle of the right clavicle and the other in front of the upper third of the right arm. The latter was slightly raised above the surface, about the size of a lentil (5 mm.) and surrounded by an areola of brownish skin roughly 2.5 cm. broad. About eight years back the mole on the arm began to grow in size and the surface “broke into scab covered black fragments”. Recently the fragments began to itch and weep. He consulted a surgeon who excised the two moles and sent the one from the arm to us for histological investigation.

Microscopic examination showed a picture similar to that of the advancing edge in Case 1, except that there were several separate buds of proliferating basal cells growing deeper down into the dermis. The bigger buds showed a central area of degeneration and necrosis, with a clear space containing a debris of pigment granules and desquamated flakes (Fig. 3). The basal cells tended to flatten as they approached the core. There was no evidence of healing. The melanoblasts appeared to proliferate and migrate away from the periphery of the buds. They were gradually involved in the degenerative process of the cells towards the center. The proliferating buds of epidermal tissue lay in a broad sheath of loosely arranged collagen fibrils. Subject to the superficially ulcerated epithelium, there was a rich cellular exudate of lymphocytes, eosinophiles and histiocytes, between richly sprouting blood capillaries.

Case 10. #E788. -- An olive-complexioned 63 year old Anglo-Indian physician had a small hairless mole on his right forearm lateral to the flexor tendons, about 6 cms. above the wrist for “many, many years.” The color of the mole was uniformly black and it was smooth on the surface. About two months back he noticed that the mole had begun to increase in size and to itch. The physician attributed this to long hours spent every day in filling a multitude of army forms. He remembered that the itching sensation began one night and the next morning there was a slight erythematous area round the mole. The surface became rough and raised with a couple of weeping points exuding a clear pinkish fluid. No scabs were formed. As the mole rapidly doubled its size, the physician consulted a surgeon who excised the mole and gave him a rather gloomy prognosis about his condition. He saw us with his excised tissue.

A naked-eye examination of the tissue showed a superficially ulcerated, small (6 mm.) brown nodule raised about 3 mm. above the surface. On cut section an ovoid, dark brown, firm mass clearly stood out from the dermis. It was darker near its outer edges. The microscopic examination revealed a sharply circumscribed nodule of neoplastic cells (Fig. 4), composed of lobules separated by filamentous processes of fibrovascular connective tissue. The cords and lobes presented the characters of a baso-squamous epithelioma (Fig. 5) with round or oval spaces in the center filled with fine concentrically arranged lamellae of keratinized material. An area of surface ulceration was dipping into dilated follicles, crypts and fissures burrowing into the tumor mass. The tumor cells in the peripheral cords were unevenly laden with dark brownish pigment. The silver preparation (Fig. 6) showed a proliferation of melano-

DESCRIPTION OF FIGURES 4 TO 7

FIG. 4.—Case 10.: A camera lucida drawing of a section of the nodule removed by operation. Faintly stained with hematoxylin. Mag. × 25.

FIG. 5.—Case 10.: Low power photomicrograph of the area marked in Fig. 4 above, showing the characters of a baso-squamous epithelioma. Hematoxylin and eosin stain. Mag. × 150.

FIG. 6.—Case 10.: Low power photomicrograph of a portion of the area marked in Fig. 4 above, showing a proliferation of melanoblasts, with a network composed of their branching protoplasmic processes. Silver impregnation. Mag. × 200.

FIG. 7.—Case 11.: Photograph showing a superficially ulcerated dark nodule on the face.
Figs. 8-10
blasts and their branching twigs creeping between tumor cells, as well as coarse grains of pigment in groups of melanophores in the dermis.

**Case 11. # 5220.**—A medium colored, 40 year old Mahar woman, mother of two children, was admitted for a small circular superficially ulcerating black growth on the face (Fig. 7). She had noticed the growth for nearly two years. It had started as a tiny sore spot, which did not cause any discomfort except that it occasionally irritated her. She accidentally injured it two months back and it began to grow rapidly. On examination, a flat black round nodule about 0.5 cm. in diameter was discovered filling the left nasogonial fold. It was slightly raised above the surface (4 mm.) and was not adherent to the subcutaneous structures. There were a couple of spots of surface ulceration. At its periphery the nodule showed a peculiar smooth, translucent appearance which is often noticed in basal cell tumors of the skin.

