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ON TUBERCULOID CHANGES IN THE SKIN IN NONTUBEROUS LEPROSY[1]

PROF. DR. JOSEF JADASSOHN

Bern, Switzerland

So many histologic investigations have been reported and discussed at this conference that I certainly would not impose on you a description of a single case, were it not for the fact that my findings acquire definite significance when considered in relation to certain other observations in the literature. The patient from whom my material comes is a native Alsatian who has lived in Algiers since 1881. I had the opportunity of observing him for only a short time. I then sent him to my colleague Gémy in Algiers, who made further studies and presented the case history at the Dermatologic Society of Paris. Consequently, I restrict myself at this time to the essential facts.

According to information obtained by Dr. Gémy, the patient lived for a number of years in a house in which a Spanish woman suffering from leprosy was employed as a maid. There was no other indication of direct contact with the disease, but it should be remembered that Drs. Gémy and Raynaud have drawn attention to a focus of leprosy in Algiers. There was no history of leprosy in the immediate family of the patient.

The first sign of the disease was a spot on the upper part of the right thigh which had increased in size slowly since the summer of 1896. In the beginning of 1897, other small spots appeared on the legs and one on the back of the right hand. As the latter grew larger the patient noticed some heaviness and weakness of the right arm, and insensitivity of the lesion on the hand. No generalized symptoms were present. Lately, a few more spots have appeared on the right upper arm, the right ear and the neck.

Before the patient consulted me he had already been seen by Dr. Gémy, whose tentative diagnosis was lupus erythematosus. My diagnosis of leprosy was based on the following findings: On the right upper thigh, an area of about the size of a one-franc piece which was slightly

[1] Ueber tuberculoide Veränderungen in der Haut bei nicht tuberöser Lepra. Proceedings of the VI German Congresses of Dermatology, 1898, pp. 508-521. Translation by R. L. Mayer, M.D., who was for many years Professor Jadassohn's assistant.

depressed in the center, had slightly elevated borders, was rather bluish in the center and brownish-red on the edges, and was completely anesthetic. There was an area of anesthesia closely surrounding the spot, with irregular limits. There were, furthermore, a few similar but smaller foci on the lower extremities. On the back of the right hand there was an anesthetic patch larger than a five-franc piece, reddish-brown in color and with sharply delimited borders. This patch was surrounded by a few bright red papules which were hard to the touch—in contrast to the first-mentioned focus, which was soft and bled readily on pressure with a blunt probe. The little finger, which was otherwise unaffected, was anesthetic. There were small, flat, bright red spots on the upper part of the right arm and on the tragus of the right ear, all of which likewise bled readily on pressure with a probe. On the neck there was a small yellowish-white papule in the middle of such a red spot. These foci were only vaguely anesthetic. Finally, the right ulnar nerve was very distinctly thickened and somewhat tender on pressure.

Under these circumstances, there was no alternative to a diagnosis of leprosy. Of course, without the anesthesia and thickening of the nerve the diagnosis would have had only a morphologic basis and would have been quite difficult. Indeed the color of the spots, a bright rose and darkish brown livid color, was quite different from that observed in the eruption of tuberous leprosy; and the foci on the hand, the ear and certain other parts had a definitely soft consistency. This latter characteristic and the color reminded me of lupus vulgaris; the bright-colored macules also resembled the early lesions of lupus when typical nodules are lacking. Upon pressure with a glass spatula, a yellowish tint remained; on the hand, the tint was a dark yellow brown.

Clinical similarities to syphilis were less evident, and antisyphilis treatment had not proved beneficial.

In thus making a diagnosis of leprosy I naturally excluded the tuberous form and decided rather upon the nontuberous (Blaschko). Clinically, however, the lesions produced the definite impression of an infectious granuloma and not merely an erythema from vasomotor disturbance such as is constantly present in an old case of typical neural leprosy under treatment at my clinic. The bright-colored macules reminded me of the well-known case of Blaschko, who pointed out the resemblances to lupus. I removed with a curette a small piece of soft tissue from the back of the hand and searched for bacilli—without success. Similar failure attended my efforts to find bacilli in the nose, and in the blood stream after medication with potassium iodide (which the patient tolerated very well).

