Johnston (Jas. G.)
Xanthoma diabeticorum
XANTHOMA DIABETICORUM (SO CALLED). ITS PLACE AMONG THE DERMATOSES.

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The selection of this subject for a thesis* was influenced by two considerations: first, the study of one of the very rare examples of this interesting affection which has fallen under my personal notice; second, the failure in the latest works on dermatology to recognize its peculiarities, both in symptomatology and pathology, and its claims for a place, distinct and separate from that of ordinary xanthoma, among the dermatoses. Among recent treatises, two of the more prominent may be cited as sufficient to show the general trend. Kaposi,† in the fourth German edition of his work, considers the question of the identity of the two forms still undecided, but thinks it worthy of further study. Heitzmann,‡ in Morrow’s System, without reviewing the evidence at hand, claims that xanthoma diabeticorum is not a distinct affection, and that the seeming differences are easily accounted for. Publication of the article may be excused on the ground of the relapse in the case, more extraordinary in many respects than the original attack already reported.

History.—An account of the initial appearance of the disease in my case will be found in this Journal (May, 1894, vol. xii, p. 205). There is no necessity for a repetition of what has already been said,

* Presented to the Society of Dermatology and Genito-Urinary Surgery.
† Pathologie und Therapie der Hautkrankheiten, p. 748.
‡ System of Genito-Urinary Diseases, Syph. and Derm., vol. iii, p. 486.

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and I shall pass on to a short account of the second attack, merely remarking that the first presented the classical features of the xanthoma, with the additional involvement of the soles of the feet.

The nodules began their involution in the winter of 1894, simultaneously with the improvement of the patient's diabetes and general health, disappearing in the reverse order of their appearance—viz., legs, back, buttocks, arms. The disease has never faded completely since its first outbreak. The lesions on the knees and the plaques on the soles, the latter the last in order of evolution, have always persisted. Ulceration has not at any time been a part of the morbid process, and the disappearance of a nodule leaves absolutely not a trace upon the skin. In March, 1894, the patient's urine contained less than one per cent of sugar, and the cutaneous disease was then confined to his right wrist, knees, and soles. In the fall of the same year he began to drink heavily; the amount of urine passed, and the proportion of contained sugar, increased day by day, until the latter reached eight per cent and the eruption began to reappear. Its development was far more rapid than in the original attack, the recrudescence being complete in December.

The activity of the process was clearly shown by the fiery red color of the lesions, in marked contrast to the pale pink seen during involution. (This observation confirms Török's statement* as to the tint, in which he is singularly correct, in view of his never having seen a case. At the same time it controverts that of Payne.) The shade may be aptly compared to that of raw beef. When stripped, the patient presented a remarkable spectacle. Over the knees the nodules had coalesced into enormous plaques, four by eight inches in size, dotted here and there with the yellow central point of the individual lesion. The extensor surfaces of the arms were in almost the same condition, the chest and abdomen were involved for the first time, and on the buttocks and backs of the thighs a ten-cent piece could not be laid on a clear surface. The dorsa of the feet and toes showed scattered and confluent papules, and the plantar plaques were increased in size. The genitalia were still uninvolved, but two surfaces, previously free, were attacked. These were the face, on the edge of the alæ and tip of the nose (not, however, on the lids), and the backs of the hands and fingers, on which the nodules coalesced as on the toes. It was impossible, of course, to count them, but the lesions could not have numbered less than twenty-five hundred. The subjective symptoms were excessively annoying, often preventing rest in the recumbent posture. Any pres-

* *Annales de derm. et de syph., Nos. 11 and 12, 1893.*
sure on them produced a sensation of tenderness and prickling, and on account of the extreme hardness it seemed to the patient as though he were lying or sitting on a bag of shot.

The disease remained in this condition for two or three months, but in April, 1895, began slowly to grow paler, after a trip to the seashore, following as before an improvement of the diabetes and the health generally. It is a curious and notable fact that, while whisky was kept from the man, no involution took place, but, on allowing him a regular daily portion (a pint and a half, ordinarily), improvement began. It seems likely that every exacerbation of diabetes will be followed by an outbreak of the skin affection. No local treatment has ever been attempted, for the reason that I have little faith in local applications except electrolysis, which the patient declines and because general improvement is surely followed by fading of the cutaneous disease.

