# TRANSFORMATION OF A CASE OF TUBERCULOID LEPROSY IN REACTION TO THE LEPROMATOUS FORM <sup>1</sup>

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In an inquiry about the evolution of tuberculoid leprosy, I wrote in 1936 (7), that I had not seen a typical case of tuberculoid leprosy—characterized clinically by its well-defined lesions, bacteriologically by the absence of bacilli, histologically by tuberculoid structure, and immunologically by a positive reaction to lepromin—undergo transformation to the typical lepromatous condition with its characteristic features—diffuse, poorly delimited lesions, abundant bacilli, lepromatous histology, and negativity to the Mitsuda test. I asked for the opinion of other specialists on the matter, and added that if the majority of leprologists should assert that they had not observed this transformation, that fact would argue in favor of recognition of the tuberculoid form as a distinct type, separate from the neural and lepromatous forms.

Up to the present time I know of no report of the transformation of a typical tuberculoid case, one which could be called complete in that it had been shown to possess all of the characteristics mentioned, into a frank lepromatous case, nor have I observed that occurrence myself until now.

With the acquisitition of knowledge of the condition known as tuberculoid leprosy reaction, first described by Wade (12) and then by Schujman (6), Fernandez (3), Souza Campos(9) and others, cases in which the process of infection is accentuated, with abundant and marked lesions and with transitorially positive bacteriology, it was thought—and with some reason—that perhaps such cases might under some circumstances evolve to the lepromatous form.

Lowe, both in replying to my inquiry (7) and in an article of his own (4), mentioned having seen the transformation developing, especially in the borders of the lesions, manifested by the disappearance of the giant cells and the appearance of the foamy cells of Virchow; but he did not complete this statement with a documentation of any such transformed cases.

Wade and Rodriguez (13, 14), in reference to the evolution of tuberculoid leprosy in reaction, especially where the bacilli persist for long periods

<sup>&</sup>lt;sup>1</sup> Translation from the Spanish, approved by the author.

of time, recorded cases in which they had suspected the transformation to lepromatous but in which that change had not occurred; the cases had only assumed a condition apparently intermediate between tuberculoid and lepromatous which those authors called "borderline." The prognosis of such cases, they added, was uncertain and needed further observation; they registered caution about speaking of lepromatous transformation since some of their cases had subsided and again regressed to their original condition, and they pointed out that factual reports of well-substantiated cases of actual transformation were lacking.

Cochrane (1) pointed out that none of his cases of tuberculoid reaction with positive Mitsuda reactions had been seen to transform to lepromatous. However, besides these frankly tuberculoid cases, there are others which are neither typically tuberculoid nor lepromatous, and which he called "intermediate." These cases he differentiated from the frank reactional tuberculoid by the following characteristics: clinically, the patients are febrile and more ill, and the lesions are less infiltrated and less limited than in such cases; bacteriologically, the bacilli are slower in disappearing; histologically, the structure is not frankly tuberculoid, the subepidermal free zone characteristic of the lepromas is to be seen, and foamy cells are present; and, immunologically, the Mitsuda reaction is negative; this condition he spoke of as "pseudoallergic." He further stated that even in such atypical or intermediate reacting tuberculoid cases he had not observed frank evolution to the lepromatous, although he had a suspicious case which, however, required longer observation for a decision.

Souza Campos (9), in his study of reactional tuberculoid leprosy, stated that he had seen lepromatous transformation in three cases, but he did not publish the histories of those cases.

Velasco (11), in 1940, saying that he had seen several cases of transformation, reported full details of one such case, with photographs and photomicrographs of the lesions before and after the change. At the time of admission the condition was tuberculoid reaction in regression, bacteriologically negative, and it cleared up and the patient was released after 8 months. Nearly six years (68 months) later, during which time he had had no treatment, he returned with typical lepromatous leprosy, clinically (diffused lesions), bacteriologically (abundant bacilli), histologically (frank lepromatous structure), and immunologically (Mitsuda negative). Unfortunately there is no information about the lepromin reactivity during the period of tuberculoid reaction. When this report was reprinted (11) Velasco added a second case, the photographs of which show well the typical reaction tuberculoid condition on admission (1935) and the advanced lepromatous condition which had developed later (1940).

Souza Lima (10) stated that he had observed the transformation of numerous tuberculoid reaction cases to the lepromatous form, a change which may occur indirectly, after an incharacteristic stage, or directly from the tuberculoid form. These latter cases, he added, are distinguished by characteristics which resemble tuberculoid leprosy on the one hand and lepromatous leprosy on the other hand, and for that reason he called them "limitantes" (borderline). Some of these borderline cases, he said, undergo regression like ordinary reactional tuberculoid ones, but others on the contrary transform to lepromatous. In a recent personal letter in reply to an inquiry, de Souza Lima says that he has in preparation a monograph dealing with anomalous leprosy in which he describes 46 cases of this transformation.