Biopsy of the focus on the hand showed such a strong lupoid picture that I inoculated a guinea-pig with tissue from the upper part of the thigh—not expecting a positive result, but remembering the discussions

on visceral leprosy and the fact that animal experiments are so often omitted in the course of these investigations. The animal lived for six and one-half months, and died from infection following injury to a foot. Unfortunately, the animal was discarded through error of a new attendant before an autopsy was made. However, Gémy inoculated two guinea-pigs on November 16, and he tells me that they were still alive and completely healthy.

There were available for histologic examination, specimens from the following areas:

1. The largest focus on the hand, which was soft, livid brown in color, and anesthetic.
2. The neighborhood of a hyperesthetic eruption in which bright-red papules of normal firmness were present.
3. An isolated lesion from the upper part of the right arm, bright red in color, flat, depressible, and hyperesthetic.
4. A lesion identical with No. 3 except that sensitivity was normal, from the tragus of the right ear.
5. A spot from the neck, one-third of a centimeter in diameter, with a light red halo and in its center a yellowish-white papule of millet size.
6. The anesthetic area on the upper part of the right thigh, about the size of a one-franc piece, with slightly elevated edges.

In describing my findings I shall omit many details and call attention only to the most important features. In all the specimens the histologic changes were essentially identical, only differing degrees of development being discernible. In every instance the areas of infiltration were embedded within the cutis, and they touched the lower border of the epidermis in the center of the lesion. In all instances the infiltration in the upper parts of the cutis was massive, replacing the entire tissue; only in what seemed to be the most recently invaded part of the lesion on the dorsum of the hand was this diffuse accumulation missing. Here, as well as in the peripheral parts of the other preparations, and in the deeper strata of the cutis reaching down into the subcutaneous tissue, there were larger or smaller round or irregular areas of focal infiltration. It was apparent that some of these had resulted from the fusion of several nodules. There were also irregular cords of infiltration, some broad, others narrow.

In general, the borders of the infiltrations were extremely sharp, sometimes to such an extent that they appeared to be separated from the surrounding normal parts by a layer of connective tissue. Often one got the impression that they had originated directly from an infiltration in the wall of a blood vessel, but such an origin was never clearly visible.

The cellular elements of these foci were the following: typical epi-

thelioid cells; giant cells, sometimes of large dimensions, mostly with typical peripheral nuclei, finely granulated protoplasm and irregular borders; and Unna's plasma cells. Mast cells were not regularly seen within these foci, but were more numerous in their environs. Sometimes a focus was formed by a mosaic of epithelioid and giant cells, sharply delimited at the periphery by a wall of plasma cells.

Quite often—especially in the plaque on the upper part of the right thigh—the central epithelioid cells appeared to be in the process of degeneration, their contours being vague and their nuclei poorly stained. Often, also, the centers of these lesions showed coagulation necrosis, with an irregularly striated or granulated structure in which small amounts of fibrin were detectable. This coagulation necrosis was especially evident in the specimen from the neck. The whole central part, which was apparently that which had appeared clinically as a yellowish-white papule, was occupied by a necrotic mass surrounded by a mantle of epithelioid and giant cells. In the center of the specimen the necrotic tissue flattened the epithelium to a thin layer.

In other slides, necrotic foci were almost completely missing in the upper layers of the cutis, although giant cells and conglomerations of epithelioid cells were also present within this diffuse infiltration. Only very rarely did I see mitoses within the epithelioid cells. In all slides I found within the infiltrations a few well-conserved hair follicles, ducts of sweat glands, and in the peripheral portions a few blood vessels.

