CUTANEOUS LESIONS ASSOCIATED WITH A DEFICIENCY IN VITAMIN A IN MAN*

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During the winter and spring of 1928 and 1929 many cases of keratomalacia were seen in the hospital of the Peiping Union Medical College. Most of these occurred among Chinese soldiers, garrisoned in villages in the vicinity of Peiping, who had subsisted for various periods of time on inadequate diets, deficient particularly in animal proteins and fats.

In addition to the classic signs of keratomalacia, the majority of these patients manifested certain cutaneous lesions of such uniform character as to suggest their being of more than coincidental significance. This assumption was given further support by the fact that they were analogous histologically to the pathologic changes in the eye and in other tissues of animals and man following deprivation of fat-soluble vitamin A. As a rule the lesions of the skin preceded the appearance of keratomalacia and responded to dietary therapy simultaneously with the ocular lesions, although much more slowly. None of the patients showed signs of beriberi, pellagra or scurvy.

The fifteen cases constituting the material on which this report is based were first studied in the ophthalmologic clinic, where the diagnosis made was typical keratomalacia of from two weeks to three months’ duration. In reporting observations on these and earlier cases, Pillat emphasized the identity of the ocular lesions with those found in infants and children under similar conditions of malnutrition. He also called attention to the generalized manifestations of deficiency in vitamin A among these patients, including involvement of the skin. Cutaneous lesions have hitherto not been described in connection with nutritional ophthalmia, although Bloch observed a dry, shriveled, scaly condition of the skin among infants affected with the disease, and Wilson

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and DuBois, among others, reported in association with keratomalacia a condition somewhat similar to that not infrequently present in patients with severe malnutrition without signs of xerophthalmia.

All fifteen patients of this series were soldiers, with the exception of one, a pedler, and were admitted to the hospital during February, March and April, 1929. Their ages ranged from 19 to 33 years, the majority being in the early part of the second decade. Each gave a history of having lived on a poor and monotonous diet for periods of from six months to one or more years. The diets consisted chiefly of rice, maize, millet, occasionally a poor grade of wheat flour, white cabbage and salted vegetables. Meats, eggs and green vegetables were rarely eaten; a few patients had never had these articles of food, and others had had them not more often than once a month. Usually the quantity of food was sufficient, but there is reason to believe that the diet in many cases was much poorer both in quality and amount than was reported. The better paid officers who were able to supplement the regular ration were not affected by the disease.

In this connection it is well to call attention to the main features of the ordinary Chinese diet. In an extensive study of the food-stuffs utilized in the common diet of several groups of the Chinese middle classes in Peiping, Wu and Wu have observed that the average diet is adequate in caloric value but below the optimum in proteins and in vitamins A and D, and low in calcium and phosphorus. Vitamins B and C are probably present in adequate amounts. Practically all the fats and oils used for dietary purposes are of vegetable origin; milk, butter and other dairy products are almost never used. It is clear, therefore, that even under ordinary circumstances of civil life, the Chinese dietary is low in vitamin A.

**History of Symptoms**

The natural history of the development of the lesions of the skin was as follows: Several weeks prior to the onset of the ocular symptoms, the skin became dry and slightly rough. Subsequently, spinous papules appeared at the sites of the hair follicles, first involving the anterolateral aspect of the thighs and the posterolateral aspect of the upper part of the forearms. The eruption gradually spread to the extensor surface of both upper and lower extremities, the shoulders and the lower part of the abdomen, and to a less extent to the chest, back and buttocks. In some cases the skin was darker than normal, turning a dull slate color. There was absence of visible sweating, and the

articul ar folds, which are usually moist, were dry and covered with closely adherent, delicate scales. The normal markings on the surface of the skin were exaggerated in places, giving it a finely wrinkled appearance.