In summary it may be said, with regard to ordinary, nonreactional tuberculoid leprosy, that no author has reported its evolution to lepromatous, nor have I observed it myself. As regards tuberculoid cases with reaction, while some authors have maintained only that they have observed a stage suspected of transformation, without certainty that it had actually occurred, pointing out that prolonged observation is needed to make sure of such a change, others are certain of having observed numerous cases undergo that transformation. The only cases reported with ample documentation that we know of are those of Velasco; those cases, at first of the reactional tuberculoid kind, undoubtedly changed to the lepromatous form.

## EVOLUTION OF TUBERCULOID LEPRA REACTION

In 1939 (8), in discussing the evolution of cases of tuberculoid leprosy in reaction, I established three types: (a) single reactions, occuring in cases which have shown no recurrence during periods as long as 15 years; (b) periodical reactions, repeated episodes but sometimes with periods of several years between them, and (c) successive (*subintrantes*), so called because the recurrences are so frequent that sometimes a new reaction may occur before all the evidence of activity of the previous one has disappeared.

It is these "subintrant" cases, which resemble in their manifest features and evolution the kind variously called "borderline," "intermediate," etc., which sometimes give the impression of undergoing transformation to lepromatous because their erythematous patches assume a brownish and bronze color and their borders are somewhat diffuse. However, on further observation we have seen that these lesions regressed almost entirely, or were followed by a new reaction, but without change to an indisputable lepromatous condition.

The only instance of transformation of tuberculoid leprosy in reaction into a frank lepromatous form among our patients has been observed very recently. Fortunately, we have ample data on its clinical, bacteriological, histological, and immunological features during the stage of tuberculoid reaction as well as the present lepromatous one.

#### REPORT OF CASE

#### 1. REACTIONAL TUBERCULOID STAGE

C. F., male 42 years old, married, was first seen in December 1943. He stated that for over a year he had had an achromic, insensitive spot on the right foot; that about six months previously this lesion had become red; and that at the same time infiltrated patches appeared on the back and tubercles of the face. Examination showed wine-red tubercles on the face, and others sparsely disseminated on the body. The general condition was good; no fever or other complaints. A smear from one of the tubercles showed a few bacilli; biopsy was not possible at that time. Clinical diagnosis: Tuberculoid leprosy in reaction. Chaulmoogra treatment (30 cc. weekly) was prescribed. The patient returned 4 months later (April 1944) with the lesions in frank regression. But after another 4 months (August) he returned because of a new and much more severe reactivation, with generalized lesions over almost the entire body. Because of the severity of the process he was hospitalized.

Condition on admission (August 1944).—The face and neck were almost entirely covered with tubercles of various sizes, ranging from a grain of corn to a nut, well elevated and clearly delimited, some pinkish in color, others frankly erythematous, and still others wine-red and ham-like; some were surrounded by a wide erythematous halo (Fig. 1).

The upper and lower extremities, the back, buttocks, chest and abdomen in their greater part were covered with similar lesions. On the right arm, besides the tubercules, there was an oval lesion with erythematous borders, elevated, infiltrated, and of smooth surface. On the back and thighs some of the tubercles were of a violet-red color, and some showed superficial desquamation. Nodules overlaid with skin of normal aspect could be palpated on the thighs. On the abdomen and thighs there were elevated, infiltrated and erythematous plaques.

The nasal mucosa was without lesions. In both inguinal regions there was marked adenopathy, the lymph nodes of noninflammatory type. The patient was slightly ill, but without fever or pain.

Bacteriology.—A smear from an erythematous tubercle revealed disseminated bacilli in the most of the fields, and globi with acid-fast granulations. A smear of material obtained by puncture of an inguinal lymph node revealed rare bacilli in a state of fragmentation (diplobacillary and streptococcoid forms).

Lepromin reaction.—Early (Fernandez) reaction negative. Mitsuda phenomenon slightly positive on the 21st day (yellowish erythematous nodule 3 mm. in diameter).

*Histopathology.*—Biopsy specimens were taken from two tubercles, and an inguinal lymph node was extirpated.

Skin lesions: Epidermis flattened. Subepidermal band respected for the most part, but in places invaded by the infiltrate. In the corium, a dense infiltration disposed in nodular form or in bands, but well circumscribed, the typical focus comprising a clear epithelioid center and a peripheral lymphocytic corona (follicular); scarce Langhans giant cells. In short, tuberculoid structure (Fig. 3).

Lymph node: The marginal sinus somewhat dilated but unaltered. In general the structure normal, but with marked proliferation of reticuloendothelial cells. At the periphery a diffuse infiltrate, centrally assuming a follicular disposition with clear zones of the epithelioid type. Admixed with those cells, multinucleate cells and some plasma cells. The general aspect resembles the sarcoid structure (Fig. 4).

