

## THE "ACUTE INFILTRATION" REACTION OF LEPROMATOUS LEPROSY<sup>1</sup>

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### INTRODUCTION

In the course of leprosy there may occur several kinds of acute reactional conditions, with such symptoms as fever, exanthematous eruptions, and erythema of pre-existing lesions. These acute syndromes vary according to the type of the disease, its advancement or stage, and other factors. Foreign workers often call these conditions "lepra reaction," or "lepra fever," frequently without discrimination between the different kinds.

Among the nonlepromatous forms of the disease—not considering here such things as acute neuritic syndromes in neural cases—it may be noted that a few leprologists, specifically certain South Americans, recognize two forms of reactions: (1) reaction in established tuberculoid cases, which is simply an activation of pre-existing lesions of that type, perhaps with the development of new ones, a condition not given special status by Japanese workers; and (2) "reactional tuberculoid leprosy," a more spectacular condition which may arise in cases with only flat macular lesions (e.g., maculoanesthetic cases), or in slight, minor-grade tuberculoid cases, or even—but not often—in persons who previously were without any lesions. This second form of reaction is what has long been called "*akuter Schub*" in Japan.<sup>2</sup>

In the lepromatous type of leprosy there can be distinguished three kinds of acute episodes. These are:

(1) *Acute lepromatous infiltration*, or "*reactivation*,"<sup>3</sup> in which there is an active aggravation of infiltrations or nodules caused by increase in the bacillus-containing lepra cells. Although the condition is acute, the aggravation of the patients' lesions occurs over a period of several weeks or months instead of days, even in the most acute cases. Later, after the lesions have been resorbed and the bacilli have disappeared, there still persist for a long time accumulations of lipid-filled foamy cells. This

<sup>1</sup> This article represents translations of two articles which appeared in *La Lepro* **23** (1954) 119-121 and 261-269 (abstracts in *THE JOURNAL* **23** (1955) 343. Those articles have been combined and extensively rewritten in the present one.

<sup>2</sup> Pictures of cases of this condition are to be found in an article in English which I published in 1936 (<sup>13</sup>).

<sup>3</sup> "Acute lepromatous infiltration" is the term usually seen in Japanese reports, and that was used in the articles on which the present one is based. At the suggestion of the editor, this is changed herein to "acute lepromatous activation" to avoid confusion. The point is that this type of reaction is an acute aggravation of the pre-existing lepromatous condition.

acute exacerbation in the lepromatous type is mainly a histopathological condition, analogous to what is often seen in the tuberculoid type (the first of the two kinds referred to above). It is very different from the "acute infiltration" which is to be discussed.

(2) *Erythema nodosum leprosum* (ENL), a distinctive eruptive condition that usually occurs in the resorptive phase, and more frequently now under sulfone treatment than previously. The erythematous eruptive elements may be few or numerous; usually they are widely scattered, and they rarely fuse; in size they may vary from the end of the thumb to the yolk of an egg; they are typically painful. If numerous, the eruption may be accompanied by fairly severe symptoms, with fever and oppressive pains in nerves and joints. The patient may be quite ill, but the leprosy itself does not show any exacerbation.

(3) The *acute infiltration* syndrome, the subject of this study, is a specific one occurring abruptly in lepromatous cases, sometimes in an early stage but more frequently after a prolonged period of regression and resorption of the disease, without augmentation and aggravation of the pre-existing lepromatous lesions—in sharp distinction from the first condition described above. It is characterized mainly by an erysipelas-like eruption—i.e., a hyperemic, more or less edematous infiltration—which may be limited or extensive. Not rarely, the eruption appears so abruptly that the face becomes markedly swollen overnight. Recession, on the other hand, is slow, and it may take one to several months for the eruption to disappear. In the event that the eruption becomes fixed, it becomes actually an exacerbation of the lepromatous condition, but it is not so originally.<sup>4</sup> The acute infiltration lesion itself consists mainly of an infiltration of lymphocytes, plasma cells and epithelioid cells, sometimes with Langhans or atypical giant cells. Young lepra cells may be present in the new lesions, but older lipid-containing cells are usually absent. Seldom, if ever, are they found anywhere except outside the newly developed lesions as if they had been pushed aside by the infiltration. Needless to say, lipid-containing cells are seen in the sites of resorption of old lepromatous lesions.