**Microscopic examination** of the excised nodule showed a slightly more advanced stage of basal cell carcinoma, dotted with small cystic spaces containing pigment granules and remains of dead tumor cells. The cells inside the tumor cords were elongated and fusiform. Many of them contained a fine dust of brown pigment in their cytoplasm. Golden brownish pigment was also seen in the bodies and branches of the many ramifying cells between the characteristic columnar and fusiform cells. The dendritic cells were easily discernible in unstained sections. There were also groups of melanophores loaded with clumps of pigment in the dermis.

**Comment**

All the tumors belonging to this group were characterized by an insidious onset, and a slow clinical course. Many of them were stated to have originated in a pigmented mole which had been present for a very long time. The tumor had sometimes attracted the attention of the patient after a negligible injury. There was no infiltration of deeper structures nor was there an involvement of regional lymph nodes or distant viscera in any of the cases. There was no preponderance of occurrence in either sex. Their location was not restricted to any particular part of the skin, although the face and particularly the nasogonial fold appeared favorite sites. The histological findings in these tumors presented several characteristics in common, and the differences were mainly quantitative as regards (a) the size of the lesion and its encroachment on the dermis (b) the relative participation of polygonal prickle cells in the cords of basal cell carcinoma and (c) the amount of pigment visible or demonstrable in the tumor mass. In none of these tumors true nevus-cell accumulations (cell nests, theques) were seen in the dermis and there was nothing to suggest an affiliation of these tumors with the group of benign or malignant melanomas. These tumors appeared to be satisfactorily eradicated by adequate excision or contact radiation therapy.

**Multiple Basal-cell Pigmented Tumors**

**Case 12. # 14612.**—A tall, thin, nervous, wheat-coloured, 51-year old Eurasian married woman was admitted for ulcerated black nodules on the skin. When she was about 30 years old a group of "pigmented moles" reappeared on her body. Some of these had begun to spread into black patches during the last 7 to 8 years. She had developed a "boil" above the pubes which burst and formed a red tumor about $\frac{3}{4}$ inches in diameter. It was excised and treated by a surgeon who examined it microscopically and had called it a "rodent ulcer". She was referred for her black patches to a specialist whom she saw after 5 years. The dermatologist found some areas with scabs on the surface. "One old one looked melanotic. This she had for 15 years. The others have been there for 6 years." As he was of opinion that "the appearance of some lesions was like a precancerous condition" and others like that of a "basal cell carcinoma," the patient was referred to the Tata Memorial Hospital. On examination the woman (Figs. 8 and 9) was found to have numerous (over 200) pigmented moles on the neck, the trunk and the thighs. There were no pigmented spots on the face. There were several flat black patches on the trunk which were roughly circular and clearly demarcated from the neighboring healthy skin. The central portions of these patches were superficially ulcerated and were covered with brownish scales of dried secretion. There was also an intensely black nodule on the back, at the waist line.

**DESCRIPTION OF FIGURES 8 TO 10**

Figs. 8 and 9.—Case 12.: Front and back views of the trunk showing numerous pigmented moles, two superficially ulcerated areas, and three intense black nodules on the skin.

Fig. 10.—Case 12.: Low power photomicrograph from a section from the flat patch behind the right thigh, showing superficial ulceration and thin branching cords of tumor cells infiltrating into the dermis. Hematoxylin and eosin stain. Mag. $\times 150$. 

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(2 X 1.5 X 1 cm.) and a flat, superficially ulcerated, slightly pigmented patch on the back of the right thigh (1.5 cm. in diameter). These last two were excised, and a biopsy taken from the edge of the patch on the right loin.

