Comparison of Methylcholanthrene Hyperplastic Epidermis with Benign Hyperplastic Epidermis in Healing Wounds*

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It is highly desirable to be able to recognize lesions likely to develop into cancer. One reason for so much difference of opinion is that the problem has not been clarified by experimental work on animals. A major research project in the Barnard Free Skin and Cancer Hospital is the integration of changes that occur in epidermal methylcholanthrene carcinogenesis of mice.

Epidermis, rendered hyperplastic by methylcholanthrene, will, after a sufficient number of properly spaced paintings in the right concentration, give rise to squamous cell carcinomas in a fairly high percentage of cases. Consequently it may be assumed that it has been rendered more surely precancerous than any lesion naturally occurring in the human body. The other desideratum is to create for comparison another epidermal hyperplasia of equal thickness in mice which is not precancerous. This can easily be done by excising small pieces of skin and by selecting the regenerating epithelial edges. Since these experimental conditions afford ample opportunity for the comparison of precancerous and regenerative (benign) epidermal hyperplasia, an intensive search has been commenced for differences between them. We think that in this way we are likely to be able to detect in the hyperplasia the essential precancerous modifications.

The literature on precancerous lesions is enormous. Dubreuilh (8) was the first to use the term "precancerous" in his thesis at the Third International Dermatological Congress in London in 1896. He applied the term to a group of skin conditions that were likely to become malignant.

Darier (7) employed the word "dyskeratoses" to indicate individual differences between cells in the epidermis which had undergone atypical evolution leading to precocious and imperfect cornification. The four conditions he called dyskeratoses were Darier's disease, molluscum contagiosum, Paget's disease, and Bowen's disease. His use of the term indicated that he considered the dyskeratoses precancerous. Masson (19), Pautrier and Archambault (22), and Kogoj (15) were of different opinions and considered the "dyskeratoses" entirely different diseases with nothing in common and not all precancerous. McCarthy (20) stated that as all dyskeratoses are not precancerous, all precancerous lesions are not necessarily of a dyskeratotic nature. Satenstein (23) made use of the qualifications "accelerated" and "retarded" for the types of keratinization to distinguish between benign and malignant dyskeratoses.

Montgomery (21) employs the phrase "individual cell keratinization" to describe the phenomenon of malignant dyskeratosis of individual cells of the epidermis as seen most clearly in Bowen's disease. He listed as "precancerous dermatoses": Bowen's disease, senile keratosis, keratosis resulting from arsenic, tar, radiation, and various forms of leukoplakia of mucous membrane of the mouth and genitalia. He found that 20 per cent or more of cases of all these conditions develop epithelioma of squamous cell type. Taussig (29) observed 39 of 76 cases of vulvar cancer to be associated with leukoplakia, or approximately 50 per cent.

Freudenthal (10), Hooker (13), and Bloch (1) have enumerated the principal histopathologic changes in hyperkeratosis senilis and verruca senilis, a combination of which is to a certain degree typical of precancerous affection. They are irregular epithelial proliferation, irregularities and unrest in the cell structure, atypical and polymorphous cells and nuclei, pathological mitoses and amitotic figures, dyskeratotic manifestations and reactive inflammation in the adjacent parts of the cuts.

Ewing (9) has stated that, "The theoretical distinctions which a general survey establishes between neoplastic and inflammatory hyperplasia are sharp and fundamental, but these distinctions fail us when we have to search for them in processes of doubtful nature. Here we assume them to exist from our general knowledge but we cannot prove their presence."

In the characterization of precancerous lesions clinical data have been supplemented by morphological data derived chiefly from the microscopic examination of sections prepared by the usual routine methods. In consideration of the great importance of the problem, it is surprising to find that information bearing on the physicochemical properties of the lesions and on their physiological properties is conspicuous by its absence. As Cowdry (4) has indicated, workers have perhaps thought the effort futile as long as it is so difficult to mention a property of malignant cells altogether absent in their normal prototypes. In this paper we have made an attempt to fortify morphological data by an investigation of displacability under ultracentrifugal force and of mineral constituents by microincineration.

