Editorial

Vitamin A Nutrition and the Skin

THE means of detecting nutritional deficiency in man are primarily three: (1) the measure of intake of the nutrients; (2) evidence of disturbed metabolism and function of the nutrient; and (3) physical changes in the tissues of the body resulting from the deficiency. Of these, the first is predictive and requires final confirmation by the other two. The second is essentially biochemical and physiologic, functional in nature, and in some instances a forerunner and producer of the physical changes comprising the third. Because of the many unknown variables (even in the meticulous study of a single subject) the first is the least accurate and less susceptible to accurate correspondence with the conditions disclosed by the other two methods. Although there are obvious factors which can cause failure of close agreement between the chemical and physical findings, the most obvious of which is the degree of functional change needed to produce physical change, there often are discrepancies which are not only difficult to explain but also interfere greatly with the interpretation of physical signs encountered in the examination of subjects.

One of the best examples of such a situation is in relation to vitamin A. Aside from night blindness, the accessible morphologic and structural changes usually found on physical examination and attributed to vitamin A deficiency are xerosis, xerophthalmia and keratomalacia of the eye, Bitot's spots, and xerosis and follicular hyperkeratosis of the skin. Of these I would like to discuss follicular keratosis and its relation to vitamin A intake and to biochemical findings in respect to its significance as evidence of vitamin A deficiency. Although some little dispute exists as to the meaning of Bitot's spots, this is less in doubt, and xerophthalmia and keratomalacia are generally accepted as expressions of vitamin A deficiency.

Before discussing the correlation or lack of correlation of follicular hyperkeratosis with biochemical findings in vitamin A deficiency, it is necessary to resolve some of the confusion which exists concerning this lesion itself. Part of the confusion is the result of misunderstanding and misinterpretation of the several terms which are used in the descriptive identification. Depending on the severity and extent of the lesions, the knowledge, experience and ideas of the examiner, the terms used range from xerosis to folliculosis, to keratosis, to follicular keratosis, to perifollicular hyperkeratosis. Other common descriptive terms are "crackled skin," "toadskin," "goose flesh" and phrynoderma.

For the purpose of clarification, let us accept for the present the description and definition of the gross and microscopic lesions of the skin given by Frazier and Hu[1] as characteristic of follicular hyperkeratosis. It is recognized that objections may be raised to the approval of this as an acceptable definition of the lesions under discussion, but this will be primarily due to the occurrence of early or minor degrees or minor modifications or variations of the lesion which have confused the situation. If moderate to well developed changes of the type described by Frazier and Hu are accepted as representing the characteristic lesion, the following discussion will be more clearly defined.

Despite the occurrence of these gross and microscopic findings under conditions which Frazier and Hu and later others related to vitamin A deficiency, increasing doubt of such a causal relationship has arisen. The reasons for this are several. In part it is the result of

semantic difficulties and failure of observers and investigators to agree on characterization of the lesion and even the names given to it. In this connection it should be admitted and emphasized that these changes in the skin may result from other causes and, even though they may be caused by vitamin A deficiency, are not specific for it. (On the other hand, this does not mean they cannot result from vitamin A deficiency.)

However, the principal objections to the view that this lesion of the skin is the result of vitamin A lack are (1) failure of positive correlation of the occurrence of this lesion of the skin with apparent levels of vitamin A and carotene intake and the amount of vitamin A and carotene in the blood and vitamin A in the liver and (2) failure, according to some reports, of the lesion to respond to treatment with vitamin A.

There are several explanations which can be offered to refute these arguments against vitamin A deficiency as the cause of the lesions of the skin under consideration, some of which have been well recognized and others which have not. First, as already stated, is the lack of agreement as to just what constitutes the lesion under discussion. Since the lesion can be expected to vary somewhat depending on the degree of severity or stage of the process, some confusion might be expected. Also, as Frazier et al.[2] have shown, the changes in the skin presumably produced by vitamin A deficiency vary with the age of the subject from infancy to adulthood. This, when combined with inexperience in the findings and interpretations of an examination of the skin, makes confusion and disagreement understandable.

Many recent studies have dealt with mild changes in the skin in which there may be some doubt as to the correctness of the diagnosis. In this connection it is worth while pointing out that in many studies in which vitamin A was reported to cause improvement or cure, the follicular hyperkeratosis was moderate to severe, extensive in distribution and presented no doubt as to the real diagnosis. For examples see the photographs of the subjects in the report of Frazier et al.[2]

More recently, it has been argued that the administration of fatty acids themselves are able to relieve the skin changes ascribed to a deficiency of vitamin A and the earlier reports of success with vitamin A have been explained on the basis that at those times vitamin A was available only in an oily menstruum (fish oils).[3] On the other hand, failure to improve or cure the lesions with the administration of fatty acids alone has been reported.[4] In some populations in which follicular hyperkeratosis has been found, the diets have apparently contained a sufficiency of fatty acids.[5]

There are other relations to fat and fatty acids which must be taken into consideration. Fat is well known to influence the absorption of vitamin A and, in particular, carotene. If one takes into consideration the range of severity of the skin lesion from borderline to marked, and the range of intake of vitamin A from barely sufficient to completely insufficient, the possible indirect effect of fat is clearly apparent. The same may be the case with protein, a low intake of which has also been suspected of being a factor in some way leading, in some relationship to vitamin A, to the production of follicular hyperkeratosis. Diets low in protein are notorious in countries in which vitamin A is also deficient.

