ACANTHOSIS NIGRICANS AS AN INDICATION OF INTERNAL MALIGNANCY*

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There is probably no clinical picture of cutaneous disease more striking and impressive than that presented by the typical case of *acanthosis nigricans*. Because of its rarity, however, and the dominant character of its skin symptoms, interest in and knowledge of this disease are practically limited to dermatologists. Yet it possesses certain features which render some acquaintance with it of importance to the general profession, and it is toward these particular features, rather than toward detailed consideration, that attention is here directed.

The disease is characterized by the definitely regional and symmetrical development of varying degrees of pigmentation and of multiple hard and soft papillary growths, the sites of predilection for these changes being the sides and back of the neck, the face, the axillae, the genitocrural region, the backs of the hands, the palms, the mucous membranes of the mouth and the vulva, and at times the orifices of the ears, nose and eyes.

More important, however, than the interest attached to it as a rare and striking disease of the skin, is its very frequent association with some form of internal malignancy. So well established is this association that *acanthosis nigricans* occurring in an adult is regarded by dermatologists as definitely indicating the presence of an internal malignant process

even though it cannot be clinically demonstrated.

Pollitzer, who, coincidentally with Janovsky, originally described it, gave a most comprehensive review of the subject before this section six years ago,¹ explaining in detail its significance and the importance of its early recognition. The desirability, however, of keeping before the profession facts of any kind, even those rarely elicited, which will assist in the earlier recognition of malignant disease, seems sufficient justification for again directing attention to the characteristic features of *acanthosis nigricans*, emphasizing its relation to internal malignancy and recording a typical case.

CLINICAL FEATURES

Two distinct forms of the disease are recognized: the adult or malignant, characterized by some serious internal disorder, particularly malignancy, short duration, intensity, and wide spread of the skin symptoms, which are at times marked by exacerbation and remissions, even to complete disappearance; and the juvenile or benign, characterized by little or no disturbance of the general health, less marked development and spread of the skin symptoms, which after a short time became stationary and persistent.

The mode of onset varies, in some cases intense itching and pigmentation about the neck and face being the first symptom; more commonly the first evidence has been an eruption of common warts over the backs of the hands and the forearms. Further development is usually rapid, involving symmetrically the regions above mentioned. The papillary growths vary within the widest limits, from small hard warts, the size of a split pea, on the back of the hands, to large soft condylomatous masses in the axillae or groins and long filiform projections on the tongue. The palms and soles may be involved in a diffuse horny thickening, causing much limitation of movement and giving the hands a claw-like appearance; the nails show nutritional disturbances and the hair may be similarly affected.

Quite as important as the papillary changes is the pigmentation, which is a most conspicuous feature of the disease, varying from a dirty grayish discoloration through shades of brown to black. It may precede the appearance of papillary overgrowth and affect areas in which the skin is only thickened and presents the appearance known as lichenification. The distribution of the two processes is, however, ultimately the same, except that the mucous membranes

are never involved in the hyperpigmentation.

The development of warty and condylomatous masses on the lips, within the cavity of the mouth and along the ciliary borders causes the patient great discomfort and distress and constitutes a most striking feature of the disease; but with the exception of itching, there are no subjective sensations complained of.

The time occupied in the development of such symptoms as above outlined is from a few months to two years, the course usually being terminated by the associated malignant process. The juvenile form, however, as previously stated, may persist indefinitely without untoward results.

In 1909 Pollitzer was able to collect from the literature 52 cases and since that time, about 20 additional cases have been reported, but this certainly does not represent the entire incidence of the disease. Of Pollitzer's list of 52 cases, 35 were of the adult type, the patients being over 20 years of age; in 28 cases, or 80 per cent., the presence of malignant disease could be definitely shown or was highly probable; and the proportion of malignant cases among those reported since that time would tend to make the percentage higher rather than lower. The organs affected have been in their order of frequency, the alimentary tract, the uterus, the breasts and in one instance, recently reported, the lung.²

A majority of the cases have occurred in women at that period of life in which malignancy is most prone to develop; that is, between 35 and 50. A typical malignant case, however, has been observed, associated with a malignant uterine neoplasm (*decidua malignum*), in a girl of 19.³ The appearance

Fig. 1.—Papillary excrescences on backs of hands and extensor surfaces of arms in a case of *acanthosis nigricans*.

1. Pollitzer, S.: *Acanthosis Nigricans a Symptom of a Disorder of the Abdominal Sympathetic*, THE JOURNAL A. M. A., Oct. 23, 1909, p. 1369.

2. Petrini de Galatz: *Ann. de dermat. et de syph.*, 1914, No. 6, p. 331.
3. Spietschka: *Arch. f. Dermat. u. Syph.*, 1898, xlv, 247.

of the characteristic features of the disease may precede by some months, or even longer, the development of symptoms referable to the associated internal disorder. Klotz' case⁴ is an example in which a sarcoma in the pelvis was not discovered for almost two years after onset of the skin disorder. To this list of the adult malignant form, I wish to add the following.