**Material and Methods**

Specimens of hyperplastic epidermis in a series of New Buffalo mice were selected. These mice were
treated with 0.6 per cent methylcholanthrene in benzene 3 times a week. The carcinogen was applied uniformly with a small brush to an area about 5 mm. in diameter at the back of the neck. A single specimen on each of the following days after the beginning of treatment was studied: 11, 18, 22, 25, 39, 43, 46, 49, 51, and 64 days.

The mice used for induction of benign epidermal hyperplasia were of mixed stock. At first we tried to work with scarlet red in olive oil because we felt sure that the resulting hyperplasia would certainly not lead to the development of cancer (Seelig, Eckert, and Cooper, 27).

A saturated solution of scarlet red in olive oil was applied to the epilated skin surface of 22 mice 6 days a week for 150 days, but no hyperplasia of sufficient extent for comparison was obtained. Another group of 23 mice was treated in the same way except that every 10 days in the first 50 days the area treated was gently scratched with a scalpel in two directions at right angles. Again the hyperplasia was unsatisfactory.

Suitable material was, however, collected from two other groups of mice. In the first, consisting of 31 mice, the hair was removed from a small area on the back of the neck with sodium sulfide. A day later about 1.5 sq. cm. of skin, full thickness, was excised and the open wounds were allowed to heal without any treatment. The very few wounds that became infected were not used for material. Tissues were removed from 6 mice after 10 days and from 11 others after 14 days.

In the second group of 51 mice similar wounds were made and saturated scarlet red in olive oil was applied to each 6 days a week. Again infected wounds were rare and were not included in this study. Specimens were excised: 6 after 10 days, 4 after 17, and 14 after 19 days.

For histological comparison of the methylcholanthrene hyperplasia and the benign regenerative hyperplasia, tissues were routinely fixed in Bouin's fluid and paraffin sections, 5 microns in thickness, were stained with hematoxylin and eosin.

The displaceability of nuclear contents was determined by ultracentrifugation as described in an earlier paper by Cowdry and Paletta (5). All tissues were centrifuged in Locke's solution in a Beams type of centrifuge, driven by oxygen pressure of 60 lbs. per sq. inch, yielding a displacing force of approximately 350,000 times gravity, operating for 30 minutes. Some of the specimens described in the above-mentioned paper were used to compare with benign hyperplasia of healing wounds. Parts of 17 healing wounds (benign hyperplasias) were centrifuged.

Scott's (24) method of microincineration was employed for mineral constituents. Twenty methylcholanthrene hyperplasias and 19 benign hyperplasias from the wounds were incinerated. First, a few sections from a methylcholanthrene hyperplasia (M. H.) were mounted on a slide and after them on the same slide were mounted some sections from a benign hyperplasia (B. H.). But in all the later work a better comparison was provided by mounting the methylcholanthrene and benign hyperplasia sections alternately: M. H., B. H., M. H., B. H., etc.

Observations

Two reservations are necessary with respect to the precancerous condition of epidermis made hyperplastic with methylcholanthrene:

1. Since we have not determined by experiment the percentage of epidermis which would eventually yield carcinomas if the treatment specified were stopped after 11 days and the animals continued to live, it is unsafe to call an 11-day hyperplasia precancerous. The chances that cancer would have developed if the tissues had not been biopsied increase with the duration of methylcholanthrene treatment. Specimens of 40 days and more are much more likely to be precancerous at the time of examination. On the other hand, it is unsafe to assume that even after brief treatment the hyperplastic epidermis has not been modified in the direction of cancer formation because the Tworts (30) have found that "cells rendered abnormal by a few applications of benzpyrene quickly pass into the irreversibly cancerous phase when stimulated with oleic acid."

2. Because the malignant change takes place in sharply limited loci within the areas treated and not evenly throughout their extent, it cannot be stated that all of the hyperplastic epidermal tissue in any of the areas, even after prolonged treatment, is precancerous. Yet it is possible that, although the malignant changes begin in small foci within the areas, the remaining parts of the areas have nevertheless been rendered potentially precancerous by the methylcholanthrene. MacKenzie and Rous (18) have observed that "A carcinogenic tar applied to rabbit skin renders many more epidermal cells neoplastic than ever declare themselves by forming tumors." They note, however, the curious fact that, in contrast to rabbits, no growths appeared during the healing of holes punched in mouse ears treated by carcinogens.