It is necessary to return here to the *akuter Schub* reaction. Fumio Hayashi (2), in discussing classification, defined *akuter Schub* as "an abrupt and extensive erythematous infiltration occurring in neural or tuberculoid cases, or in recessive ones of the lepromatous type" (*italics mine*).<sup>5</sup>

<sup>4</sup> When the acute infiltration condition occurs repeatedly it may happen that the eruption remains long unresorbed and changes to the proper lepromatous infiltration clinically and histologically. In such cases it is difficult to say which condition is being dealt with, "acute infiltration" or "acute lepromatous reactivation."

<sup>5</sup> In this connection he also said that "acute infiltration is an acute and extensive appearance of lepromatous infiltration," which is a different concept from mine, as stated. What he called "acute infiltration" I would now call "acute lepromatous reactivation" (see footnote 3).

For a long time this was the accepted application of the term *akuter Schub*, and consequently there was confusion. It is true that, regardless of type of case, there are close resemblances in the manifestations of the two conditions (i.e., infiltrative lesions resembling erysipelas, with fever and other general symptoms), and also in the mechanism. There are, however, differences in the course and other features between on the one hand the *akuter Schub*, which occurs in tuberculoid and neural cases, and on the other hand the "acute infiltration," which occurs only in lepromatous cases. It is necessary, therefore, to make a distinction between them.

At the Sixth International Congress of Leprology, held in Madrid in 1953 (4), it was decided to insert a "borderline (dimorphous) group" as an intermediate one between the two polar types, lepromatous and tuberculoid. As for the definition of this group, there are doubts and objections among some workers. As I understand it, the borderline group would seem to include the acute infiltration, but there are important differences in that in acute infiltration the Mitsuda reaction is positive and the prognosis is favorable, contrary to the description of the borderline group. (See, however, the addendum to this article.)

The question of type classification of acute infiltration will not be discussed now. For the present, the condition is situated in an interesting but undefined field, and the groundwork has not yet been consolidated. Only recently have many leprologists in Japan come to recognize the fact that this condition is a specific and clearly-distinguishable syndrome in the course of leprosy. Considering that fact, I have named it "acute infiltration" anew, a term which I used in my first article on the subject (11) and which Mitsuda used in his Atlas of Leprosy (7).

As for descriptions of acute infiltration in the literature, there are a few reports of mine (11, 12). The writings of Fumio Hayashi contain a description of one such case (9). Yoshinobu Hayashi (3) reported four cases of this syndrome (Table 1). Mitsuda (8, 9) employed the term "acute infiltration" clearly in discussing the classification of leprosy, and its histology is shown in Figure 44 of his atlas and in an article by him and associates (8).

#### DESCRIPTION OF ACUTE INFILTRATION

*Stage of occurrence.*—Most cases of this condition appear in the resorption stage of lepromatous leprosy. All four of the cases of Y. Hayashi shown in Table 1 occurred in that stage, and four out of my five cases. Occasionally, however, a case will be seen in which it appears earlier, soon after transition to the lepromatous type from the original form.

*Cause of acute infiltration.*—Concerning causative factors, Mitsuda (8) has pointed out how numerous and varied are the locations in which the leprosy bacilli may lurk, liable to be displaced or mobilized and to

enter the blood stream as a result of stresses and strains of various kinds. From there they may be deposited in the skin of any part of the body, and thus give rise to exanthematous eruptions of one kind or another. Furthermore, acute infiltration, and also *akuter Schub*, may be precipitated by repeated injections of iodine, or tuberculin, or salvarsan, and

TABLE 1.—Data on cases of acute infiltration observed by Tajiri and by Y. Hayashi, with special reference to the stage of the disease, the Mitsuda reaction, and the histological findings.

Case No.	Onset of leprosy (age)	Became lepromatous (age)	Acute infiltration reaction			
			Occurred (age)	Stage of disease <sup>a</sup>	Mitsuda reaction (mm.)	Biopsy, type
<i>Tajiri's cases<sup>b</sup></i>						
1	69	-----	72	Late	10	Tbd
2	25	-----	26	Late	5	Tbd
3	22	26	27	Late	10	Tbd
4	23	40	60	Late	7	-----
5	14	16	24	Early	8	-----
<i>Hayashi's cases<sup>c</sup></i>						
1	-----	24	26	Late	2+	Tbd
2	25	36	75	Late	2+	Tbd
3	21	24	39	Late	2+	Tbd
4	-----	23	50	Late	—	Tbd

<sup>a</sup> Late = stage of resorption.