The follicular papules varied in size according to the stage of development and the degree of perifollicular infiltration. The largest were approximately 5 mm. in diameter, hemispherical, rather firm and usually deeply pigmented. The hyperpigmentation extended in a narrow zone beyond the base of the lesion. Each papule held in its apex a keratotic plug which in most instances projected above the surface of the lesion as a hard spinous process, or was covered by a loosely adherent scale that bridged the occluded follicular recess. When expressed, the plugs left gaping central craters in the summits of the papules. The eruption was usually abundant and symmetrical, but occasionally the lesions were few and widely scattered, or more rarely, restricted to a single area.

In five cases there was a marked tendency to pustulation, usually on the extremities, leading to the formation of ecthymatous ulcers. Although as a rule there were not over four or five such ulcers, in one case they were so numerous and so sharply formed as to resemble secondary ulcerative syphilids. Cultures of Staphylococcus aureus and Streptococcus hemolyticus were obtained from the ulcers in several cases. Scabies was a complicating infection in four instances.

Large numbers of conspicuous comedones were present on the face at the sites commonly involved by acne. In one case, that of a patient 28 years of age, these were the only lesions of the skin besides the general xerosis. A few acneiform papules were also distributed over the same areas. Unlike acne, the skin of the face was dry and without any sign of excessive sebaceous secretion. Occasionally it had a puffy appearance suggesting edema.

The hair was dry but otherwise normal. No remarkable changes in the nails were observed, although two patients had slight transverse ridging of a single nail on each hand. Other than a slate-colored pigmentation of the buccal and lingual mucosa in one patient, and a mild atrophic rhinitis in another, the mucous membranes of the oral and nasal cavities showed no visible variation from the normal.

Examination of the nervous system did not reveal any significant abnormality, and there was no instance of cardiovascular disease in this group of cases. Two patients had pulmonary tuberculosis, and three an acute tracheitis or bronchitis. One of the patients with pulmonary tuberculosis was thought also to have tuberculosis of the intestine. This was the only case in which there were gastro-intestinal symptoms.
Ova of *Ascaris* were found in the stools of eight patients, ova of hookworm in five and cysts of *Entamoeba histolytica* in one. Four of the fifteen patients were apparently free from intestinal parasites.

Chemical and microscopic examination of the urine gave negative results, with the exception of the patient with advanced tuberculosis, whose urine contained a trace of albumin. This patient also had edema of both feet and ankles of two months' duration, and a severe secondary anemia. Four other patients had anemia of moderate degree. The Wassermann and Kahn tests of the blood gave positive results in two cases, neither of which showed active manifestations of syphilis.

**RESULTS OF TREATMENT**

After admission to the hospital, the patients were observed for periods of from one week to two months. During this time they were fed a well balanced Chinese diet, chiefly vegetarian, to which were added liver, butter and eggs Cod liver oil was administered daily in quantities of 30 cc. Each patient also received one lemon a day. In order not to modify the cutaneous lesions, no local medication was employed, and baths were restricted to the minimum required for cleanliness.

Under this regimen there was rapid improvement in the keratomalacia, although there was but little restoration of vision in cases of advanced degeneration of the cornea. In the cases in which the patient was under dietary treatment for two weeks or more, moisture of the skin was definitely increased, and in several visible sweating was observed. Ulcerative lesions healed promptly and completely. The keratotic papules decreased in size more slowly, and many of the central cornified plugs were extruded. In the cases in which the eruptive lesions completely disappeared, delicate atrophic scars, surrounded by a zone of brownish pigmentation, remained at the follicular orifices. Two months was the longest period any patient was under observation, which was not sufficient time for the skin to regain its normal appearance and texture.

Histologic examination of the cutaneous lesions in various stages of growth showed the pathologic process to be essentially one of hyperplasia and hyperkeratinization of the epithelium of the epidermis and hair follicles, with associated metaplasia of the epithelium of many of the sweat ducts to the keratinizing type, degeneration of the glandular structures of the skin and infection.

The horny layer was moderately hypertrophied and of homogeneous structure. The mouths of the hair follicles were greatly dilated by dense masses of horny substance arranged in more or less concentric lamellae. These either projected from the follicles or were flush with
the surface and covered by a continuation of the horny layer. Nuclei were not present in any of the cornified cells. Coiled atrophic hairs were found in some of the follicular plugs. In the region of the hair follicles, and in other areas of epithelial hyperplasia, there was a definite increase not only in the amount of intracellular pigment but in the number of pigment-bearing cells. Very few chromatophores were found in the corium.