Parts of the epidermis from which cells were invading the underlying dermis were themselves considered cancerous and were of course excluded from this comparison. We are well aware that some lesions listed arbitrarily in this way as precancerous might be regarded by others as cancerous since they may resemble, for instance, the carcinoma in situ of Broders (2). Portions of hair follicles extending into the dermis were also excluded. Only the epidermis forming the
surface of the skin and surrounding the openings from which the hairs formerly projected was included.

In the case of the healing wounds care was also taken in the selection of hyperplastic epidermis though none of it could be considered precancerous. The thin sheet of epidermal cells beginning to cover the exposed surface of underlying tissue was excluded. The comparison was usually limited to the area of the original epidermis surrounding the excised tissue for a distance of about 6 mm. In this the number of layers of epidermal cells was increased by benign hyperplasia from the normal of 2 or 3 to from 10 to 14. It had attained approximately the same thickness as the methylcholanthrene hyperplastic areas of epidermis.

Structure.—Methylcholanthrene hyperplasia is often characterized by diversity of structure as compared with the uniformity of structure of the benign hyperplasia. Marked variation occurs in the size of the nuclei of basal cells after treatment with methylcholanthrene over a period of 18 days, which is earlier than such a variation is usually found (Fig. 1). A variation of this magnitude was not observed in benign hyperplasia (Figs. 5 and 6).

Fig. 2 shows a not unusual degree of nuclear hyperchromatism and enlargement of nucleoli in methylcholanthrene hyperplasia (25 days). In benign hyperplasia the nuclei may stain intensely and the nucleoli may be prominent but seldom to the same extent.

Figs. 3 and 4 are of different areas in the same, probably precancerous, specimen (46 days). The first represents a degree of irregularity of growth not observed in any of the benign hyperplasias and the second a uniformity of growth not suggestive of precancer. But in this second specimen the nuclei are large and there are many mitoses. The highest incidence of mitosis is in the area showing the least departure from typical cell shape. It is possible that the irregular growth appears not in an area of hyperplasia but in one in which for a time mitosis has not been frequent.

In the benign hyperplasia there is also regional diversity of structure but this depends upon the distance from the healing wound. At a given distance uniformity in structure is very definite. Benign hyperplasia at a distance of about 2 to 3 mm. from the margin of the excised area, 10 days after the excision, is represented in Fig. 5. In it there is greater uniformity in cellular size and structure than in any of the methylcholanthrene hyperplasias illustrated except that shown in Fig. 4. The intercellular spaces are less marked than in Figs. 1, 2, and 4 of methylcholanthrene hyperplasia, indicating less edema.

Benign hyperplasia within 1 mm. of the margin of the excised area is shown in Fig. 6. In this region, much nearer the excision than Fig. 5, there is extensive intercellular and intracellular edema far greater than that observed in any of the methylcholanthrene hyperplasias. It will be noted that the width of the intercellular spaces is often twice that of those in Figs. 1, 2, and 4, and that the intercellular bridges (spines) have been stretched considerably and their number decreased since some have probably been broken. The edema is greater proximally (near the basement membrane) than distally, as is to be expected because the blood vessels are proximal. There is fair uniformity in cell size and shape.

Other histological differences between methylcholanthrene and benign hyperplasia in our series, include in the former: (a) a more definite basement membrane with greater tendency to bulge into the dermis; (b) more acanthosis and less affinity of spinous cells for eosin; (c) less leucocytic infiltration than that at the edge of the wound; and (d) more prominent granular layer and slightly more hyperkeratosis.

Intranuclear viscosity.—The displacement by ultra-centrifugal force of nuclear contents in a methylcholanthrene hyperplasia of 11 days is shown in Fig. 7. The force is from above downwards. In most of those nuclei which are cut approximately through their greatest diameters, the nucleoli and basophilic chromatin have shifted in a centrifugal direction—a phenomenon not observed by Cowdry and Paletta (5) in untreated, normal epidermis. Judging by the uniformity of the shift in the small area represented, the intranuclear viscosity of the majority of the cells is about the same. Those included in the photomicrograph are of the spinous variety. No basal cells are included, but
Figs. 1 to 4.
Figs. 5 to 8.
the spinous cells at the lower right corner are smaller than the others and not far removed in their properties or topographically from basal cells. In two or three cells the centrifugal cytoplasm stains more intensely and appears to be denser than the centripetal cytoplasm. The spinous cells involved do not exhibit either the hyperchromatism illustrated in Fig. 2 or the atypical features shown in Fig. 3. As in our previous work such areas of displacement were found to be of patchy distribution. In some parts of the methylcholanthrene hyperplastic epidermis none were encountered.