<sup>b</sup> Reference No. 15.

<sup>c</sup> Reference No. 4.

sometimes by administration of other drugs (e.g., cepharantin). Yoshie and Fujita (16) reported four cases of acute infiltration excited by recent chemotherapeutic substances (Promin, Promisole, etc.).

I agree with all this about causative factors, but at the same time I believe that the immunological condition of the body with respect to the leprosy bacillus has an essential relationship to the causation of acute infiltration. In other words, judging from the facts that this type of reaction may appear at an early stage of transition toward the lepromatous type, or long after the resorption of lepromatous nodules and infiltrations, it appears that—as Mitsuda conceived it—the lepra bacilli that exist in various places are latent in such periods. In tuberculosis, the body and the tubercle bacilli reach an equilibrium in the form of a primary lesion, and the disease does not then progress. So in the neural type of leprosy, or the resorption phase of the tuberculoid type, the bacilli seem to be prevented from disseminating from the places where



they exist and so from producing other lesions. When, however, the physical strength and resistance of the person are reduced, due to some factor such as pregnancy, parturition, overwork, malnutrition, intoxication, or perhaps some cause not recognizable, then lepra bacilli may get into the circulation as Mitsuda described, or multiply in and infiltrate the local lesions. If such circumstances occur the body's immunity, which decreases during transition to the lepromatous type, and which is restored again long after resorption of the lepromatous infiltrations, operates to restrain the bacilli. The ensuing reaction causes the appearance of fever and an eruption, and in the most severe cases the acute infiltration will appear. The severity of the condition generally parallels the positivity of the Mitsuda reaction.

*Clinical features.*—All sorts of gradations of acute infiltration can be seen, varying from a mere apparent aggravation of activity of existing lesions to the appearance of a very intense, erysipelas-like eruption, the differences of the manifestations depending primarily on the sensitivity and immunity factors of the patient.

**Fever:** In many cases there is a remittent fever ranging from 37° to 39°C. This fever is usually alleviated before the eruptions wholly disappear, commonly within several weeks or a few months, although sometimes it lasts longer.

**Eruption:** The eruption appears abruptly and is an intensely inflammatory one, elevated and often erysipelas-like in appearance. Sometimes it is like a tuberculoid macule or plaque with an elevated border, having the appearance of the reactional condition which many workers (although erroneously) call major tuberculoid. That reactional tuberculoid type of lesion, however, is more intensely inflammatory in appearance, with more marked hyperemia and central elevation.

Unlike the bright red or scarlet color in *akuter Schub* or the tuberculoid reaction, the eruption of acute infiltration is of a dark red color, or brownish-red, even when most active, so with experience the two kinds of eruption can be distinguished.

In either acute infiltration or *akuter Schub* the erysipelas-like eruption is to some extent edematous. That condition is recognizable histologically as well as clinically.

Desquamation is a valid element of differential diagnosis. It will be seen in many cases of both *akuter Schub* and acute infiltration. Pityriasis-like or ichthyosis-like desquamations, and still larger ones, occur in the stage of resorption of the eruption. In the condition when lepromatous lesions are actively enlarging, desquamation is usually not seen.

**Depilation:** Infiltration of the face and head in a marked reaction is often complicated by loss of eyebrows and hair of the scalp. The hairs grow back again, however, after the eruption disappears.

**Neuralgia and arthralgia:** The eruption is often accompanied by neuralgia and arthralgia, and conjunctivitis is also not rare. Thickening

of peripheral nerves (especially N. auricularis magnus, N. ulnaris and N. radialis) or of cutaneous nerves near eruption lesions, is also found.

**Anesthesia and paralysis:** Anesthesia naturally occurs in acute infiltration eruptions. Sometimes there is atrophy of hand muscles (thenar, hypothenar), and flexing of the fingers occurs, with marked reduction of the grasping power of the hand. Tibialis paralysis will cause ataxia. Facial paralysis may complicate the picture. In one case studied (12), temporary affection of the medulla oblongata caused the symptoms of bulbar paralysis.