Microscopic examination.—The material obtained after excision was available for study and showed a great variety of structure of basal cell carcinoma type. Curiously enough the flat patch behind the right thigh showed greater anaplasia 15 years, during which time he had developed similar lesions over other parts of the body. The latest of these was about three years old. The ulcer or the lumps did not pain him but he felt an itching sensation over them. On examination a black, firm, flattened mass (3 X 2 X 0.5 cms.) was felt in the skin over the body of the left mandible just in front of its angle. The mass was ovoid, raised above the surface and ulcerated in the center. The surface of the ulcer was covered with dried black scabs. It was freely movable over the subjacent structures. There were three other similar nodules on the trunk. These stood out more prominantly and were less pigmented than the lump on the jaw. They were located over the tip of the left costal cartilage in the right groin and on the left thigh near the attachment of the scrotum. On careful examination, a rhomboid, rough, dry, scaly area on the skin of the left lower abdomen (Fig. 12) was seen that had not attracted the attention of the patient. The area was 4 cm. long at its widest extent and was clearly defined by a black, uneven margin. All these lesions were excised with about 1 cm. of normal skin beyond them and were available for histo-

![Fig. 11.—Case 13.: Photograph showing the pigmented ulcerating nodule on the left lower jaw.](image1)

![Fig. 12.—Case 13.: Photograph showing pigmented nodules in the two groins and the rhomboid dry scaly area in the left hypogastric region.](image2)
logical study. A full-thickness skin graft was placed on the raw area left on the face after the excision of the mass. The patient made an uneventful recovery and has not reported since with any recurrence of his disease.

Microscopic examination.—All the lesions including the dry, scaly area showed the structure of a basal cell carcinoma, with slight variations in type in the different nodules. These lesions afforded excellent material for a study of the proliferative changes in melanoblasts, by dopa reaction and silver impregnation. These changes will be referred to later while considering the nature of pigmentation in these tumors.

Comment

Multiple tumors of this type are very rare in published reports. The cases reported by Nomland (16), Pautrier and Archambaut (17), and by Nisbet (15) probably belong in this category. In view of the discussion following the case reported by Nomland (19), it is necessary to point out that the areas of predilection for epithelioma adenoides cysticum, viz. the lower eyelids, nose and portions of the cheek, were exempt from disease in both the patients described above. Case 13 was a male and there was no evidence of a familial tendency to disease in either case. Further it was found that even though the lesions in both patients were present for a long period the onset of disease was not in early life, nor was an accelerated growth associated with the time of puberty. The similarity between these cases and those reported in the literature consisted in the following features:

1. A clinical resemblance to pigmented nevi without the presence of nevus cells arranged in cell nests (theques), or strands in the dermis.
2. A slow evolution with probable origin in a preexisting pigmented mole. An absence of regional or distant metastases even after many years' existence.
3. Variation in form, color and histological details in different lesions in the same person.

Multiple Squamous Cell Pigmented Tumors

Case 14. # 5608.—A fair-skinned Hindu bania, owner of an electrical appliances shop, was admitted to the hospital on Nov. 16, 1943 with an ulcerated growth at the base of the left palm. He gave the following history about his complaint. A few small dark spots had suddenly appeared at the root of the palm just below the middle of the right wrist 10 years previously. These spots increased slowly in size and had fused to form a firm, dark nodule causing itching and some discomfort. He was treated by his physician with ultraviolet rays which seemed to arrest the growth of the nodule. It started growing again after 2 years. He was treated by “application of radium.” The condition improved under this treatment. The lesion became active again after an interval of two years. He was treated with deep x-rays in 1937 and 1940. He denied having had any medicines containing arsenic. He was unable to supply exact information regarding the dosage of the x-ray and radium therapy. On examination a firm ulcerating growth about 5 cm. in diameter was seen in front of the wrist spreading on to the palm of the hand (Fig. 13). The growth was surrounded by a broad zone of depigmented skin and a darkly pigmented ring outside it. The growth was partly fixed to the tendons of the flexor muscles. There was a black rough patch with uneven fissured surface on the right wrist. This was excised and showed closely packed black papillary proliferations of the skin moulded on thin strands of connective tissue. A similar lighter patch was present on the palmar surface of the right middle finger. Both palms showed numerous minute discrete translucent nodules in the skin. A small node was felt in the left axilla. The physical examination revealed no other abnormality except a number of large and small café au lait spots on the back, chest, abdomen and scalp. The face was free from any blemishes. X-ray examination showed marked decalcification of the bones subjacent to the ulcer but there was no destruction or evidence of involvement of bone structures.

