A CASE OF ARSENICAL KERATOSIS FOLLOWED BY CANCER.

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[With Special Plate.]

THE late development of epithelioma on a pre-ex's'ing basis of hyperkeratosis produced by prolonged arsenical medication is a rare phenomenon, and MacLeod,¹ in his textbook of skin diseases, states that only about fifteen authentic cases have been recorded in the literature. The part played by arsenic in the production of cancer has been disputed in some quarters,² on the ground that malignant disease is apt to develop in patches of psoriasis, etc., in which the drug has never been administered. If this objection be conceded, there still remain cases in which it was given over a prolonged period for conditions other than dermatological and in which epithelioma of the skin subsequently occurred.³ The argument is really beside the point, for most authorities are now agreed that the etiology of such growths is multiple, and that arsenic may be regarded as a predisposing factor of malignant degeneration, in virtue of its property of producing hyperplastic growth in surface cells, which are particularly exposed to traumatic and irritating influences, such as sunlight, variations of temperature, dust, friction, and recurring physical stimuli of all kinds.

Carcinoma linguae, from the etiological point of view, is more strictly akin to "arsenical" cancer than are "tar" or "x-ray" cancer, for in these the predisposing factors are local, while in the former two they may fairly be regarded as systemic (that is, syphilis, which produces leucoplakia, and arsenic, which produces an almost identical histological condition—hyperkeratosis). The credit of priority in the discovery of the relationship under discussion belongs to Jonathan Hutchinson, and the evidence which he first brought forward in 1887⁴ has since accumulated and received confirmation from the pens of such well-known dermatologists as Dubreuilh,⁵ Darier,⁶ and Hartzell,⁷ while, among the surgeons, Bland-Sutton⁸ published a case in this JOURNAL as recently as 1916.

The possibility of an impending increase in the incidence of the disease, as a result of the world-wide injection of arsenical compounds for syphilis, yaws, etc., has been raised by K. Ullmann.⁹ Salvarsan dermatitis, however, is an acute eruptive condition which tends to a *restitutio ad integrum*, and does not go on to keratoderma, which is the necessary preliminary to epithelioma.

Most of the cases of arsenical keratosis reported have followed the oral administration of the drug, but the dosage and the duration of treatment were by no means constant. In the cases published by Dubreuilh⁵ a keratosis of the palms and soles was noted as early as six months from the date of commencing the treatment, but the average incidence of cutaneous change is about two years, and the usual dose given has been from 15 to 30 minims of Fowler's solution thrice daily. The same author states that gastric and intestinal intolerance are danger signals, and that the occurrence of pigmentation, which usually precedes the development of keratosis by some weeks, is an absolute indication for cessation, or at least a prolonged intermission, of the drug. My own case conforms in every particular with the classical picture first enunciated by Hutchinson.

The patient, aged 40, who was referred to me by Dr. H. C. G. Pedler (London), had a more or less generalized psoriasis at the age of 12, and as the eruption was controlled by arsenic he persisted with its administration, and without further medical advice, for seven years. By this time (1901) pigmentation of the abdomen and warty growths on the palms and soles had developed; and his father consulted Sir Malcolm Morris, who at once recognized the cause, and forbade any further treatment with arsenic in any form. In 1905 he consulted the late Sir Lauder Brunton for oedema of both feet, one wrist, and the dorsum of the left hand.

In 1914 (that is, fourteen years after cessation of the drug) the hyperkeratosis on palms and soles was as obvious as ever, and a small painless ulcer made its appearance in or around one of the warty growths on the outer border of the right sole. The ulcer persisted, and was not regarded as serious apparently, for from February until July of the current year (1922) he received treatment by ionization in a country town. The size and appearance of the neoplasm, when I saw him on August 16th, is so well illustrated in the accompanying photograph (Special Plate, Fig. 1)

as to need no further description. The associated plantar and palmar keratosis is also clearly depicted (Figs. 2 and 3), and it only remains to say that the skin as a whole was remarkably dry, free from any abnormal pigmentation, showing a trace of psoriasis on the knees, elbows, and chest only. A slight degree of oedema, which pitted on pressure, and was therefore subcutaneous and not confined to the epidermis, was noted on the dorsal aspect of both feet.

The right leg was amputated through its lower third by Mr. T. T. Higgins on August 18th, and recovery was uneventful.