*Diagnosis.*—Tuberculoid leprosy in reaction, with weakly positive immunological reaction.

Treatment during hospitalization.—Because of his reaction condition he was first given a series of 10 injections of calcium, after which he was put on chaulmoogra, 30 cc. weekly. The lesions started to subside and flatten, and after 45 days the patient went home slightly improved.

#### 2. STAGE OF LEPROMATOUS TRANSFORMATION

Despite his promise to continue the treatment and to return periodically, the patient was lost to sight for five years. In July 1949 he returned presenting a picture of ordinary lepra reaction with features of the lepromatous type. His account of events during that period is as follows:

He had continued the prescribed treatment, he said, for one year and took an approximate average of 15 to 20 cc. of chaulmoogra weekly; and his lesions almost completely disappeared. In October 1945 he fractured an arm, and so clean of lesions was he that the physicians attending him in the sanatorium in which he was treated noticed nothing. After that he completely neglected the treatment for more than a year, and then, about the end of 1946, several erythematous spots appeared on the abdomen. He resumed a moderated treatment he says, and although some of the lesions faded out others of a maroon or brownish color appeared. In October 1947, and again in the middle of 1948, he had two reactions with edema of the legs, malaise and fever, which obliged him to stop working. Treatment caused those lesions to become pale, but they never disappeared. Some assumed the color of tea with milk; they were not elevated, but they increased in size. Others became infiltrated, but with indistinct borders, like those of the face. A few tubercles began to appear, especially on the extremities.

Two months before readmission (i.e., May 1949) a new reaction appeared, with the same general symptoms as before and also the appearance of lesions of the erythema nodosum type. This reaction showed no tendency to regress; on the contrary, the temperature rose to about 39°C. and also the pains and other symptoms increased, and for that reason he decided to be hospitalized.

Condition on readmission (July 1949).—Patient very weak, temperature 39°C., complaining of pains in the joints and in some of the reaction lesions. Involving almost the entire face there is a diffuse lepromatous infiltration, the color maroon or bronze, slightly elevated but with poorly defined outer borders (Fig. 2). Elsewhere, disseminated over the whole cutaneous surface, are flat, diffuse-bordered lesions of the colors already described and of different sizes. Some are confluent, especially on the arms and thighs. In these lesions there are a moderate number of erythematousbrownish or yellowish-brown tubercles.

Attention is especially drawn to the presence of, besides the erythemanodosum elements commonly observed in acute lepromatous reaction, other reaction elements of the size of a hen's egg, elevated, quite red and inflamed, and with ulcerated and purulent centers—elements resembling abscessed tumors, which at their beginning were also red nodosites.

The nasal mucosa presents erosions and ulcerations on both sides of

the septum. The pharynx and larynx are not affected (Dr. Litmanovich). Eye examination reveals no changes attributable to leprosy (Dr. Soto). There is marked inguinal adenopathy of noninflammatory type.

Bacteriology.—Nasal mucosa: From the erosions, abundant granulated acid-fast bacilli. Skin: From the bronze-colored spots, moderate number of homogenous bacilli, but especially diplobacillary forms. Tubercles: Markedly positive, with globi and free bacilli in the majority of the fields. Ulcerated nodular lesions: Abundant globi.

Lepromin reaction.—Early (Fernandez) and late (Mitsuda) reactions both negative.

Histopathology (Dr. Castañé Decoud).—A biopsy specimen from a diffuse, bronze-colored lesion: In the subpapillary network is seen proliferation of the fixed cells disposed in diffuse accumulations composed of lymphocytes and fixed cells, some of which are vacuolated in the manner of the Virchow cells. In the middle and deep layers of the corium the infiltrates are of the same type but larger, located around the vessels, nerves, and glands. Here the vacuolization is more manifest, producing the appearance of unicellular cysts—the typical lepromatous aspect. There are zones of perineuritis, and distinct vacuolization in the interior of some nerves (Fig. 6). Moderate number of bacilli are found. In short, lepromatous structure.

Tubercle: The subepidermal band is unaffected. The whole corium is filled with a very dense infiltrate, composed especially of Virchow cells in different stages of vacuolization, in places so marked as to form veritable microcysts. Abundant globi with homogenous and fragmented bacilli. Typical lepromatous structure (Fig. 5).

Lymph node: Capsule without notable changes. Marginal lymph sinus partly unchanged, partly dilated, and partly obstructed. There are significant changes, but the architecture of the ganglion with its follicles and sinuses is preserved. In the interfollicular spaces there is great proliferation of reticuloendothelial cells, the majority markedly vacuolized (Virchow foamy cells); and intermingled with them are plasma cells and a few eosinophiles. Giant cells of the foreign body type are also seen. Abundant globi. Typical lepromatous structure (Figs. 7 and 8).