The lesion was treated with deep x-radiation. A total dose of 4000 r units was administered to him during the course of 10 days (85 kv. 1 A1, T. S. D. 15 cm. circular field 6 cm. diameter). The ulcer rapidly healed and the wrist movements improved under treatment. At a follow-up 2 months later it was noticed that he had residual disease and he was given a further total dose of 1500 r units over a period of 1 week (200 kv. 0.5 cu + Al, T. S. D. 50 cms. circular field 5 cms. in diameter). The lesion on the palm became cleaner, but some disease still persisted. One month later the patient appeared with a raised pigmented lesion on the scalp, 2 cm. in diameter which bled easily on touching. This lesion and those on the right hand regressed completely with x-ray therapy, but the lesion on the palm persisted. It was therefore decided to amputate the limb at the middle of the forearm.

The patient returned after six months with a small pigmented papillary lesion on the scrotum and again four months later with similar small lesions on the right thumb and the fingers of the
Fig. 13.—Case 14.: Photograph of the palms showing the malignant lesion on the left hand, the darkly pigmented patches on the right, and the minute translucent whitish nodules in the skin covering the palmar surface of the fingers on both hands.

Fig. 14.—Case 14.: High power photomicrograph from one of the minute discrete nodules showing hyperkeratosis, disorganisation of the normal arrangement and stratification of cells, and individual cell keratinisation. Hematoxylin and eosin stain. Mag. × 200.

Fig. 15.—Case 14.: A higher power photomicrograph of a nodule similar to that shown in Fig. 14 presenting the clumping of nuclei, corps ronds and monstrous cells. Hematoxylin and eosin stain. Mag. × 375.
right hand. All these lesions rapidly regressed with contact x-ray treatment for 10 days giving a total dose of 4800 r units (50 kv. 1 Al and 4 cm. T. S. D.)

Microscopic examination.—The left hand and the excised lesion from the right hand (b) were available for histological study. The growth on the left palm showed the characteristics of a squamous carcinoma grade III. The pigmented piece excised from the right hand was made up of dermal papillae extended into long branched processes covered with altered stratified squamous epithelium. There was hyperkeratosis, a disorderly arrangement of the cells in the stratified malpighian layer and large monstrous cells with two or three hyperchromatic nuclei. Some cells showed hydropic vacuolation of cells with small pyknotic nuclei. The basal layer of cells was regular, intact, sharply demarcated from the subjacent fibrovascular connective tissue. The small greyish nodules on the palm of the left hand showed the following interesting features.

The surface was covered with several layers of fine lamellae of keratinized material. The epithelium indented the dermis unevenly due to elongation broadening and fusion of rete cones. The minute discrete nodules which were visible to the naked eye were composed of broad epithelial buds pushing into the dermis (Figs. 14 and 15). The cells in the nodule showed a disorganization of the normal arrangement and stratification of cells. There was a wide variation in the size of adjoining cells, with some monstrous cells, and others with several nuclei clumped together, interspersed between normal polygonal cells. Some of the cells showed a characteristic intracellular vacuolation with a preservation of intercellular bridges. In the substance of the neoplastic mass "individual cell keratinisation" (13) and "corps ronds and grains" (7) were seen. These features suggested the change to be Bowenoid in character. It seemed probable that arsenic might have been administered during the course of the varied treatments received by the patient. The skin from the amputated forearm and the hand was therefore analyzed. It gave the following interesting data:

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Arsenic (as As %) mgm. per 100 gm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy skin in Indians*</td>
<td>0.150 (0.125 minimum)</td>
</tr>
<tr>
<td>Normal-looking skin from the forearm of the patient†</td>
<td>0.198</td>
</tr>
<tr>
<td>Cancer tissue from the wrist†</td>
<td>0.924</td>
</tr>
<tr>
<td>Skin containing hyperkeratotic nodules from the palm†</td>
<td>3.036</td>
</tr>
</tbody>
</table>

*From data published by Bagchi and Ganguly (1). †Technic employed by Maechling and Flinn (10).

