CORRESPONDENCE

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LEPROSY AND SARCOID

In view of the interesting questions raised by the parallel between certain forms of leprosy and the so-called Besnier-Boeck disease, which Rabello draws in an article reprinted in full and discussed elsewhere in this issue, an effort has been made to obtain other opinions on the matter. To this end Rabello's ten-point summary, as below, was sent to a number of men with an invitation to comment on it or to discuss the matter otherwise.

1. Leprosy may affect systematically the reticulo-endothelial system in the skin, the lymph nodes, the bone marrow and the spleen.

2. It may, and does with significant frequency, produce clinically the sarcoid character in the cutaneous, lymph-node and other lesions.

3. It frequently causes the same purely epithelioid formations, without mixture of other cellular types (55 percent of 105 histological examinations of tuberculoid leprosy).

4. It provokes a specific rhinitis which, when the bacteriological examination is negative, is not distinguishable from sarcoid rhinitis and which resists arsenic but improves with chaulmoogra esters, as does sarcoid rhinitis.

5. It is accompanied in nearly 95 percent of cases by a torpid, discrete adenopathy that is perfectly analogous, clinically and histologically, to that of sarcoid.

6. It causes pulmonary and osseous lesions that radiologically are not distinguishable from those of sarcoid.

7. It shows, even in its most flourishing and bacillate forms, cutaneous anergy to tuberculin, as does the Besnier-Boeck disease.

8. It, especially its tuberculoid forms, is cured by antileprol, as is sarcoid; and in the course of treatment there occur sarcoidic reactions with eosinophilia, as in sarcoid.

9. Cultures of leprous tissues give, with the same frequency as do cultures of sarcoid tissue, the same microbes: diphtheroids, streptothrices, gram-positive organisms.

10. Inoculation of leprous tissue and of sarcoid tissue give, with much the same frequency: failure, local infection with acid-fast bacilli, and in rare instances tuberculization.

In order to give emphasis to some of the questions involved, the summary as sent out was accompanied by notes which in

effect constituted a questionnaire. They are given in essence below, the items referring seriatim to those of the summary.

1. This statement is correct as a general proposition.

2. Are "sarcoid" (i.e., tuberculoid) lesions known in leprosy except in the skin and nerves of the tuberculoid form of neural leprosy? Lesions suggestive of tuberculosis in other organs are usually considered to be ascribable to tuberculosis itself. [See letter from Arning, and discussion, *Internat. Jour. Lep.* **4** (1936) 102–106.]

3. Is not the stated proportion of unmixed epithelioid ("sarcoid") lesions higher than the rule? Are not the tuberculoid lesions very variable in this respect (apparently dependent largely upon the activity of the case), with sometimes considerable variations in different lesion-foci in the same specimen?

4. What is known about a nonbacillary leprous rhinitis that is similar to sarcoid rhinitis but amenable to chaulmoogra treatment?

5. Adenopathy in cutaneous-type leprosy is well known, but it is typically lepromatous, not tuberculoid ("sarcoid"). But do the lymph nodes in neural (including "tuberculoid") leprosy show any particular or characteristic pathological changes?

6. It has not been proved that there is any significant leprotic affection of the lungs, except possibly in a rare case. Leprotic changes in the bone are well known. But has the occurrence of histologically tuberculosis-like ("sarcoid") changes of leprotic nature in either of these locations been established?

7. The basis of this statement is not understood. Many reports have been made concerning the tuberculin test in lepers, with plenty of positive reactions. (The leprolin test, though negative in cutaneous-type cases, typically is strongly positive in cases of the tuberculoid variety.)

8. The amenability of leprosy to chaulmoogra treatment need not be discussed. Does eosinophilia occur in significant degree or regularity in any form of lepra reaction?

9. Discussion of the statement concerning the micro-organisms cultivated from true sarcoid lesions would require familiarity with the literature of that subject.

10. It is generally understood that failure to produce tuberculous infection by inoculation of true sarcoid material is the rule, but can that be thought to be indicative of a relationship to leprosy?