**Etiology.**—The origin of the disease is, like many others in the field of dermatology, more or less shrouded in obscurity. The connection, causal or otherwise, between diabetes and this form of xanthoma is not understood; its very existence is denied, and with apparent reason, in view of the cases with an identical clinical history and histological characters bearing close resemblance to those found in so typical a case as mine.

Twenty-one cases have been reported up to this time (see appended bibliography). The light which they shed upon the etiology of the affection is not brilliant. Twenty of them have occurred in men; one only in a woman, reported by Hillairet. These patients, with the single exception of the first—that of Addison, a young man of twenty-six—had arrived at middle life. In seventeen, diabetes mellitus was present; in Bristowe's case it followed the eruption; in Cavafy's and my own it preceded the xanthoma. Hutchinson, Besnier, Vidal, and Payne failed to discover a glycosuria in their cases. The eruption itself led Crocker to the discovery of diabetes in the man under his care. It seems to me that too much has been made of the absence of sugar in the urine of these people attacked by a transient xanthoma. The glycosuria (I use the word here in its most limited sense) may have been temporarily absent, but it is not necessary now to have recourse to this explanation. Von Noorden and Oertel, in their respective articles on Diabetes and Obesity recently published in vol. ii, *Twentieth Century Practice*, give the weight of their opinion to the theory of the identity, etiological at least, of these two conditions. Sir Dyce Duckworth * in-

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clines evidently to the same belief from his recent utterances. A discussion of this belief would be out of place here, but it is interesting to note how often obesity in varying degrees occurred in the twenty-one cases. Including those frankly described as diabetic (Barlow’s case is omitted for the reason that much doubt attaches to it), no less than eleven are described as remarkably stout, of florid appearance, or obese; in two the condition was well nourished, stoutness not being marked; two more were cooks and presumably suffered from their occupation and its temptations; two were drinkers and addicted to the pleasures of the table; in the remaining three nothing is reported concerning the nutrition, but the number includes Addison’s case, a diabetic. Payne, who failed to discover diabetes, says his man “was inclined to be stout and florid.” In view of their all but uniform occurrence there seemingly must be a connection between the vice of constitution expressed in the obesity and diabetes and the transient xanthoma occurring in these cases.

Chambard * believes that the disease is due to a special diathesis—i.e., it is a xanthomatosis. This is an explanation which explains nothing. There is certainly a tendency in the constitution of the individual to the formation of these lesions, but that offers no solution of the difficulty. The theory that they owe their origin to the same factors which give rise to the diabetes (nervous, pancreatic, gouty, or rheumatic [Duckworth], poisoning by phloridzin [von Noorden]) is difficult if not impossible of proof. The most, and to my mind the only, reasonable explanation is that xanthoma diabeticorum is an irritative process, the irritation being supplied by the excess of glucose or some faulty product of metabolism circulating in the blood—a theory suggested by Török and Kaposi. What the particular substance may be will doubtless be discovered when the pathogeny of diabetes is fully elucidated. Color is lent to this proposition by the fact that the nodules of the disease begin in the corium in the neighborhood of the sweat glands and hair follicles with their attached sebaceous structures, all of which are supplied by the same set of vessels, part of the excretory apparatus of the skin. It has occurred to me that the irritation might be occasioned by the effort of the organism to rid itself of the sugar excess through this channel, as well as through the renal filter, an analogue of the process in scarlatina.

Hallopeau,† after studying his case of transient xanthoma, still believes that xanthomata are naevi localized in the same way. The glycosuria in the particular affection under discussion he regards as due to

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† Ibid., vol. iv, No. 8.
a visceral localization of the lesions in the pancreas, and consequently holds that the xanthoma is even here the primitive process. He thinks that the possibility of involution and change of size according to the degree of repletion of the vascular system explains the intermittences of diabetic symptoms. There is no report of an autopsy on these cases, so that his theory, ingenious as it is, lacks confirmation. His reasoning, it should be said, is from analogy with icteric xanthoma, in which lesions have been found in the bile ducts (Kaposi).

It will be noticed in the bibliography that eleven of the cases had been reported in the last five years, while forty were required to collect the first ten. It seems likely that with a wider spread of knowledge of dermatology the instances will be multiplied until xanthoma diabeticorum ceases to be classed among the rare dermatoses.