Fig. 8 is of a benign hyperplasia (19 days) from the edge of a healing wound centrifuged under the same conditions as the methylcholanthrene hyperplasia (Fig. 7). All the cells are of the spinous variety except the two in the lower left corner which are basal cells. The displacement of nuclear contents is quite noticeable, though it appears to be less than in Fig. 7 and there are no signs of centrifugal concentration of cytoplasm. But if in Fig. 8 an equally large proportion of the nuclei had been cut through their centers, as in Fig. 7, the displacement of nuclear contents might have looked about the same.

Examination of tissue outside the limited space shown in these illustrations, and of many other specimens, shows that in both methylcholanthrene and benign hyperplasia the nuclear contents of basal cells are more resistant to displacement by centrifugal force than those of spinous cells indicating a higher intranuclear viscosity as we have previously reported in our carcinogenic series. Certainly in both types of hyperplasia the intranuclear viscosity is lower than in normal (nonhyperplastic) epidermis of mice, in which, since mineral constituents. All the photomicrographs were taken with the same optical combination, distance, and exposure of tissues, prepared as nearly as possible in the same way. The finely divided, faintly bluish, white ash, said to be of Na and/or of K, is difficult to photograph and the illustrations are deficient as far as it is concerned.

A microincineration preparation of a 40-day methylcholanthrene hyperplasia, as seen in the dark field, is represented in Fig. 9. The heavy-looking white ash, consisting chiefly of Ca and Mg, is abundant in the basal cells, spinous cells immediately distal to them, and in the cells of the corneum, but is less in amount in the intervening spinous cells just beneath the corneum. In general it is more concentrated in the nuclei than in the cytoplasm except in the corneum.

When similar sections are stained with hematoxylin and eosin, or the Feulgen reaction for thymonucleic acid is applied to them, it is found that nuclei like those yielding this dense white ash are hyperchromatic as was reported by Horning and Richardson (14) in their study of cancer, and also by Scott and Horning (26).

A 50-day methylcholanthrene hyperplasia (Fig. 10) shows a further stage of mineral redistribution. Here the dense white ash of the cells forming epidermal projections into the dermis is conspicuous. The corneum is more mineralized than in Fig. 9 and the intervening band of spinous cells, with less mineral, is much wider.

A 70-day specimen appears in Fig. 11. While the amount of mineral is greater in the proximal and distal layers than in the intervening one, there are distinct regional differences in mineralization. It is fairly dense on the extreme right, then, passing to the left, is seen a vertical band of partly demineralized tissue. This is followed by a large epidermal peg which is rich in minerals and a wider vertical demineralized band. On the extreme left the mineralization is again considerable. It will be recalled that in rapidly growing embryonic skin, Scott (25) observed somewhat similar irregularities in the amounts of minerals.

A more extensive methylcholanthrene hyperplasia, though in a specimen treated only during a period of 60 days (as compared with 70 days), is pictured in Fig. 12. Here the demineralization is still more marked both proximally and distally. The outlines of the epidermal pegs can, however, be made out by the dense white ash, often of a single row of basal cells.

A contrast of the mineral constituents in two stages

**DESCRIPTION OF FIGURES 5 TO 8**

Fig. 5.—Benign hyperplasia of epidermis (19 days) in mouse of mixed stock. Note the organized type of cellular growth and uniformity in size of the cells in their respective layers. Compare with Fig. 3, particularly the spinous cells. Hematoxylin and eosin stain. Mag. X 1040.

Fig. 6.—Benign hyperplasia of epidermis (19 days) in mouse of mixed stock. There is marked intercellular and intracellular edema and prominence of intercellular bridges. Hematoxylin and eosin stain. Mag. X 1040.

Fig. 7.—Methylcholanthrene hyperplasia of epidermis (11 days) in New Buffalo mouse. Centrifuged specimen. Note the displacement of nucleoli and basophilic chromatin toward the centrifugal pole. Response is uniform throughout the spinous layer. Hematoxylin and eosin stain. Mag. X 1040.