Replies have been received from men some of whom deal with leprosy primarily, others being dermatologists who have had more or less experience with leprosy. These replies are given below, with the exception of one which was received and is published in the form of an original article.—EDITOR.

Comment by Professor J. M. H. MacLeod, London, England:

The question of the true nature of sarcoid still remains undecided, but in the multiple benign sarcoid of Boeck there is a histological architecture which strongly suggests a reaction to lipid of bacillary origin. It seems to

me that, apart from the histology, the occasional occurrence of sarcoids together with definite tuberculous stigmata such as pulmonary tuberculosis, and also the fact that tubercle bacilli have been found in the early lesions, are strongly in favor of their being tuberculous.

I have little experience of tuberculoid leprosy, but from what I have seen of it I have come to the conclusion that it is allied to sarcoid. The similarity of its histology to that of sarcoids would also suggest that it is due to the action of bacillary products of lipid nature derived from the leprosy bacillus, which so resembles the tubercle bacillus in its morphology and staining reactions as to be difficult to distinguish from it microscopically.

Comment by Dr. E. H. Molesworth, Sydney, Australia:

I have read with great interest the paper by Dr. Rabello, Junior, entitled "Données nouvelles pour l'interpretation de l'affection de Besnier-Boeck: rôle de la lèpre." The limits of the sarcoid of Besnier-Boeck are admittedly vague. A decision as to whether lupus pernio and Boeck's sarcoid are of the same nature, differing only in situation, can only be given as a matter of personal opinion at present.

It is admitted that leprosy, having just succeeded in establishing itself against a strong natural resistance in the case of an individual patient, may produce lesions which are indistinguishable on histopathological grounds from Boeck's sarcoid. Although in Australia we have very few cases of leprosy in whites, I have seen among five or six patients with tuberculoid leprosy, two whose lesions consisted of closely packed epithelioid cells without any giant cells. Wade has also seen a number of such cases. Strangely enough, all my tuberculoid cases occurred in Europeans, while Wade's occurred in native African and Oriental patients. In all my cases, however, there was one distinguishing clinical feature, viz., anesthesia or at least diminished sensation over the patches. This symptom, of course, does not occur in Boeck's sarcoid.

Jadassohn, during a personal discussion with me in 1927 on the subject of tuberculoid leprosy, mentioned that in cases of the variety which showed no giant cells he was unable to distinguish on the histopathological evidence between lesions due to leprosy on the one hand, and those which are designated as Boeck's sarcoid and lupus pernio on the other. To these conditions must be added granuloma annulare, which also provides a histopathological picture of closely packed epithelioid cells without giant cells. I do not think there can be much doubt that Boeck's sarcoid, granuloma annulare and tuberculoid leprosy (without giant cells) are three separate entities, though Jadassohn was inclined to believe that granuloma annulare was a tuberculide.

The mere fact that the lesions of these three diseases have the same histopathological structure cannot be regarded as proof that they are due to the same cause. There are certain features, especially anesthesia—and if I may mention it the presence of acid-fast bacilli in a cutaneous nerve leading from the leprous patch described by Tebbutt and myself in 1926—that very definitely distinguish the leprous patch from Boeck's sarcoid and granuloma annulare. It is to be admitted at once, however, that it is quite possible and even likely that occasionally tuberculoid leprosy without giant cells may be wrongly diagnosed as Boeck's sarcoid if the histopathological evidence alone is considered. Jadassohn, in the 1913 edition of the Handbuch der patho-

genen Mikroorganismen, drew attention to the "formes frustes" occurring, for example, in Brittany. It is more than probable that similar cases may occur in other parts of the world among other races in which leprosy is dying out, and that some of these cases may be mistaken for Boeck's sarcoid.

To my mind all this only leads to the conclusion that patients who show lesions which on histopathological examination are found to consist of closely packed epithelioid cells, and which might on this evidence be diagnosed as Boeck's sarcoid, should be closely examined for signs of anesthesia and for other evidence of leprous infection, even though they live in a country where leprosy has become a very rare disease.