**Hematology.**—I have made blood examinations in only a few cases. According to Onishi (10), there are no marked differences in this matter between acute infiltration and *akuter Schub*. At the height of the reaction there is only slight—virtually negligible—leucocytosis. In the cases examined the number of leucocytes averaged only 9,186.

In the differential count, polymorphonuclear neutrophils increase to as much as 64 per cent at the height of the condition, decreasing slowly as the reaction subsides, to reach 55 per cent on the average, which is a little less than the average number in the quiescent phase of leprosy. The lymphocytes, on the other hand, become 20 per cent, somewhat less than the average in healthy cases, increasing to 25 per cent as the symptoms subside, usually remaining within the range for healthy cases. Some of the patients have more lymphocytes, over 30 per cent, in the inactive period after symptoms have wholly disappeared. Eosinophils are increased in number, both during and after the reaction; in general, there are about 7 per cent of them at the height of the reaction, 6 per cent during the stage of resorption, and 7.5 per cent in the inactive period afterward. Mononuclear leucocytes are as many as 9 per cent at the climax, and reduce to less than 7.5 per cent in the resorption phase. There is nothing noteworthy about the young forms of leucocytes or other abnormal cells.

The number of erythrocytes remains within normal limits. The hemoglobin index, measured with the Sahli hemoglobinometer, is normal.

**Bacteriology.**—It is difficult to find lepra bacilli in smears from the acute infiltration lesions, although not as difficult as in the case of the eruption of tuberculoid type. The same is to be said of the search for bacilli in histological sections. Bacilli are much fewer than in lepromatous nodules, or the lesions of the acute lepromatous activation. In sections of the acute infiltration lesions they are more easily found in the histological foci of the condition than in tuberculoid lesions, and they present forms which are not degenerated. This is a remarkable feature.

**Immunology.**—The Mitsuda reaction is discussed in detail in a later section of this article. Suffice it to say at this point, as before, that most cases of acute infiltration give negative Mitsuda reactions before that event but are transformed to positive reactors during it and for some time afterward.

**Prognosis.**—As might be expected, those cases that turn Mitsuda posi-

tive show favorable changes in the evolution of disease. Instead of the disease progressing indefinitely as it so often does in lepromatous cases, the infiltration and nodules undergo resolution and leave the patient in the condition called secondary neural leprosy. Such cases acquire stability, and healing of the disease occurs. On the other hand, some patients become Mitsuda negative once more, and the lepromatous infiltrations reappear. Some suffer from progressive and irrevocable paralysis of sensory and motor nerves. In general, most cases with acute infiltration do not evolve in the malign pattern; the reaction gives them a chance to take a favorable turn.

#### HISTOPATHOLOGY

The histopathological findings in the lesions of acute infiltration are quite different from those of the lesions in the acute lepromatous reactivation that has been described, although both of these reactional conditions belong to the lepromatous type. In a previous publication (14) I have discussed the findings in acute infiltration, but will describe them anew here because there are things to be added.

Relatively little abnormality is to be found in the epidermis or the basement membrane. Just under the papillary zone and in the upper part of the corium there is usually a thin zone where relatively rare lepromatous changes are to be seen. When the lepromatous infiltration is resorbed, the skin is usually atrophied and the papillary zone flattened. The principal changes are found deeper, in the stratum reticularis. Here there is marked infiltration of small round cells, and also of epithelioid cells. Langhans giant cells or cells which resemble them may also exist, but sometimes such cells are absent. Mast cells and plasma cells also appear.

The epithelioid cells and giant cells stain faintly with Sudan III, but there is no comparison with the degree of staining of ordinary lepra cells, or of foamy cells which contain the leprosy lipids. Ordinarily, lipid-containing cells do not exist in these lesions to anything like the extent that they do in the ordinary leproma. The epithelioid cells are swollen, and those that show some staining with Sudan III are usually scattered individually, most numerous around the small blood vessels. In general, such findings are relatively marked in the mid-level of the corium.

The leprosy bacilli that are present stain well by the Ziehl-Neelsen method, not being degenerated. They are not clumped together in the cigarette-bundle arrangement commonly seen in lepromas, but they make aggregates consisting of a few bacilli. Bacilli are found in the epithelioid cells of the lymphoid-epithelioid-cell infiltrates, in which giant cells are occasionally formed. Few are found in the papillary zone, or in connective-tissue cells, or around sweat glands, or in the interstitial cells of nerves.