Fig. 8.—Benign hyperplasia of epidermis (19 days) in mouse of mixed stock. Centrifuged specimen. Compare with Fig. 4. Note that the spinous nuclei with large nucleoli show displacement toward the centrifugal pole. The basal layer shows very little displacement. Hematoxylin and eosin stain. Mag. X 1040.
of benign regenerative hyperplasia is given in Figs. 13 and 14. Fig. 13 shows at the left the epidermis at the edge of a wound which has become hyperplastic (10 days). This dips down on the right into the wound where the epidermal sheet grown over the exposed dermis is thinner. The position of the basement membrane is not distinct in the photomicrograph. It is situated in the figure about 1.8 cm. below the surface on the right and extends toward the left roughly horizontally. Much of the white ash below it is of leucocytes. The hyperplastic epidermis represented is evidently somewhat demineralized but not so much so as the methylcholanthrene hyperplasia in Fig. 12. Supplementary stained sections seem to indicate that this demineralization is correlated with intense cellular activity. Fig. 14 illustrates a noticeably later stage in benign hyperplasia although the tissue was only taken one day after that used for Fig. 13; that is, 11 days subsequent to the making of the wound. The epidermis is from about 6 to 9 cells in thickness. It is heavily mineralized, especially the basal cells, proximal spinous cells, and corneum. That a reaccumulation of minerals has occurred is obvious. Moreover, the distribution of ash is fairly uniform. There is no lack of minerals in the upper spinous layer, as in Fig. 10, or in vertical bands, as in Fig. 11, both representing methylcholanthrene hyperplasias. MacCardle, Engman, and Engman (16) have reported a somewhat similar demineralization in the active lesions of neurodermatitis followed by a reaccumulation of minerals in healed lesions.

**Discussion**

By ordinary routine methods of fixation and staining we have found localized areas in the methylcholanthrene hyperplasias which differ markedly from anything observed in the benign hyperplasias. In them there is diversity of nuclear size (Fig. 1), hyperchromatism of both nuclei and cytoplasm (Fig. 2), and slight multinucleation (Fig. 3).

According to Guldberg (12) the appearance of the precancerous stages of tar cancer in mice "reminds one very much of the changes found in the epidermis of Bowen's precancerous dermatosis in man." Ewing (9) quotes Grutz as saying that "the histological picture of Bowen's disease is exactly reproduced by the later stages of epithelial overgrowth, occurring in animals receiving inunctions of tar products."

Comparison of our methylcholanthrene hyperplasias in mice with preparations from Bowen's disease in the Barnard Free Skin and Cancer Hospital collection reveals both similarities and differences. The "disorganization of the normal arrangement and size of the cells of the epidermis" mentioned by Montgomery (21) as one of the features of Bowen's disease, is present in our preparations but we are not sure of its absence in other sorts of hyperplasia. The "amitosis as well as the mitosis resulting in the formation of epithelial giant cells and giant epithelial cells," which he mentions, may occur to some extent in our specimens. It is possible that the cells possessed of two or more nuclei represented in Fig. 3 may have resulted from amitotic division of nuclei unaccompanied by division of cytoplasm. In a previous paper Cowdry and Paletta (6) described occasional gigantic epithelial cells, but these were in methylcholanthrene hyperplastic epidermises in which the neighboring cells departed but little from type and were unlike any giant cells illustrated by Montgomery though they resembled a cell possessed of a very large nucleus shown by Szodoray (28) in Bowen's disease. We do not regard them as an essential feature of the precancerous lesions. Mitosis is fairly common in our specimens. We have not, however, seen clumps of cells in mitosis immediately beneath the flattened cells of distal epidermal strata resembling those shown in Montgomery's Fig. 2a. There is some irregularity in keratinization, but we are doubtful as to how closely it approximates to the "individual cell keratinization" which he emphasizes. A few "corps ronds" may be seen though we have not observed in our specimens any significant number of cells with deeply stained nuclei and clear chromophobic cytoplasm, somewhat resembling Paget cells, and like those encountered in the Barnard Hospital's collection of Bowen's disease and illustrated in MacKee and Cipollaro's (17) Fig. 202 of Bowen's disease. Obviously, therefore, a more detailed comparison between our methylcholanthrene hyperplasias and Bowen's disease as well as the whole group of precancerous dermatoses

