The Role of Sebaceous Glands and Hair Follicles in Epidermal Carcinogenesis

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Squamous cell carcinoma develops more quickly and in a higher percentage of young New Buffalo mice, 2½ to 3 months old at the time of the first painting with methylicholanthrene, than in mice of the same strain 12 to 13 months old (2). In this paper we report the results of treating the skins of still younger mice with methylicholanthrene.

OBSERVATIONS

Individual pregnant Swiss mice were separated and carefully watched for delivery. Thirty young mice, 2 to 10 hours after birth, were subjected to a single application of 0.6 per cent solution of methylicholanthrene in benzene supplied by one stroke of a camel's hair brush, No. 4, extending from the neck down the back to the rump. After 5 months, 1 died; after 7 months, 5 were sacrificed because of body wounds resulting from fighting; and after 10 months, another died. None of these showed any signs of cancer. The remaining 23 mice are now alive and well, 18½ months after this single application of the carcinogen, and show no skin lesions of any kind.

This lack of responsiveness of the skin of newborn mice led to a microscopic study of the skin from the time of birth, or shortly thereafter, until complete development of this structure. Sections of whole skin were examined after treatment with osmic acid, staining with Sudan IV,1 and coloration with hematoxylin and eosin. Study of the skins of control, untreated, baby mice showed at increasing intervals after birth the following:

10 Minutes.—The epidermis well-differentiated, consisting of 5 to 7 strata of cells, covered with a heavy layer of keratin. Sebaceous glands not present, but rudimentary hair follicles visible without hair. (Fig. 1).

30 Minutes.—Similar except that a few hair follicles have hair. (Fig. 2).

8 Hours.—Epidermis well-differentiated, hair follicles have hair, some of which reaches to the surface of the epidermis. Some small sebaceous glands present. (Fig. 3).

24 Hours.—Many sebaceous glands and many follicles with hair in a considerable percentage of cases extending out through the well-differentiated epidermis. (Fig. 4).

72 Hours.—Approximately complete development with sebaceous glands attached to every hair follicle, but still not all of the hairs reach out through the epidermis. (Fig. 5).

Adult.—Epidermis only of about 2 cell layers in thickness with very little keratin covering them. Sebaceous glands attached to every hair follicle, and all hairs extending to exterior. (Fig. 6).

Particular attention was paid to the hair follicles and sebaceous glands because of the investigations of Lacassagne and Latarjet (4). These authors have shown that the skin of newborn mice (1 day after birth) which was rendered hairless by destruction of the hair follicles and sebaceous glands by ultraviolet radiation, was refractory to the carcinogenic action of methylicholanthrene. On the other hand, a skin which had become repaired after photo-dermatitis and in which some hair follicles and sebaceous glands were restored or were newly formed, gave rise in their experiments

DESCRIPTION OF FIGURES 1 TO 3

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Fig. 1.—Skin of mouse after birth showing well-differentiated epidermis covered with keratin. There are some rudimentary hair follicles, but no sebaceous glands. Hematoxylin and eosin stain.

Fig. 2.—Skin of mouse 30 minutes after birth. Similar to Fig. 1 except beginning growth of hair in hair follicles. Osmic acid stain.

Fig. 3.—Mouse skin 8 hours after birth revealing thick epidermis, which is covered by much keratin. Some hair of the hair follicles protrudes through the epidermis. Anlage of some sebaceous glands is present, as identified directly below letter “A”. Osmic acid stain.
to rapidly growing cancer after subjection to the same carcinogen. They, therefore, suggested that the hair follicles and sebaceous glands play an important role in skin carcinogenesis.

The experiments of Simpson and Cramer (7, 8) on the distribution of methylcholanthrene after a single application to the skin of mice has led to a better understanding of its mode of action. They found that, immediately after the carcinogen was applied, it localized in the sebaceous glands and in the free lipids of the keratinized epithelium. Four to 5 days later there was degeneration and disappearance of the sebaceous glands, accompanied by a massive excretion of sebum, containing the carcinogen, into the hair follicles and then onto the surface of the epidermis. The fluorescence of the methylcholanthrene in the sebum was blue-violet in contrast to the yellowish-green fluorescence of the unchanged carcinogen on the keratinized surface indicating, perhaps, that the sebaceous glands are in some way concerned in the metabolism of methylcholanthrene.

**DISCUSSION**

The absence of cancer production by methylcholanthrene in the epidermis of new born mice (2 to 10 hours after birth) may be due to several factors. That it is not due to the amount of carcinogen delivered is evident from the observations of others who have studied the effect of a single application of methylcholanthrene to the skin of mice. Mider and Morton (5, 6) were the first to demonstrate that one treatment with this carcinogen was sufficient to induce epidermal cancer in the C57 brown strain, but not in the C57 black mice. Later on Cramer and Stowell (3) found that about 43 per cent of young Swiss mice (2½ to 3 months of age) developed cancer after a single treatment with the same carcinogen, and Simpson and Cramer (9), likewise, showed that 3 out of 12 young New Buffalo mice responded, by cancer formation, to the carcinogen administered under the same conditions. In the experiments of Cramer and Stowell (3) and of Simpson and Cramer (8), each mouse received 3 strokes of the brush with the carcinogen on a large unepilated area. Since baby mice are hairless, the single stroke given to them in our experiments is comparable to the 3 strokes by these authors to the older mice. Probably our new-born mice received per unit area an amount of the carcinogen equivalent to those painted in the unepilated condition.

How, then, are we to explain the fact that cancer did not develop in the epidermis of the new-born mice? Failure to respond by cancer formation to a dose of carcinogen which appears to have been adequate for older mice may have been due to one or more factors. Their epidermis was thicker than that of older mice and this circumstance may have prevented its entry. Their hair follicles were few in number with only occasional hairs reaching the surface and their sebaceous glands were few, small and incompletely developed, which might result in the portals of entry supplied by these structures for the carcinogen being less open than in older mice.

 Mention should be made, also, of similarity between epidermis of new-born mice and epidermis of adult mice repeatedly treated with methylcholanthrene. Both are thick, keratin-coated and deficient in sebaceous glands. It would appear that the sebaceous glands, when present, have a conditioning effect upon the epidermis, and that the decreases in the calcium, iron, copper, zinc, and other constituents in hyperplastic epidermis (1) are definitely associated with their disappearance. The chemical alterations induced throughout the hyperplastic stages are maintained in the absence of these dermal structures. It is apparent, therefore, that the role of sebaceous glands and hair follicles in skin carcinogenesis is a very important one.

**SUMMARY**

The epidermis of new-born mice (2 to 10 hours after birth) has been found refractory to a single application of methylcholanthrene. The hair follicles and sebaceous glands at this time are still rudimentary, becoming almost completely developed at 72 hours after birth. The importance of sebaceous glands and hair follicles in the development of skin cancer is discussed, and the conclusion is reached that their condition in new-born mice is related to the resistance of such mice to the carcinogenic effect of methylcholanthrene.
REFERENCES

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