**Histology.**—The pathological anatomy has been investigated by Robinson, Crocker, Clarke in the second of Morris's cases, Payne, and recently by Schamberg. There is little to add to their reports. The general consensus of opinion seems to be that the diseased process bears some resemblance under the microscope to that of ordinary xanthoma, but that inflammatory changes are more marked and connective-tissue increase less noticeable in the diabetic form. The papule begins and remains throughout its whole course localized in the corium in the neighborhood of the sweat glands and follicles chiefly, as has been said. The corium is at first attacked superficially or toward the center, the process later involving the whole depth. The epidermis remains unaffected, except that the rete pegs disappear to a great extent and some of the cells become vacuolated. At the outset vascular dilatation takes place and persists, a slight oedema separates the tissue elements, and is followed by an infiltration of round cells, lymphoid corpuscles, and, according to Robinson, a proliferation of the connective-tissue cells.

"Xanthoma cells," large, multinucleated cells with a fine membrane, including tiny droplets of fat, are found in xanthoma diabeticorum as in ordinary xanthoma, but are very few in a beginning lesion. They increase later and are proportionate in number to the size of the papule. Crocker describes them as epithelioid or giant cells.* The bundles of fibrous tissue swell, thicken, become translucent, and finally disappear or "appear rarefied," with large intervals. In the meshes a granular material is seen, composed chiefly of minute oil drops, not solely contained in the xanthoma cells, but resulting from their degeneration, finally taking their place, together with that of the connective tissue, and forming a confluent mass in the center. This mass of fatty

* Such they are undoubtedly, and in consequence little importance can be attached to them in view of their presence in numerous other pathological conditions.
granules gives the yellow center to the xanthoma nodule. There is then an entire central degeneration, with little or no connective-tissue increase, according to all investigators except Payne, who says that the elastic tissue "appeared to be much increased in amount, with little intervening tissue." He does not, however, himself regard it as a hyperplasia, but as a preponderance of elastic tissue in consequence of degeneration and absorption of the other constituents of the corium. Resolution presumably takes place by the absorption of the central granular mass and a regeneration of the fibrous tissue of the corium by the proliferated fixed cells already mentioned. In the words of Török (loc. cit.), "the lesions of xanthoma diabeticorum are caused by a local irritative process resulting in a granulo-fatty degeneration."

Classification.—I took occasion in the opening remarks in this paper to call attention to the place accorded xanthoma diabeticorum among skin affections. Opinion on the subject is fairly divided. Besnier and Doyon* unequivocally state that the sharp clinical points of differentiation and the histological findings in xanthoma vulgare and xanthoma diabeticorum establish only the variety, not the nonidentity of the two forms of the disease. Morris, Crocker, and Payne give this dictum only half-hearted support. Payne thinks that "the association of morbid changes seems to suggest that there is at least a common element in the three forms (including elastic xanthoma), and that the differences may not be essential but may depend on necessary circumstances." Török (loc. cit.) advances a diametrically opposite view, classing the glycosuric as a distinct affection with no relation to the common form.

It is necessary, therefore, to review the clinical and microscopic points of diagnosis between the two varieties. The former have been embodied in a report by Sangster and Crocker† to the Pathological Society of London on the first of Malcolm Morris's two cases, a report which has since been extensively quoted. The clinical differential points are these: (1) The most important, and a divergence sufficiently great of itself to demonstrate the dissimilarity of the two forms, viz., the sudden evolution and involution of xanthoma diabeticorum, the latter invariably taking place spontaneously at some time in the history. In ordinary xanthoma involution is extremely rare, and when it does occur takes place almost imperceptibly. In fact, such an event is very doubtful. (2) The lesions in xanthoma diabeticorum are firm and solid, inflammatory, discrete or confluent papules; in xanthoma they are soft, inflammatory phenomena are absent, and the disease occurs