**Description of Figures 9 to 11**

Fig. 9.—Methylcholanthrene hyperplasia of epidermis (40 days) in Swiss mouse. Microincinerated section. Observe the heavy deposits of white ash (Ca, Mg, Si) in the basal and spinous cells. The minerals are deposited most in the nucleus in the basal and suprabasal layer, except in the distal spinous cell layers and granular layers where much may be perinuclear. Mag. X 550.

Fig. 10.—Methylcholanthrene hyperplasia of epidermis (50 days) in Swiss mouse. Microincinerated section. There are heavy deposits of calcium and magnesium in the cells of the hyperplastic downward projections. The keratin layer produced highly refractive white ash. Mag. X 550.

Fig. 11.—Methylcholanthrene hyperplasia of epidermis (70 days) in Swiss mouse. Microincinerated section. The irregularity of mineral residue is marked. Mag. X 550.
is necessary before reaching any conclusions as to the exact degree of similarity.

The areas described as showing diversity are probably foci in which the malignant transformation is likely to occur soon, if indeed it has not already taken place. We regard such lesions as probably "precancerous" arbitrarily restricting the term "cancer" to lesions in which there is evidence of invasion of the dermis. To recognize the latter is easy so that our demonstration of their presence in methylcholanthrene hyperplasia and of their absence in benign hyperplasia is of no practical value in determining the future of "precancerous" changes. It is necessary to find an earlier change which so conditions the epidermis as to make way for malignancy.

By ultracentrifugation we have tested intranuclear and to some extent cytoplasmic viscosities and have discovered that there is a decrease in intranuclear viscosity from the normal in both methylcholanthrene and benign hyperplasia. The photomicrographs (Figs. 7 and 8) show that this can occur in cells whose shape has not become atypical. The difference between methylcholanthrene and benign hyperplasias is that in the former this decrease in viscosity is progressive, as pointed out by Cowdry and Paletta (5), whereas in the latter it subsides. The much greater decrease in intranuclear viscosity of squamous cell carcinomas is characteristic, but unless it is more marked than that found in this and other types of benign hyperplasia it cannot be regarded as indicative of a precancerous condition. Moreover the technic is not such that it can be conveniently employed in the examination of a suspected lesion.

By microincineration we have noticed a regional variability in mineral constituents in methylcholanthrene hyperplasia (Fig. 11) not seen in benign hyperplasia. It is quite widespread and obtains in parts of the epidermis which do not exhibit focal areas of disorganization. Perhaps it is evidence of a basic instability, or lack of regulation, in mineral metabolism. Fortunately the method is not complicated so that it would not be a difficult task to compare the mineral skeletons of precancerous dermatoses with other dermatoses which seldom if ever become cancerous.

We hope to compare these methylcholanthrene and regenerative hyperplasias in mice by other micro-

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**DESCRIPTION OF FIGURES 12 TO 14**

Fig. 12.—Methylcholanthrene hyperplasia of epidermis (60 days) in Swiss mouse. Microincinerated section. Note extensive demineralization. Magn. X 550.

Fig. 13.—Benign hyperplasia of epidermis (10 days) in mouse of mixed stock. Microincinerated section. The extreme right is the edge of the active healing wound. Note the demineralization of the cells at the edge of the wound. Magn. X 550.

Fig. 14.—Benign hyperplasia of epidermis (11 days) in New Buffalo mouse. Microincinerated section. Note the reaccumulation of white ash (Ca, Mg, Si) in the basal and suprabasal cells of the hyperplastic epidermis when compared to an active healing wound of Fig. 13. Magn. X 550.
5. In both methylcholanthrene and benign hyperplasia the intranuclear viscosity, determined by displacement of basophilic chromatin and nucleoli under ultracentrifugal force, is less than in normal epidermis. The difference is that in the former the decrease continues to malignancy while in the latter it is only temporary.

6. In both there is a demineralization, particularly in the distal part of the spinous layer, but in methylcholanthrene hyperplasia there are local variations in mineral content not found in the benign hyperplasia.

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