Case 15. #2936.—An elderly emaciated Hindu beggar woman, 60 years old, was admitted for a black warty growth on her abdomen. She stated that the growth had started as an intense black spot 7 years earlier and that she was sure that it was not there before that time. The spot had slowly increased in size and had became rough on the surface. Black warty excrescences had slowly grown out of it. She complained of much itching, and occasional bleeding after scratching. On examination, a verrucous mass, roughly lozenge-shaped (17 X 12 cm.) was seen covering most of the left lower abdominal wall (Fig. 16). The edges were serpigenous and stood out clearly from the adjacent normal skin by their deeply pigmented color and elevated contour. The main mass was deep black except towards the middle where it was depigmented and atrophic in places. A second smaller pigmented patch composed of bunches of large and small papillae was discovered in the right loin. The patient did not remember when it had started. The larger growth emitted a faint fetid odor and the warty projections could be peeled off with little trouble and slight bleeding. Clinical examination and skiagraphic studies did not reveal any morbid condition in the gastrointestinal tract. Both lesions were excised along with a narrow margin of normal skin beyond the pigmented border. Skin from the thigh was grafted on the raw excised surface of the bigger lesion. The patient made an uneventful recovery. She has not reported a recurrence of the lesion nor of any fresh outcrops of pigmented spots for the last four years.

Microscopic examination.—(a) The flat heavily pigmented peripheral portion of the tumor mass showed a thickening of the epidermis with broadening, elongation and fusion of rete cones. There was hyperkeratosis and parakeratosis of the epidermis. Many cells in the malpighian layer were swollen, dyskeratotic cells with pyknotic nuclei and markedly acidophilic cytoplasm. These cells were always surrounded by a clear space. The basal layer of the stratum germinativum was heavily pigmented. There were numerous diffusely pigmented branching cells scattered between the epidermal cells. In the superficial layers of the dermis there were several melanophores stuffed with pigment, besides numerous clumps of free pigment scattered between connective tissue fibers. The transition between the normal and the affected skin was sharp and sudden.
FIG. 16.—Case 15.: Photograph showing the lozenge-shaped verrucous pigmented mass on the left lower abdomen.

FIG. 17.—Case 15.: Low power photomicrograph showing cords and strands of proliferated epithelial cells with central areas of keratinisation infiltrating the subjacent tissue. Hematoxylin and eosin stain. Mag. X 80.

(b) The intermediate zone showed several branched filamentous epidermal processes which were covered with several layers of closely applied keratinized lamellae. The epithelium was thickened by an increase in the cell layers and a more pronounced Bowenoid alteration in the character of cells. The peripheral processes were deeply pigmented whereas the more centrally placed filaments of epithelial cells were completely devoid of pigment.

(c) The central portion of the lesion shows a relative thinning of the epidermis accompanied by an invasive proliferation of epithelial cells (Fig. 17) into the subjacent dermis. The proliferating...
cells were arranged as cords or strands in the dermis with the development of characteristic epithelial pearl. In some areas the cells of the stratum malpighi showed hyperplastic prickle cells without any of the Bowenoid changes described above. There was a well developed stroma reaction in the dermis mainly consisting of lymphocytes, with few histiocytes and newly formed blood capillaries. The remarkable feature of this area was a complete lack of pigment in epithelial cells and an absence of the branching melanoblasts. There were no melanophores or free pigment clumps in the dermis.