REPORT OF CASE

Patient.—Mrs. T., aged 54, referred by Dr. J. N. Hall, Jan. 21, 1915. Previous history unimportant, except for indigestion during many years; two years ago sudden pain in stomach and sharp hemorrhage necessitated operation and excision of an ulcer, since that time no digestive disturbance aside from constipation. Has three children, never any pelvic trouble.

Present Illness.—This began eight months ago; first noticed an intense itching over abdomen, next sudden appearance of numerous warts over backs of hands and forearms, soon followed by discoloration about neck and face. Four months ago growths began to appear on tongue and palate; since that time progress has been very rapid.

Examination.—General condition good. Heart, lungs and kidneys apparently normal. Blood pressure 120. The backs of the hands and the extensor surfaces of the arms (Fig. 1) are occupied by innumerable hard papillary excrescences of all sizes up to that of a pea; about the wrists the skin is thickened and fissured and the affected parts are here a dark grayish color. The palms are greatly thickened and almost horny, giving to them a translucent yellowish hue. The axillae are deeply pigmented and there are many soft filiform warts. The sides and back of the neck and the shoulders show pigment changes, ranging from gray to a sooty black, and there are numerous papillary growths over the whole of this region (Fig. 2). The face shows pigmentary changes and few warty growths on the forehead; there is also a growth of coarse white hair. The ciliary borders are granular and there are many large soft papillomas. The auditory canals and the nasal orifices also are surrounded by a rim of small filiform growths. The mucous membrane of the mouth, however, is the site of the most extensive changes. The vermilion borders of the lips are wholly occupied by small and large papillary excrescences; the dorsal surface of the tongue is covered by long filiform projections; the hard palate is completely filled in by a dense condylomatous mass until it is level with the superior teeth, the outer surfaces of the gums above and below are involved and a condylomatous growth protrudes from each interdental space. The inner surfaces of the lips and cheeks are but slightly affected and the fauces and pharynx are entirely spared.

The genitocrural region is not involved in the papillary overgrowth, but is deeply pigmented. The scalp is dry and scaly and the hair falling rapidly.

With such a clinical picture, a diagnosis of acanthosis nigricans was made, and in view of the history of ulcer of the stomach, a cancer of that region was predicted. A most careful examination by Dr. Hall, however, failed to reveal evidence of any intra-abdominal growth; nevertheless we felt justified in having the abdomen opened, and this

was done by Dr. Freeman on January 27. Much to our chagrin, after a most careful search, absolutely nothing was found in the abdomen, except a single gallstone of very unusual shape. For a few weeks following the operation, the patient seemed much better, and hope was entertained that removal of the gallstone would be of benefit, but soon the lymphatic glands below the clavicle on each side began to enlarge, indicating, in our belief, the existence of a malignant process somewhere within the cavity of the chest. A careful roentgenographic examination failed to reveal anything in the chest, but the further progress of the case seems, notwithstanding, to point in that direction. Since glandular involvement has increased, the patient has become more cachectic, and no evidence has developed of difficulty with the stomach, which would certainly have occurred had that organ been the seat of a progressive malignant disease.

THEORIES AS TO ETIOLOGY

A satisfactory explanation of the pathogenesis of acanthosis nigricans cannot be given, although it is generally assumed that it is in some manner dependent

on disturbance of the abdominal sympathetic, the "mechaniconervous theory" of Darier. This theory assumes the production in the abdominal cavity of pressure from primary or metastatic malignant neoplasms, and a consequent functional disturbance of the nerve structures in that region. It is difficult to reconcile this theory with the juvenile and other benign cases in which no neoplasm is present; moreover, the great frequency of intra-abdominal neoplasms, accompanied by localized pressure, should more often lead to the development of acanthosis nigricans if such pressure were really the cause of that disease. It is also evident that acanthosis nigricans may be associated with malignant

Fig. 2.—Pigment changes and papillary growths over the back of the neck and shoulders.

growths elsewhere than in the abdominal cavity, as shown by the case of pulmonary cancer previously referred to and my own case.

Porias, in a recent article,⁵ develops the theory that the skin dystrophy is brought about by a derangement of certain internal secretions on the action of which the normal condition of the skin is dependent, the active factor in this derangement being some debilitating condition, the most common of which is cancer. Such a theory is not inconsistent with rapidly accumulating evidence of the relation of disordered internal secretions to the production of various dystrophies, and particularly to pigmentary changes; and would more nearly explain the juvenile and other benign cases. In this connection may be cited the case reported by Juan de Azua⁶ of an adult in whom no evidence of malignancy could be discovered but who was much benefited by administration of salvarsan, suggesting that syphilis may therefore be the disturbing factor in some cases.