![Fig. 1.—Area of skin on the thigh showing follicular papules with projecting horny spines and hyperpigmentation.](image)

The lower part of the hair follicles was atrophic, and in some places the tip was completely severed from the rest of the follicle by rather dense connective tissue. On the study of serial sections, the detached segments were found to be occasionally cystic and filled with desquamated epithelial cells. Surrounding such follicles, and to a less extent those in which the keratosis was minimal, were fairly well circum-
scribed areas of loose reticular tissue containing lymphocytes, fibroblasts and occasional endothelial cells. Numerous blood capillaries were present in these areas.

In the sections examined no normal pilosebaceous structure was seen, and only a few remnants of sebaceous glands were found in the midst of the inflammatory zones. The mouths of many of the sweat ducts were dilated and occluded by conical masses of keratinous material. In places the epithelial lining of the upper part of the ducts was increased in thickness and was desquamating. The epithelial cells of the tubules were frequently shrunken and irregular, or the lumen of the glands was dilated and the epithelium greatly compressed.

Pustulation occurred primarily in the follicular plugs and from there extended into the perifollicular tissues. The earliest sign of

Fig. 2.—Same area as that in figure 1, showing residual pigmentation and scars at follicular orifices two months after dietary therapy was commenced. The large scar at the lower part of the picture followed a biopsy wound.
ulceration was found in the walls of the distended hair follicles. Hemorrhage did not occur about the follicle or elsewhere in the skin.

A comparison of the changes in the skin of these patients with those in the eye and related structures in human and experimental cases of keratomalacia is of particular interest and offers strong presumptive evidence of the specific nature of the cutaneous lesions. In keratomalacia, according to Mori and others, there is cornification of the conjunctival and corneal epithelium and, in the later stages, hyperplasia of the epithelial cells of these structures. The keratinizing process extends into the ducts of the para-ocular glands, and the acini may undergo complete disintegration with conversion of the gland into a series of cavities lined by stratified epithelium and filled with desquamated cells. There is an accompanying element of infection, which in the terminal stages of the process constitutes a major factor in the production of corneal disintegration.

In a study of the pathologic changes in rats fed on diets deficient in fat-soluble A, Wolbach and Howe concluded that the specific morbid process is a widespread keratinization and replacement of many different epithelia by stratified keratinizing epithelium, which they observed in various parts of the respiratory and alimentary tracts, in the eyes and para-ocular glands and in the genito-urinary tract. They were of the opinion that the loss of secretory function in various glands throughout the body and the distinctive changes observed in other tissues were due to the mechanical factors consequent to the formation and retention of the desquamated epithelial cells.

From the study of the patients observed in Peiping with respect to the sequence in which the various pathologic changes occurred in the skin, it appears that the primary process was an excessive epithelial keratinization, resulting in the mechanical occlusion of hair follicles and sweat ducts, and in secondary degeneration of the sebaceous and sweat glands. Necrosis was a terminal event presumably dependent on the decreased resistance of the tissues to infection.

Cutaneous lesions essentially identical to those of this series of cases have been described by Nicolau, Willshire and others as a manifestation of scurvy. In correlating changes in the tissues with deficiency in a specific vitamin it should be remembered that single dietary faults rarely occur alone, as a diet that is lacking in one factor

is generally deficient in others. It is doubtful whether an uncomplicated deficiency disease ever exists in man, and it is only by carefully planned experimental diets that a specific deficiency disease can be produced in animals.

In view of such facts, one may question the justification of assuming any causal relationship between the deficiency of vitamin A in the diets of the patients at Peking and the cutaneous lesions; nevertheless, the essential changes in the skin, when compared with those produced in experimentally controlled cases of disease due to deficiency in vitamin A were of such nature as to suggest their being a part of this specific syndrome rather than of that produced by deficiency in other vitamins.