Comment by Dr. F. Reiss, Shanghai, China:

1. This statement is, for the time being, undoubtedly correct.

2. The material which has come under my observation has not been autopsied, therefore no remark can be made on this point.

3. Observations on this question are very scanty. However, cases are known in which lupus vulgaris changed into sarcoid, and the tuberculin reaction turned from the anergic to the hypersensitive allergic stage.

4. There is not only a nonbacillary rhinitis present in sarcoid, but true ulcerations appear frequently on the septum. These changes are sometimes amenable to chaulmoogra-oil treatment.

5. The changes in the lymph nodes in neural and tuberculoid leprosy cases are of sarcoid-like nature, whereas in cutaneous leprosy they are of lepromatous structure.

6. Radiological observations of sandpaper-like mottling in the lungs of lepers (Murdoch and Hutter), and cystic changes in the bones (Fiehrer, Nielsen, and Murdoch and Hutter) have been made, but no histological evidence of the lepromatous character has yet been given of either of these lesions.

7. While negative results have generally been observed in the cutaneous type, the neural and tuberculoid types frequently give positive cutaneous allergic reactions to leprolin. This is not in line with the sarcoids in relation to tuberculin, where the presence of the so-called anticutins prevents the reaction (positive anergy).

8. Eosinophilia has not been observed in a significant degree during lepra reaction.

9 and 10. The only reports which deal with positive findings of acid-fast bacilli in sarcoids are those of Kyrle, Ruete and Dietrich, but all of them have been unable to give cultural or experimental proof. The only successful inoculation with sarcoid material has been reported by Hudelo, Montlaur and LeForester. These authors not only produced a caseous node in a guinea pig, but acid-fast bacilli could also be found by microscopic examination.

No conclusive proof can be yet given of an established relationship between sarcoid and leprosy. We can only speak of a clinical and histopathological syndrome which may be produced by both Koch's and Hansen's bacilli, but may histologically be mimicked by syphilis (Pautrier, Stein, Darier), leishmaniosis (Dupont) and also by foreign bodies (Gougerot, Darier, Oppenheim, etc.), all of which are most probably only an expression of an immunological response.

Comment by Dr. H. P. Lie, Bergen, Norway:

The question of Boeck's sarcoid has become more and more complicated, especially since its combination with lupus pernio (Besnier) and lymphogranulomatosis benigna (Schaumann). It is certain only that the question is still far from settled and requires further study. For several reasons I cannot now discuss this confusion on a broad basis, but I would like to mention something to which attention has previously not been called, namely, that terms like "tuberculoid," "leproid," "epithelioid," are all so unclear, indistinct and vague that they cannot form a sure and safe basis for a distinct description of the pathological changes in question. It may therefore happen that they are used by different authors for rather different changes. The term "reticulo-endothelial" that has been used so generally in late years can also, in my opinion, cause confusion. As far as I know it is a general or at least wide-spread opinion that leprosy is only an affection of the reticulo-endothelial system. This must be wrong; or do the ganglion cells also belong to the reticulo-endothelial system?

As I cannot discuss on a broad basis the questions that have been raised by Rabello's statements I shall confine myself to my personal experience that pertains to them.

1. It is generally accepted that *Mycobacterium leprae* can affect the reticulo-endothelial system of man in the skin, mucous membranes, glands, bone marrow, spleen and liver; but it also affects the ganglion cells of the nervous system. Do the sarcoids also do this?

2. Tuberculoid leprosy must be rare in Norway, because only one single case is known in this country. In all other cases with tuberculous or tuberculosis-like changes *M. tuberculosis* has always been demonstrable, either microscopically, by culture or by inoculation, when search has been made for them. Leprosy bacilli have been found in most of the cases of tuberculoid leprosy that I have examined. On the other hand acid-fast bacilli have never been found in any case of sarcoid in Norway, except Boeck's uncertain finding. Some of these sarcoids were large, with tumors not unlike those of nodular leprosy. I think this must be a very important fact.