The ducts of the sweat glands (Fig. 18) and the hair follicles in all these sections were involved in the neoplastic process without being altered. The lining of some ducts in the central area however showed the characters of an intra-epithelial carcinoma. The elastic tissue was pushed deeper in all these sections by the inflammatory exudate and the newly formed connective tissue stroma underlying the altered epithelium. The dopa reagent evinced an intense positive reaction in the proliferated and migrating dendritic cells in the peripheral pigmented regions of the tumor mass.

The histological study of the tumor tissue suggests that it belongs to a type of Bowenoid dermatosis, beginning as a deeply pigmented patch which becomes depigmented in the central older area. The depigmented area is characterized by the development of a slowly invading carcinoma of the prickle-cell variety.

**Comment**

The last two cases show the development of a Bowenoid change in the epidermis antecedent to an invasive cell proliferation and the formation of a typical squamous-cell carcinoma. The interesting feature of these cases is the melanotic pigmentation of the tumor tissue. Bloch (3) had suggested that in the basal cell tumor described by him the pigmentation was the essential feature and that the rest of the structure was secondary. Subsequent pigmentation in patches of Bowen's disease of the skin has often been described, but in both the patients referred to here, the lesions started as black patches and the growing peripheral areas of the fully developed tumor were deeply pigmented as a result of the proliferation and activity of dendritic melanoblasts. This activity and proliferation did not keep pace with the neoplastic growth of epithelial cells. The older, central, fully developed portions of the tumor therefore remained unprovided with pigment-elaborating cells, and became colorless.

**I. Deposition of Pigment in Tumors of the Epidermis**

(a) **Nature of the pigment.**—The pigment gives the usual chemical reactions of melanin. It is insoluble in all the ordinary solvents except strong solutions of alkalis, in which it dissolves with some difficulty. It could be slowly bleached by the action of strong sunlight. It does not give the Prussian blue reaction for iron, but is easily impregnated with silver solutions.

(b) **Distribution of the pigment in tumor tissue.**—A naked-eye examination of unstained sections shows that the pigment is unevenly distributed in lobes of tumor tissue (Fig. 4). It is more densely deposited in the peripheral cords and is scantier in the central areas. It occurs as, (I) a fine dust of golden or dark brown particles in the cytoplasm of cells in stratum germinativum and some tumor cells; (II) as diffuse homogenous brown coloring material in the cell body and dendrites of degenerating melanoblasts; (III) as coarse dark brown grains in the dermis or as clumps in the bodies of melanophores, and (IV) as large amorphous masses in cystic spaces in the center of tumor lobules. In the cells of the stratum germinativum it tends to be more closely aggregated in the zone immediately outside the nuclear membrane.

(c) **Pigment-forming cells (Melanoblasts).**—The most interesting feature of these tumors is a proliferation of dendritic cells. The change in the epithelial cells, as one approaches the tumor mass, is accompanied by an alteration in appearance and an increase in number of the dendritic cells (Fig. 19). In this zone the melanoblasts become more numerous and send out a rich brush of long thin processes between the epidermal cells, while still retaining their place in the basal layer of the stratum germinativum abutting against the dermis. These dendritic cells are not easily recognizable by the usual staining methods. They are, however, clearly depicted owing to the presence of a dopa-oxidase in their cell cytoplasm and the fine protoplasmic ramifications, and by their ability to reduce silver salts from solutions. As the expanding epithelial cones fuse and assume the shape of a growing bud the proliferated dendritic cells form a rich protoplasmic network on its dermal surface (Figs. 20 and 21). The dendritic cells move away from the periphery as the epithelial bud grows in mass. They however retain contact with the dermis by a thick process which usually ends in a globular or mushroomed terminal (Figs. 22 and 23). The dendritic cells
assume an elongated spindle shape on receding from the basal layer. The dendrites become fewer, longer and more filiform as the cells migrate away from the periphery and are caught up in the mass of neoplastic epithelial cells. This migration of dendritic cells has been elegantly described by Masson (11) and by Caudière (5). These cells appear to be unable to transfer the precursor of the pigment to the adjacent tumor cells, or alternatively the tumor cells lose the capacity of accepting and elaborating the pigment. The pigment, therefore, begins to accumulate in the cell body and branches of the dendritic cells. After their being bereft of their dermal associations, the dendrites thicken and coarsen. Gradually the cells become shrunken and are shorn of most of their branches (Fig. 24). A thick short stump may remain attached to the shrunken, degenerating cells, before they are sloughed off into the amorphous debris. Similar degenerative changes in melanoblasts have been described by Schneider (20) in luetic infiltrations of the epidermis with Treponema pallidum and observed by us in a case of a fungus granuloma of the nipple in a 55 year old male.