Apart from the flattening and occasional mitotic cells, the epithelium did not present changes worth mentioning.

Except for a somewhat large accumulation of nuclei, the dermal tissue situated between the areas of infiltration was normal. Its elastic tissue was well preserved, and was well walled off from the infiltration. As a rule the elastic tissue was missing from infiltrated zones, only occasional remnants of it being observed. The well-known peculiar onion-like concentric forms, first described by Sudakiewitsch, similar to those seen in the giant cells of lupus (Lang's striated corpuscles), were found in the sections especially within the Langhans' cells.

From the outset I tried to demonstrate bacilli, but encountered great difficulties. Although I embedded the tissues in paraffin or colloidin and used the most diversified staining methods, including the one recently described by Darier, I could not detect bacilli for a long time. So far I have found them only in sections of the lesion on the neck and of that on the upper thigh, but they were extremely rare. In the large specimen from the thigh I saw sometimes only one or two, at the most four or five, in any section. They were demonstrable in the specimen from the neck slightly more often, with a tendency to locate at the borders of necrotic areas, sometimes inside necrotic tissues. I found

them very rarely between the epithelioid cells, and on three occasions one bacillus was seen in a giant cell. They were never found in blood vessels. The well-known globi and bundles were not present.

Most of the bacilli were short, often distinctly pointed, and only partially stained. Close to the bacilli I saw very fine red corpuscles (stained with fuchsin) and somewhat larger globules, mostly within the cells. I also noticed the well-known acid-fast globules within the coils of the sweat glands, especially in preparations from the hand and ear. Finally, I wish to point out that I was able to stain the bacilli with an aqueous solution of gentian violet.

These are the histologic findings, and it is unnecessary to add further proof to support the diagnosis of nontuberous leprosy. The principal points may be summarized: Absence of any accumulation of bacilli and of the free subepithelial clear zone which seems quite characteristic of tuberous leprosy. The animal experiment excludes mixed infection with tuberculosis, and it is *a priori* improbable that so many leprous lesions in the skin should represent a combination with tuberculosis.

Recently, more and more leprologists have come to disagree with the principal points which are used to differentiate the "neurolepride" from the "leproma," insisting on the great similarity in their histologic structure. In fact, Dehio and others did not find essential histologic differences between the two forms in Blaschko's case (Blaschko has shown me some of his slides). In all these cases, as well as in tuberous leprosy, we are dealing with granulation tumors. The same is true of the majority of Darier's observations.

From Darier's paper we can recognize without difficulty four groups: (1) Cases with an enormous number of bacilli in which the only difference from a true leproma is that the lesions are not elevated above the level of the skin. There is no involvement of the subepithelial zone. On the basis of my own investigations I agree with Neisser that these cases should not be separated from the lepromatous, and I think that the majority of leprologists would consider the lesions in Darier's cases to be lepromatous macules. Darier himself has agreed with this view (see Lepra Conference, II, p. 52).[2] (2) A case (No. 8) which presented pathologically the pure picture of the neuroleprides of Unna, that is, a perithelial increase of cells and no bacilli. (3) A case (No. 6) with similar changes but relatively numerous bacilli. (4) A case (No. 7) with extensive diffuse and localized infiltration invading the papillary bodies, with Langhans' cells and very rare bacilli. Of these last three groups, each comprising only one case, Groups 2 and 3 (cases No. 8 and No. 6) are histologically similar, the only essential difference being the content of bacilli, but even in case No. 6 their number was apparently not so important as in the cases of the first group. The findings in

[2] Referring to the transactions of the Berlin Conference, 1897.—EDITOR.

these two cases were very similar to those of a patient in my clinic suffering from a chronic erythema. Dohi has examined a specimen from this patient, but did not find a real inflammatory process, granulation process, or bacilli.