3. In no case of leprosy have I found the so-called epithelioid cells in such numbers and in such arrangement as in the sarcoids I have examined. However, I wish to say that I have not had the opportunity to examine many cases of tuberculoid leprosy. It must always be borne in mind that the microscopic pictures of the tissues are different in reaction and nonreaction states.

4. I do not know a leprous rhinitis without leprosy bacilli. There is always great risk in a leprosy diagnosis *ex juvantilens.*

5. There is practically always an adenopathy in nodular (C) leprosy of some duration, and leprosy bacilli are always present in these glands. In glands with tuberculous changes tubercle bacilli are always present. In maculo-anesthetic (N) leprosy adenopathies are more rare; these also are in pure cases, caused by the leprosy bacillus. I have never seen sarcoid structure in the glands in leprosy patients.

6. I have not succeeded in finding definite leprous changes in the lungs in pure leprosy, in spite of searching for them during more than forty years. In a few cases I have found leprous bronchitis, and leprosy bacilli in hilus

glands and in the connective tissue round these glands, but that was only in nodular (C) cases, never in maculo-anesthetic (N) leprosy. Regarding radiologically demonstrable leprous changes in bones, I have found affections similar to those in sarcoid but have not yet seen in leprosy as typical an osteitis cystica as one often sees in sarcoid.

7. Nearly all lepers examined here have shown positive reactions to tuberculin. Danielssen found that all cases tested with tuberculin for cure reacted positively.

8. About this question I have no experience of value.

9. Cultivation of *M. leprae* has, in my opinion, not yet been accomplished. It has not been proved that the contaminations of these cultures are characteristic only to leprosy and sarcoids. Further research on the matter is necessary.

10. Regarding this point one must always be very cautious in drawing positive conclusions from negative experiments.

It is to be borne in mind that sarcoid (Boeck) and lymphogranulomatosis (Schaumann) are benign. Is leprosy also a benign disease? Regarding the differential diagnosis between sarcoid and leprosy I have not found it very difficult in my cases. It may, however, be different at times, because there is a point of great importance, viz: the difference of the microscopic pictures of the tissues in reaction and nonreaction states.

Comment by Dr. S. Schujman, Rosario, Argentina:[1]

1. Perfectly admissible, especially in the nodular forms of cutaneous leprosy.

2. The "sarcoid" structure I have as yet encountered only in skin lesions of tuberculoid leprosy and in the thickened nerves sometimes observed in that condition. I have not found it in the numerous cases of enlarged glands that I have studied, nor in the clinical manifestations of visceral leprosy; I have yet to see if the autopsy gives evidence of histological lesions that have not provoked clinical changes.

3. It is especially in tuberculoid leprosy in reaction ("tuberculoid lepra reaction") that I have found the sarcoid histology, with its well delimited nodules in which the epithelioid cells especially predominate, with the lymphocytes to a lesser degree; but in the great majority of cases I have also encountered giant cells, scanty in some and more abundant in others. It may be necessary to look for them for a long time and in serial sections.

4. We have not observed nasal lesions in cases of ordinary tuberculoid leprosy. Only in severe tuberculoid lepra reaction have we encountered, together with the infiltrated plaques of the skin, rhinitis and plaque-like infiltrations of the nasal mucosa which made respiration difficult. In one case the infiltrated plaque ulcerated, leaving a cicatrix adherent to the nasal wall. The rhinitis and infiltrations of the nasal mucosa at times regress with chaulmoogra treatment, and at other times spontaneously, simultaneously with the lesions of the skin.

5. Glandular enlargement in varying degrees I have found in almost all the advanced cutaneous forms, in which gland puncture gives evidence of abundant

[1]From a translation by Dr. M. B. Lara of the Spanish original.

bacilli and globi. Histological studies of these glands reveal a lepromatous structure with Virchow cells loaded with bacilli. In the tuberculoid forms and even in tuberculoid lepra reaction my attention has been called to the absence of enlarged glands, for which reason we have not been able to make histological studies of them.