It is necessary, however, to determine whether the evident increase in the number of dendritic cells at the growing edges of these tumors is genuine or spurious. Rous (18) and Beard (2) have observed that Shope papilloma in rabbits is genuine or spurious. Rous (18) and Beard (2) have observed that pigmented tumors developed "only where the hair was pigmented. . . When the first epithelial thickening took place, melanoblasts similar to those nearby the unaffected epidermis proliferated in the basal part of the papillomatous epidermis and often became extraordinarily abundant, and black with pigment." They were of the opinion that "pigmented growths arise because these cells (melanoblasts) become involved in the pathological process though not themselves affected by the virus." Masson (12) while discussing the appearances in macular pigmented nevi has expressed the following view. "At first it was attempted to show this excess of branching cells to be the result of their hyperplasia. I do not believe this to be true." He attributes the apparent increase in number of these cells "to an exaggeration of amboceptric differentiation, to the detriment of malpighian differentiation." Caudière has also expressed the opinion that No part of them [pigmentary cells] shows signs of proliferation. The tumors that do present these characteristics are symbiotic, pigmenitary cell epitheliomas." (5). These views deserve most careful consideration, although it must be admitted that the appearances observed in the tumors described above are very suggestive of a true hyperplasia in the spreading zone of the tumor tissue. It is also difficult to accept the opinion of Caudière that "They are not pigmentary tumors, they are pigmented tumors" (5), as in several cases the lesions start as a deeply pigmented patch, which may later grow discolored towards the central part of the lesion. The pigment-producing cells are actively associated with the growth of neoplastic tissue, although they fail to keep pace with the increase in number of other epithelial cells and are later completely choked by them.

(d) Accumulation of pigment in tumor tissue.—The dark color of these tumors is due not only to the presence of pigment particles in the melanoblasts and some tumor cells, but also to a lack of normal elimination of dead epithelial cells. Towards the center of the tumor lobes the keratinized bodies of epithelial cells and the degenerated bodies of melanoblasts are cast off in the debris of necrotic material. The pigment, however, remains unaltered and is retained in cystic spaces and fissures or in the widened follicles involved in the neoplastic process. There appear also groups or circumscribed masses of bulky ovoid or fusiform cells in the superficial layers of the dermis heavily loaded with coarse granules of brown pigment (Fig. 25). They often lie in close proximity to the lobes and cords of tumor tissue and are evidently macrophages which have engorged themselves with pigment. The exact source of pigment in these cells is not very clear. These macrophage cells are never encountered in the body of the neoplastic cords. They are only seen in the connective tissue stroma separating the lobes. These appearances suggest that the macrophages take up formed pigment which is "spilled over" in the dermis and which is not retained by tumor cells. These macrophages have, therefore, been correctly termed melanophores and are distinct in origin.

DESCRIPTION OF FIGURES 19 TO 21

Fig. 19.—A composite picture of camera lucida drawings of seven fields, from a biopsy of tissue in case 13. It shows an increase in the number and the alteration in the morphological characters of the melanoblasts in the peripheral zone of the tumor mass. Dopa reaction.