The pathologic findings in Darier's case No. 8 and in the patient whom I am reporting today are very different from these. I would like to add also two cases of Hodara's in which he described neuroleprides with giant cells. In all of these we are dealing with histologically typical granulation processes within the cutis, and one may say that in these cases—and so far only in these—the differences between the histologic findings and those of the true lepromas are possibly only quantitative.

According to Neisser (Lepra Conference, III, p. 204)[2] these cases are neither leprides nor macules in the sense of the Hansen's macules of the maculoanesthetic forms. Here something else is present besides "lymphocytes or cells of the connective tissue" which are transformed into spindle-like elements without the presence of specific lepromatous disease, without the formation of true lepra cells, and without vacuolization, etc. Here there is present a granulomatous tissue which we generally regard as "specific" but which does not possess the characteristics of the leproma probably because bacilli are so rare. Consequently, we should now distinguish three principal forms: first, the typical leproma; second, the typical "neuroleprides," macules without any histologic changes corresponding to those of granulomatous tumors; and third, those with granulation tissue composed of epithelioid and giant cell—nodules with coagulation necrosis. Clinically this third form apparently belongs with nontuberous leprosy but lacks its characteristic histologic picture.

As far as bacilli are concerned the true leproma is characterized by an enormous richness in numbers, while the other two forms are conspicuous for the rarity or absence of microorganisms. However, while it is possible to conceive that leprides are formed without the direct action of bacilli on the tissue, the histologic configuration of the third form indicates without any doubt that here the infectious agent must have been present *in loco* or is still present. Here the concept of an affection of the central nervous system (neurolepride) is certainly not justified. And nothing supports the idea of Unna that we are dealing here with bacillary emboli in neuroleprides. Hodara does not mention this possibility, but he apparently believes that some nervous influence may cause the formations of granulation tissue with giant cells.

We must therefore, for the time being, isolate this group of nontuberous leprosy cases, with few or undetected bacilli, which present the whole picture of a granulation tumor; but we must always realize that transition in either direction is possible—towards the nodular leproma or towards the pure neurolepride.

Numerous giant cells were present in the cases of Hodara and Darier, and especially in my own case. Here, as in Darier's case, most of them were of the Langhans type. I have also found within them elastic fibers of the Sudakiewitsch kind which Unna has not found in lepromas. (Unna has never seen giant cells in neuroleprides. Neither have I seen elastic fibers in the Langhans giant cells of tuberous leprosy.)

In addition, my own case presents another most important feature, namely, central coagulation necrosis. As far as I know this has rarely been described in leprosy of the skin (Babes saw it once in an old leproma), and especially not in the nontuberous forms. In one lesion of my patient this necrosis was so pronounced that it was clinically visible as a small, yellowish-white nodule. The simultaneous presence of diffuse infiltration, with interspersed epithelioid and giant cells, isolated round foci with a periphery of plasma cells, epithelioid cells and giant cells, and with central necrosis, necessarily leads to the histologic diagnosis of tuberculosis. The tuberculoid character of my preparation was so evident that our pathologist Langhans, to whom I showed it without mentioning a diagnosis, said in his usual cautious manner, "But this looks just like tuberculosis."

I have already stated that we can exclude a mixed infection with tuberculosis almost with certainty. Darier thinks that the presence of giant cells of the Langhans type suffices to prove that there occurs also in leprosy a "degeneration of the protoplasm."

The only essential difference between my preparations and lupus is the necrosis which, as is well known, is very rare in lupus; the relatively well-preserved follicles, sebaceous glands, sweat glands and blood vessels within the infiltrations, and also the particularly sharp delimitation of the infiltrated areas.

I cannot discuss in detail the significance of the red granules found in the vicinity of necrotic foci. I believe that they have some connection with the bacilli, but so far it is not possible to attribute any diagnostic significance to them, any more than we can do so in the case of the well-known acid-fast granules in the cells of the sweat glands which Babes has described in tuberculosis and I have seen in a case of tertiary syphilis. In general, the bacilli were surprisingly small, and they often showed unstained parts; but Babes and others have described this condition in older cases. A few of the bacilli were of the usual appearance.