Summary .- This patient was seen for the first time nearly 6 years ago, in 1943, with a clear-cut tuberculoid reaction which regressed under chaulmoogra treatment. He returned nine months later in a most severe reaction condition, the entire cutaneous surface being covered with lesions which clinically and histologically were of the tuberculoid reaction type although they showed "borderline" or "intermediate" aspects. This reaction also subsided entirely, but after abandoning treatment for over a year new eruptions appeared. This time the lesions did not disappear; on the contrary, they increased and assumed a more diffuse aspect. The patient then returned, five years after he had last been seen, in a frank lepromatous condition with typical lesions of the skin and nasal mucosa, and lepromatous histological changes were found in the skin lesions and lymph nodes. Smears and sections revealed very abundant bacilli, and the immunological (lepromin) reaction was quite negative.

### DISCUSSION

As has been said, tuberculoid reaction cases may differ greatly in their evolution. In some the reaction regresses definitively, leaving no traces or only achromic or atrophic lesions. According to Cochrane and our own observations, such cases are strongly positive to the lepromin reaction. In other cases there are successive reactions, with between them more or less prolonged periods of relative inactivity. These latter cases, according to certain authors, may evolve to the lepromatous form, a transformation which is highly exceptional in our experience.

What is the reason for such different courses of evolution? In an article now in preparation on the evolution of tuberculoid reaction cases in relation to their immunology the matter is to be discussed in detail. It may be said here that I believe the latter course of evolution does not depend on the severity of the reactions or on the number of lesions, but that it is entirely a matter of specific resistance to the leprosy bacillus, and that resistance or lack of it is revealed by the results of the lepromin reaction.

As for the present case, I have seen others with tuberculoid reactions no less severe yet they regressed definitively, and such cases have been observed for periods as long as twelve years without relapse. It is probable that reinfection was not a factor in this case, for during the five years when he was lost to sight he was not in a bacilliferous environment such as a leprosarium. I believe that the essential factor which influenced this unfavorable transformation was an organism with low resistance to leprosy as shown by the weakly positive response to the original lepromin (i.e., that that was a case of "pseudoallergy" of Cochrane, which may also be called "hypoallergy").

As I have said elsewhere, I have never seen a strongly positive Mitsuda reaction become negative. On the other hand, patients giving weakly positive reactions (erythematous or yellowish papules 3 mm. in diameter after 21 days) may either change to strongly positive, or remain with reactivity unchanged for years, or show decrease until the reaction is frankly negative, the patient anergic.

In the present case the resistance at the outset, though low, sufficed to give rise to a clinically and histologically tuberculoid reactional response, with subsequent recession of the lesions. Later the suspension of the treatment for more than a year and the gradual dimunition of the weak resistance, which ultimately was lost (Mitsuda negative), permitted the infectious process

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to acquire a new impulse and to change to a progressive form, developing the frankly lepromatous picture with clinically, histologically, and bacteriologically lepromatous lesions of the skin, mucosa and lymph nodes.

## SUMMARY AND CONCLUSION

The first case of transformation from tuberculoid leprosy in reaction to the typical lepromatous form observed by the author is described, and the following conclusions are arrived at:

(a) That this transformation is observed only exceptionally in Argentina.

(b) That the prognosis of tuberculoid leprosy in reaction does not depend on the severity of the reaction or on the number of lesions, but rather on the specific organic resistance indicated by the intensity of the Mitsuda reaction; and that only those reactional tuberculoid cases with weakly positive or negative Mitsuda reactions may evolve to the lepromatous form.

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# DESCRIPTION OF PLATE

# PLATE 1.

FIG. 1. The patient in 1944. Tuberculoid reaction, with erythematous tubercles and plaques.

FIG. 2. The patient in 1949. Lepromatous transformation, with typical diffuse-bordered infiltrations.

FIG. 3. Photomicrograph of a nodule of the tuberculoid reaction condition, showing a typical follicle with epithelioid-cell centers and a giant cell.

FIG. 4. A biopsied lymph node in the tuberculoid state, showing large epithelioid collections (sarcoid structure).



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PLATE 1.

# PLATE 2.

FIG. 5. A section from a tubercle after lepromatous transformation, showing large numbers of Virchow cells in the subpapillary network.

FIG. 6. High magnification field of a bronze-colored macular lesion. Lepromatous changes involving a nerve, with perineuritis and several vacuoles within the nerve.

FIG. 7. A lymph node after lepromatous transformation, showing the great abundance of foamy cells.

FIG. 8. High magnification field of the lepromatous lymph node, showing the prominence of the spongy cells of Virchow and the unicellular cysts.

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PLATE 2.