6. I have seen pulmonary and bone lesions in cutaneous leprosy, but in the cases which present a sarcoid structure (i.e., proved cases of tuberculoid leprosy) I have not yet had an opportunity to observe such lesions. Recently I have examined radiologically with a competent specialist (Dr. Chaves Goyenechea) eight cases that presented clinical skin lesions that histologically were of sarcoid type, and in none of them did the x-rays reveal any bone or pulmonary changes. According to Dr. Chaves Gayenechea some of these presented a discrete increase of the hilar shadow, but this is frequently observed in normal adults. In one case which we have seen with Prof. Fidanza, in which the skin lesions were typical of Boeck's sarcoid, repeated x-ray examination of the lungs and bones showed them to be perfectly normal. On the other hand the patient presented sensory disturbances and a marked enlargement of the ulnar nerve, biopsy of which revealed a typical sarcoid structure, similar to that of the lesions of the skin.

7. We have made numerous intradermal injections with tuberculin (Mantoux reaction) and have found that, as a rule, the test is positive in the cutaneous forms of leprosy. In the tuberculoid forms, on the other hand, the results are extremely variable, being negative in some and positive in others.

8. Unquestionably chaulmoogra oil and its derivatives is the drug that benefits most the tuberculoid forms of leprosy, but I have also seen this type of lesion regress with arsenicals and even spontaneously. Hence in making therapeutic experiments in lepers one ought not to do it in the tuberculoid forms, as in these the allergic state is of more benefit than the medication.

9 and 10. I have no personal experience with cultivation of the leprosy bacillus. In 1934 I inoculated dilutions of triturated leprous tissues into rats, guinea pigs and children, subcutaneously and intraperitoneally, with completely negative results in spite of having done more than 30 inoculations.

To summarize, in tuberculoid leprosy I have observed with relative frequency lesions of the skin clinically and histologically identical to the descriptions of Boeck's sarcoid, but I have not found the glandular enlargements or the osseous and pulmonary lesions that complete the Besnier-Boeck syndrome, as appears to be more frequently observed in tuberculosis.

Comment by Dr. P. H. J. Lampe, Batavia, Java:

My comments on the statement of Dr. Rabello, Jr., concerning the relationship between Besnier-Boeck's sarcoid and leprosy will seem of little value. I got the assistance of a pathologist (Dr. Müller, of Soerabaya), a dermatologist (Prof. Verbunt, of Batavia) and Dr. Lobel, and the few remarks to be made are the result of that cooperation.

At first I was impressed by the statement of the dermatologist that, in his large dermatological practice of more than ten years, he had observed four cases of Boeck's sarcoid of whom three were lepers. I had the opportunity to see two of the three lepers concerned, but I could not agree with the

diagnosis of "sarcoid," as biopsies did not show any tuberculoid reaction but merely lepromatous lesions with numerous large globi. The lesions were small, prominent, discrete ("circumscript") nodules of cutaneous leprosy, a form that is extremely rare in this region.

I believe that it is very difficult and often even impossible to differentiate between the histopathological pictures of Bœck's sarcoid, lupus pernio, erythema induratum and tuberculoid leprosy. As for the tuberculoid lesions in the viscera of lepers, Müller repeats the statement which he made at the leprosy conference at Batavia, that such visceral changes (those of the glottis excluded) are due to tuberculosis, which is opposed to the opinion of Arning [THE JOURNAL **4** (1936) 102] but is in agreement with that of Mitsuda and Ogawa [THE JOURNAL **5** (1937) 60].

With regard to your comments on the ten items of Rabello's argument, I agree completely with the view expressed regarding items Nos. 3 and 4. Concerning items 5 and 6 I have had no personal experience. Rabello's statement in No. 7 is probably wrong, if sarcoid is compared with tuberculoid leprosy. Items Nos. 8 to 10 seem to me problematical.

Comment by Professor John Reenstierna, Stockholm, Sweden:

[Professor Reenstierna's remarks on this matter were received in the form of an original article, which appears elsewhere in this issue.—EDITOR.]