Figs. 20 and 21.—A rich protoplasmic network of the processes of dendritic cells on the surface of epithelial buds from case 13. Dopa reaction. Fig. 20, Mag. X 200; Fig. 21, Mag. X 375.
and evolution from the melanoblasts described above or the nevus cells encountered in benign or malignant melanomas

II. Regression of Neoplastic Changes
The central area of the lesion in Case 8 showed a tendency towards healing and a replacement of the neoplastic cells by epithelium without evident proliferative activity. Similarly in several centrally located areas in Case 15 there was a disappearance of the Bowenoid change and its replacement by a normal looking stratified squamous epithelium. Such retrogression of experimental tar cancer has been reported. Rous and Kidd (18) observed a raised ulcerated disc after 5 months tarring in one of their rabbits. The growth took on an invasive character during the next 4 months. Later it began to grow smaller and disappeared completely in another 4 weeks. A similar carcinoma with metastases was described by Yamagiwa and Ichikawa, which retrogressed after 630 days of growth. The suggestion therefore that proliferating epithelial buds or Bowenoid changes should be interpreted as a carcinoma could not be accepted without reservations. These conditions should be looked upon as precancerous changes which have the potentiality of developing into a carcinoma with the introduction of other factors which are not so well understood at present.

III. Development of Cancer in the Altered Epidermis
The invasive character of cell proliferation in the central portions of the lesions in Cases 11 and 15 reemphasize the importance of a distinction between tumor inception and tumor formation. The latter condition ensues only when appropriate conditions exist in an area for an infiltrative growth of tumor tissue. This question has been fully discussed previously (9) and need not be entered into again. The importance of a precocious stroma reaction some distance away from the proliferating epithelial buds has been stressed as an influential factor in the limitation of invasive characters in some of the skin cancers by Masson (12) (stroma reaction précocce) and it is likely that only when this character fails in the altered dermis, a true carcinoma results.

IV. Spread of Tumors
The spread of these tumors presents certain interesting features. In basal cell carcinomas one is struck with multiple microscopic foci of epithelial proliferation, and the spread along the surface and in depth of the lesion is to a certain extent due to a fusion of these foci and to a growth in mass which results from continued cell division. In the case of the Bowenoid changes in the skin there are two possible methods of lateral spread: (I) an intra-epidermal migration of neoplastic cells as in Paget's disease of the nipple [Muir (14)], or (II) a progressive Bowenoid transformation of normal epithelium in response to an inducing agent continuously being elaborated by active or degenerating neoplastic cells. The latter possibility appears more likely in view of the fact that the line of demarcation between the normal and altered skin is usually very sharp and also because of the arrest of disease after surgical extirpation of affected area of skin. A careful study of the epidermis at the border zone shows few swollen prickle cells just above the normal cells of the basal layer, but no frank neoplastic cells could be detected between normal cells of the malphigian layer as in Paget's disease of the breast. The material at our disposal is inadequate for a solution of this problem, and its elucidation would probably follow the experimental studies now in progress under Cowdry at St. Louis (6).

SUMMARY
1. Fifteen cases of pigmented lesions of the skin which were not melanomas have been reported. Four cases of single pigmented epitheliomas of the skin and four others with multiple lesions have been described.
2. The necessity of a histological diagnosis in all these cases has been emphasized and their relatively benign course has been described.
3. The biological nature of these lesions and the role of melanoblasts in their evolution has been discussed.

DESCRIPTION OF FIGURES 22 TO 25

FIGS. 22 and 23.—Case 13.: Photomicrographs showing the migration of melanoblasts and the thick processes abutting against the dermis. Dopa reaction. Fig. 22, Mag. X 375; Fig. 23, Mag. X 80.

FIG. 24.—Case 12.: Photomicrograph showing the degenerative changes in the migrated melanoblasts, with a shrinkage of cells and loss of dendrites. Silver impregnation. Mag. X 80.

FIG. 25.—Case 13.: A higher power photomicrograph showing the three types of accumulation of pigment in the growing tumor buds, (1) in the debris of necrotic material at the center of tumor lobes (2) in the bodies and process of melanoblasts (3) in groups of melanophores in the dermis. Dopa reaction. Mag. X 150.
Figs. 22-25
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REFERENCES

Pigmented Precancerous and Cancerous Changes in the Skin

V. R. Khanolkar