As in a somewhat similar case reported by Sir John Bland-Sutton,⁷ no glands, either in the popliteal space or in the groins, could be regarded clinically as containing malignant deposits. Bland-Sutton writes (loc. cit.): "It is said this form of cancer does not reproduce itself in the lymph nodes."

The histological appearance of the tumour is reproduced in the microphotographs (Figs. 4 and 5), and I am greatly indebted to Dr. G. W. Nicholson, of Guy's Hospital, for the following note on its structure:

"1. A squamous-celled carcinoma with extensive keratinization and formation of cell nests. The stroma is loose and oedematous, and contains numerous areas of inflammatory reaction. At its periphery the section is covered by hypertrophied epidermis, with lengthened irregular papillae. Its centre is ulcerated, the base of the ulcer being occupied by granulations, most of which possess a covering of squamous epithelium obviously derived from the cells of the neoplasm itself. There is extensive infiltration of the cutis and subcutaneous tissues by columns of new growth, some of which are definitely within lymphatics.

"2. A section through a keratodermic nodule shows a strip of skin with irregular papillae, a well-marked stratum granulosum, and a greatly hypertrophied stratum corneum. The cutis and superficial layers of the subcutaneous tissue are fibrotic, the walls of the small blood vessels much thickened, and the sweat glands and their ducts small and atrophied."

The presence of thickened blood vessels noted by Dr. Nicholson affords a possible clue to the persistent oedema of the feet, and the paucity of sweat glands and the atrophy of their ducts doubtless account for the general xeroderma. The thickened blood vessels—the Wassermann reaction being negative in this case—may be presumed to have followed a preceding endarteritis, such as has often been described in the *post-mortem* records of the brains from fatal cases of salvarsan poisoning. If this theory is correct, it is not difficult to explain the oedema which is the result of the transudation of lymph through endothelium damaged or paralysed by the action of a protoplasmic poison.

Summary.

1. The case illustrates the danger of prolonged arsenical medication by the mouth.

2. Where keratosis has occurred as a result of this the drug must be immediately suspended, and every effort made, by keratolytics, x rays, etc., to destroy the small warts and check their continued formation, and their pronounced tendency to spontaneous degeneration and necrosis.

3. For a growth of the size depicted there is, of course, no effective treatment other than amputation. The site of the removal will depend on the situation of the tumour, the presence of infected glands, and other considerations of surgical importance.

For small growths of recent appearance, without evidence of gland infection, the treatment by x rays or radium should receive a trial. Local excision is not recommended.

REFERENCES.

- ¹ MacLeod: *Diseases of the Skin*, 1920. ² De Silva: *Med. Press and Circular*. ³ Dubreuilh: *Annales de Derm. et de Syph.*, 1897, p. 65. ⁴ J. Hutchinson: *Transactions of the Path. Soc.*, 1887-8. ⁵ J. Darier: *Mélanodermie et hyperkératose d'origine arsenicale*, Soc. de Derm., 1902. ⁶ Hartzell: *Amer. Journ. Med. Sci.*, September, 1899. ⁷ J. Bland-Sutton: *BRITISH MEDICAL JOURNAL*, 1916. ⁸ K. Ullmann: *Wien. klin. Woch.*, June, 1917.

THE first course of lectures under the Charles E. Dohme Memorial lectureship was given at the Johns Hopkins Hospital, Baltimore, on October 10th, 11th, and 12th, by Dr. H. J. Hamburger, professor of physiology at the University of Groningen, Holland. The lectureship was established in memory of the late Mr. Charles E. Dohme, a well-known chemist of Baltimore, and its purpose is to promote the development of a more intimate relationship between chemistry, pharmacy, and medicine. The lectureship, which is of the annual value of 1,000 dollars, is open to scientists from any part of the world, and the selection of a lecturer is made by a committee representing the departments of pharmacology, chemistry, and medicine of the Johns Hopkins medical school.

FIG. 1.—Plantar aspect of squamous epithelioma and hyperkeratosis, following arsenical administration.

FIG. 2.—Keratosis plantaris (arsenical).

FIG. 3.—Keratosis palmaris (arsenical).

FIG. 4.—Microphotograph (1/3 Zeiss objective). Squamous-celled epithelioma with cell nests, and neoplastic endolymphatic extension, etc.

FIG. 5.—As Fig. 4 (1/7 Zeiss objective). Note cell nest.