4. Klotz: Jour. Cutan. Dis., 1913, xxxi, 306.

5. Porias: Wien. klin. Rundschau, 1913, No. 38, p. 671.

6. Azua, Juan de: Abstr., Jour. Cutan. Dis., 1913, xxxi, 966.

Whatever may be the direct cause of the disease, however, there is no doubt of the clinical fact that in a large majority of acquired cases of acanthosis nigricans in adults, there is present, earlier or later, some form of internal malignancy. Most commonly, the growth is within the abdominal cavity and may be amenable to modern methods of treatment, the possibilities of which have been greatly increased by recent advances in Roentgen-ray technic for both diagnostic and therapeutic purposes.

CONCLUSIONS

1. The development of acanthosis nigricans in the adult is an indication of some serious internal disorder, the most frequent of which is cancer.

2. The frequency of this association justifies the assumption of a diagnostic relation between the two conditions.

3. Notwithstanding its rarity, acanthosis nigricans should be promptly recognized, and an effort made to locate and if possible, to remove an associated malignant growth, even though no other evidence of its presence exists.

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ABSTRACT OF DISCUSSION

DR. OLIVER S. ORMSBY, Chicago:

In the report of cases which Dr. Markley spoke of, prepared by Dr. Pollitzer, was one of the juvenile type in which I was interested. I saw that patient eight or nine years ago, and this case was classical of the juvenile type.

The patient consumed an amount of spirits which was entirely out of proportion to anything I had ever seen in a young person. After a single examination he disappeared. Last year I sent for him to appear at the annual meeting of the American Dermatological Association, and although he preferred not to come he reported himself as well. It is an interesting fact that the type occurring in children is benign, while the adult form is malignant.

Fig. 3.—Extensive changes in mucous membrane of mouth.

Mixed Races.—The words “hybrid” or “mongrel,” terms of reproach as usually applied to the human race, relate commonly to the union of widely different peoples. But the question of “race or mongrel” can not be settled by *a priori* assertions as to superiority of pure over mixed races. There is no general law that mongrels are sterile, inert and non-resistant. It is to be determined by a study of the results. Experiments have no pertinency unless best is mated with best, and even then they might prove conclusive only if many times repeated. And no result shown in individuals need be valid as a general law of crossing. It would apply only to the particular types in question. No important information could be expected from the study of the first generation. One would need to know the nature of the recessive characters involved as well as of the dominant ones. The final mendelian disposition of mixed race characters must determine the final answer.—D. S. Jordan in *Pop. Sc. Month.*

ILLUSTRATIONS OF THE HISTORY OF LEPROSY *

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The term “leprosy” is now restricted to a chronic infectious disease caused by Hansen’s bacillus, which has a special tendency to involve the skin and the peripheral nerves. This special involvement of the skin and the peripheral nerves produces external symptoms of a coarsely repulsive character, in the main easy of recognition. This is one of the peculiarities that renders leprosy so interesting historically, as even imperfect descriptions by men untrained in clinical observation enable it to be traced back through the ages.

Leprosy, as we now know it, is a well-defined disease with definite and marked symptoms, and a precisely determined cause. This precision, however, is an acquisition of recent years. Previous to the work of Danielssen and the elder Boeck in 1842, the symptomatology of leprosy was not at all fully known. The hazy ideas of the middle ages, and in fact of all previous ages, still persisted. This late clinical study of the disease was a natural historical sequence. Almost all disease, especially that running a chronic course, constituted, up to the end of the eighteenth century, an inextricable jumble. Then began the segregation into groups.

Bichat (1771-1802), by his investigations in pathologic anatomy and in physiology, may be considered the founder of modern medicine. Quickly following him came Laënnec (1781-1826) with his studies in the auscultation of the chest. Ever since, there have not been wanting brilliant men throughout the centers of Western civilization who, by clinical observation, by necropsies and by the shrewd application of the natural sciences, have gone on deepening and broadening our knowledge of life both in health and in disease. At first these observers did not study leprosy, because other material, under their hand, requiring investigation, was abundant, and no leprosy was then present in those cities in which the study of medicine was most active. Students, however, were being continually drilled in the habit of clinical observation and pathologic investigation, and when Danielssen and Boeck, so disciplined, undertook the delineation of a group of lepers in Norway which constituted the chief focus remaining in civilized Europe from the great epidemic of the middle ages, they, in 1842, were enabled to give the disease a well-rounded, satisfactory, scientific standing, as an independent morbid entity.

Shortly after Koch’s discovery of the tubercle bacillus (1882), Armauer Hansen discovered the presence of an acid-fast bacillus in the lesions of the above-mentioned group of cases in Norway. This bacillus has been demonstrated as present so constantly and so abundantly in most of the lesions of leprosy that it now constitutes one of the best examples of this kind of parasitism in the tissues.

It is clear that the conceptions of this disease by a well-educated physician of the present day, having at his hand all the correlated knowledge represented by the work of Danielssen and Boeck and their successors, is very different from the hazy ideas previously exist-

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