† Path. Tram., 1883 p. 284
chiefly in flat patches or striae, which are never found in the first form. (3) The yellow center is not visible at first in the diabetic affection nor in all the papules at any time; in xanthoma vulgar the chamois-leather appearance is always to be seen. (4) An unimportant distinction—xanthoma diabeticorum is never found upon the eyelids; its preference is for the joints and extensor surfaces generally. (5) Subjective symptoms, though they may be slight, are the rule in the first variety. They are totally absent, except in case of ulceration, in ordinary xanthoma. (6) Jaundice has never been found in xanthoma diabeticorum. (7) Glycosuria, often transitory, has been found in a large majority of the cases, and those in which it was absent showed at least a related condition of plethora and obesity. Moreover, it is possible that the nutritive disorder was in abeyance at the time of examination. Diabetes has never been found with the ordinary form except in a case of Besnier’s, to which little importance need be attached, since it is an isolated instance of a concurrence of two totally unrelated diseases. (8) The lesions of xanthoma diabeticorum occur in the neighborhood of the hair follicles and skin glands, a localization not observed in the common disease. To these may be added: (9) Ulceration is never a part of the process in diabetes; it has been seen in xanthoma multiplex (Morrow’s case).

Histologically, the only point of resemblance in the two processes is the presence of so-called xanthoma cells, giant cells in reality, in xanthoma diabeticorum containing minute droplets of oil. Their importance in diagnosis has already been discussed. I shall refer here again to Török’s able paper (l. c.) for a comparison of the pathological conditions. The tissue of xanthoma multiplex presents a striking analogy to adipose tissue, the analogy being borne out by the cells, which are identical with those of physiological fat in process of formation; further, by the formation of these cells around the vessels, in their adventitia even; by the discovery of cells analogous to those of xanthoma in imperfectly developed adipose tissue. The fat formation does not proceed to the point of occupying the whole cell as in true fat, nor does the cell break down into a granulo-fatty detritus as in xanthoma diabeticorum. To explain this arrested development, Török concludes that “ordinary xanthoma * is formed of adipose tissue in a heterotopic situation, and that it is constituted, by reason of that heterotopia, of fat cells of incomplete, interrupted evolution.” To the formation of fat must be added, in some cases, that of fibrous tissue. The cells are of connective-tissue origin, as are those of fat in other situations.

Xanthoma vulgare is then "an anomaly produced under the influence of congenital and hereditary conditions by proliferation of connective-tissue cells and by their transformation into fat cells in places which are normally free from adipose tissue." It is an anomaly of formation." In other words, it is a benign tumor, and its place is with its analogue—lipoma. Contrast this with a formation showing every evidence, clinically and microscopically, of inflammation resulting in a degeneration en masse of the central portion of the papule. Does it seem proper to class them together as varieties of the same disease, ignoring the fact that xanthoma multiplex is an anomaly of formation, and xanthoma diabeticorum an inflammation due to an irritative process ending in a granulo-fatty degeneration? It seems to me that it has ceased to be a matter of opinion; one must recognize facts.

In accordance, then, with the differences pointed out, xanthoma multiplex is properly placed and named—there is no necessity for the name "ordinary or common xanthoma"—xanthoma vulgare. It is xanthoma par excellence, a yellow tumor. Xanthoma diabeticorum has never been satisfactory. Lichen, proposed by Sangster and Crocker, is objectionable on many grounds. Török's term—"a papular eruption of diabetics due to a granulo-fatty degeneration"—is too long for convenient use. I would propose as a substitute dermatitis xanthomatoides diabeticorum—in other words, an inflammatory skin disease which occurs in diabetics who have a personal idiosyncrasy leading to the formation, and which resembles xanthoma. That seems to cover the ground. Further, the affection should be classed among the inflammations with the other "dermatoses diabeticæ," not with tumors, tumors even of inflammatory origin, such as the syphilides and lupus, because dermatitis xanthomatoides has a tendency to spontaneous resolution. I should retain the term diabeticorum, for the reason that I believe diabetes is the true underlying condition, and see no object in a change to glycosuricum, even if the disease is manifested in a transitory fashion.

BIBLIOGRAPHY.

CASES.


* Whatever may be the individual opinion of the adequacy of Török's explanation of the arrested development in xanthoma cells, the fact remains that they are of connective-tissue origin. Hence the objection in no wise weakens my argument.


5. Hardaway. A Case of Multiple Xanthoma. St. Louis Courier of Medicine, October, 1894.


7. Colcott Fox. Case shown to Dermat. Soc. of London.


The report of Vidal’s and Hutchinson’s cases I have been unable to find; the case reported, according to Besnier, to Chambard by Hillairet, a glycosuric woman, is undoubtedly identical with that published by Gendre in his Thèse de Paris. Barlow’s case should really be omitted, since so much doubt has been cast upon it, but I include it for the sake of completeness.

Other Literature.


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