There remains one question, namely, the significance of my findings with respect to the current discussion of visceral leprosy and its association (symbiosis) with tuberculosis. There have been a few positive inoculation experiments. However, the question arises as to whether one is justified in claiming the presence of a double infection from the histologic picture alone.

Rikli has claimed that purely tuberculoid changes occur in the liver in uncomplicated leprosy. On the contrary others, especially Philippson and Schaeffer, have tried to prove histologically that such tuberculoid changes in the viscera are actually tuberculosis. Babes has noted, correctly of course, the absence in Rikli's report of definite proof of the nontuberculous nature of the lesions by animal experiment. This point of view was justified as long as tuberculoid changes of a nontuberculous character were unknown in leprosy. My case makes it at least very probable that such changes do occur at the site of election in leprosy, namely, in the skin.

Last summer Schaeffer could still say, "In contrast to leprosy, tuberculosis is characterized by typical aggregations of epithelioid cells surrounded by lymphocytes, with poorly staining and perhaps necrotic centers, and often with numerous Langhans giant cells. The bacilli are usually rare, sometimes extremely so, this being in contrast to the strong and destructive tissue reaction which they produce. We cannot insist too strongly upon the distinction from lepromatous disease."

At that time Schaeffer's remarks were justified—at least in the case of tuberous leprosy. However, it is now erroneous to make such a generalization, although I can oppose it with only a single case. I must insist, nevertheless, that my observation is not an isolated one but rather is the final link in a chain of other findings that I have cited.

If leprosy, with only a few bacilli present, can cause granulation tumors with giant cells, then it can also lead to necrosis. This could be accepted *a priori,* but my case as well as those of Arning[3] have proved it. The disproportion between the number of bacilli and the tissue reaction is present in leprosy as in tuberculosis.

We have learned very recently that tuberculoid changes exist also in syphilis, which animal experiment proves to have nothing to do with tuberculosis (cf. Proc. Internat. Congr. Dermat., London). Now we must admit the same for leprosy. Although it is readily possible to distinguish clinically and histologically the chronic infectious diseases from one another as long as they follow a typical course, they may imitate in their atypical varieties one or another of their fellows to such an extent as to lead to diagnostic error. In leprosy as well as in syphilis we have arrived at the most interesting conclusion that lesions which are clinically lupoid in character may be tuberculoid on histologic examination. I have been much impressed by the softness and compressibility of the lesions of lupoid syphilis; now I have seen the same phenomenon in the leprotic lesions of the present case.

We do not know why leprosy assumes this special characteristic in these cases. Nor do we know as yet anything about the frequency of such cases, although judging from the few reports they are apparently

[3] Arning, in the same meeting at which this report of Jadassohn's was read, presented a paper on necrosis of nerves in leprosy—tuberculoid of course.—EDITOR.

rare. As far as visceral leprosy is concerned we cannot any longer dispute, *a priori,* the simultaneous presence of typical tuberous and atypical tuberculoid changes in the same organ; we know very well that both forms can exist simultaneously in the skin. If the tuberculoid foci in leprosy are really leprosy, their simultaneous presence with typical lepromas would be no more surprising than the coexistence of induration in the apex and a caseous pneumonia. If in a skin in which only leprides were present lepromas develop we usually say, explaining or paraphrasing, that the resistance of the skin to the growth of the bacilli has changed. One has to think of the possibility that also in visceral leprosy the tuberculoid areas are the older, the lepromas the more recent.

I am of course far from denying that a visceral symbiosis between leprosy and tuberculosis may exist. A mixed infection with tuberculosis is also recognized in syphilis of the skin. However, the simultaneous presence of both processes in leprosy must be demonstrated not only histologically but also bacteriologically. If Schaeffer's color reaction proves to be selective it should be possible to make this distinction microscopically.