Poor agreement between the occurrence of perifollicular hyperkeratosis and the intake of vitamin A and its level in the blood is well documented. In particular the recent surveys of populations conducted by the ICNND repeatedly have been shown a general failure of reasonably close correlation of these two criteria of vitamin A nutrition.[6]

There are several explanations of this discrepancy, none of which is convincing as an all-inclusive cause. Interference with the absorption of vitamin A and carotene has been mentioned as a possible explanation for the lack of correspondence between apparent intake and the occurrence of skin lesions. Recently it has been recognized that many carotenoids giving a positive reaction in the chemical tests for carotene are not true precursors of vitamin A and give false values for the intake or blood levels of carotene, and hence vitamin A.

Less frequently appreciated is the time relationship between the course of the skin lesion and the intake or blood levels of the vitamin. The lesion of the skin is a physical, anatomic change. It takes a period of weeks to appear and may take even longer to disappear under treatment or in spontaneous response to natural changes in the diet. On the other hand, the intake of vitamin can vary overnight or, more practically, in a period of days. Similarly the blood level of vitamin A can be increased rather rapidly, and it may be that in instances of borderline storage (on chronically low intakes) the level can drop relatively rapidly. Thus it is entirely possible, theoretically and probably in fact, to have *no* changes in the skin when the intake and blood levels are low, and well defined changes when the former are normal or high. In looking for correlations, these time relationships are important. However, in recent tests of the effect of fats and/or vitamin A on the skin lesions, adequate control of this factor was employed. All in all, when the evidence for and against vitamin A deficiency as a cause of hyperkeratosis follicularis is balanced, it must be concluded that the question remains unsettled.

Until recently the relation of vitamin A to perifollicular hyperkeratosis (and abnormalities of epithelium generally) has been generally thought of only in terms of intake, absorption, body stores (primarily liver) and concentration in the blood. Indeed it has been the failure of the last to correlate with the lesions of the skin that has cast the greatest doubt on vitamin A deficiency as a cause of the latter. Relatively little attention has been paid to the more detailed metabolism of the vitamin, its deposition in tissues other than the liver, its excretion, destruction or transformation into related forms. Neither has the fate of carotene in the body been fully determined.

Actually only a small part of the body store of vitamin A is found elsewhere than in the liver. Despite its apparent important role in the metabolism of the epithelial cells, little can be demonstrated in these tissues. Little is excreted. Some is destroyed in the function of visual adaptation to light. As would be expected from the occurrence of normal or near normal blood levels in patients with skin lesions, biopsies of the liver have revealed a normal concentration and distribution in that organ in patients with keratosis follicularis.[7]

Recently, more attention has been directed to the occurrence of vitamin A and carotene in the skin. Only minute amounts of carotene and vitamin A are found in normal skin and sebum by chemical tests and neither have actually been demonstrated by delicate (sensitive) fluorescent histologic technics.[7] However, Greenberg, Cornbleet and Demovsky,[7] by the intracutaneous injection of a water-solubilized suspension of carotene in the form of carrot oil, have demonstrated with fluorescent microscopy the presence of vitamin A in the sebaceous glands within thirty minutes of the injection; somewhat later it was found in the sebum in the sebaceous duct emptying into the hair follicle, in the depression at the follicle orifice and in a thin layer of the superficial epidermis. Later many yellow gold flecks, presumably carotene, were seen in the sebaceous gland cells which had contained vitamin A, but not in the fatty droplets or in the sebum.

Topical application followed by brisk rubbing resulted in the presence of much smaller amounts of carotene and vitamin A in the respective locations.

These investigators hypothesize that normally the same situation exists; namely, the conversion of carotene to vitamin A in the sebaceous cells and later elsewhere, except that the amount of vitamin A is much less and is not detectable chemically or histologically.

These findings raise the question whether or not the function of vitamin A in the skin operates by a mechanism which is independent of the storage of the vitamin in the liver, its concentration in the blood and its metabolism in other situations. That it is entirely independent of the amount in the plasma seems unlikely if one accepts the benefit apparently obtained when the blood values are low and relatively large doses of vitamin A are given. On the other hand, it is conceivable that the ordinary mode of action is conversion of

carotene to vitamin A *in situ* in the cells of the sebaceous gland under the influence of some other agent (as in the conversion of provitamin D to the active vitamin under the action of ultraviolet light). Under these circumstances it is possible that the lesions of the skin are a manifestation of vitamin A deficiency but mediated through a mechanism involving other factors which at present are unknown.

Recent speculation involving vitamin A in the synthesis of glycogen[7,8] and relating it through glycogen to the mitochondria and the process of mitosis are intriguing in the light of the changes which have been observed experimentally in the skin in a recovery from the lesions of vitamin A deficiency. It takes no stretch of the imagination to link them with the concept of vitamin A's function of preserving the health of the cell and not participating in its function. However, such speculations should not substitute for an intensified study of the metabolism of vitamin A and carotene in the skin itself.

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