The collagenous connective tissue of the corium is split as if pushed aside by the infiltrations, which therefore seem to be divided into lobulations. Elastic fibers are almost normal in the papillary zone, but are liable to disappear in the lepromatous infiltration lesions. However, they are seen, in compact form especially, around the infiltrations in the lower zone of the corium. Thus the location of the collagenous connective tissue is not necessarily the same as that of the elastic fibers. Thickening of the capillary vessels of the mid-dermis is found in the infiltrative lesions.

Generally speaking, the lesion areas are much more moderate in the deeper zone of the reticularis than in the upper zone. Occasionally the infiltration involves the sweat glands, in which case they will usually be atrophied and will disappear in the end. The subcutaneous tissue, on the other hand, is hardly invaded at all.

#### MITSUDA REACTION IN ACUTE INFILTRATION

One of the most interesting features of the acute infiltration condition is the frequent change, temporary or prolonged, of the reactivity of the patients to the Mitsuda test, as mentioned. This matter has been studied at some length.

*Reading of the reaction.*—In my experience it has seemed desirable to change slightly the readings of the reaction from what has been standard in the past, based on the size of the late reaction lesions after fourteen days. To show how the criteria I have used compare with those adopted recently by responsible bodies, they are given parallel with the recommendations of the WHO Expert Committee on Leprosy (15) and the Madrid Congress (4).

Grade	Tajiri	WHO Committee	Madrid Congress
Neg.	0-2 mm.	< 3 mm.	None
±	3 mm.	3-4 mm.	< 3 mm.
1+	4-6 mm.	> 4 to 7 mm.	3-5 mm.
2+	7-10 mm.	> 7 to 10 mm. <sup>a</sup>	> 5 mm.
3+	11 mm. & more	> 10 mm. or ulcerated <sup>b</sup>	Ulcerated

Under the WHO heading above, reference (a), the 2+ reaction is specified as without ulcer; reference (b), the 3+ reaction is more than 10 mm. without ulcer, or any size with ulcer. The 3+ of the Madrid schedule must be ulcerated, otherwise the reading is 2+ no matter how large the reaction nodule may be.

Mitsuda's antigen consists of 1 gm. of leproma nodule in 20 cc. of physiological saline. My experience has shown that this concentrated suspension may be diluted with saline two times, or even as much as four times, with very slight differences in the resulting reactions.

In total, 24 cases were tested during the acute infiltration episode. Most of them also had tests either before or after the reactions, or both. The results of these tests are shown in Table 2.

The first point to be noted is the reactivity of the cases during the acute infiltration, the tests made within three months of its onset. Only 2 of them were negative by the criteria employed, while 22 were positive



in some degree; 12 were 1+, 9 were 2+, and 1 was 3+. Moreover, one of the negative cases was found to have become positive when tested some two years later.

This finding is especially striking because these were lepromatous cases, i.e., belonging to the type that is Mitsuda negative almost by

TABLE 2.—Mitsuda reactions in 24 cases tested during the acute infiltration (A.I.) together with tests made before and afterward.

Case No.	Reactions prior to A. I.		Reactions during A. I.	Reactions after A. I. <sup>a</sup>			Prognosis <sup>b</sup>
	>6 mos.	<6 mos.		<1 year	1-3 years	>3 years	
1	—	—	2+	—	1+	3+	Good
2	—	—	1+	1+	—	1+, <sup>c</sup>	Good
3	—	—	1+	2+	1+	—	Good
4	—	—	2+	—	1+, 1+	—	Good
5	—	—	1+	—	—	—	Bad
6	—	—	—	—	—	—	Good
7	1+	—	1+	—	—	—	Good
8	—	—	2+	2+	—, <sup>2</sup>	—	Good
9	—	—	—	—	1+, <sup>2</sup> , — <sup>3</sup>	1+, <sup>4</sup> , <sup>d</sup>	Good
10	—	—	1+	—	1+	—	Bad
11	—	—	2+	—	1+, <sup>1</sup> , <sup>2</sup>	2+, <sup>6</sup> , 1+, <sup>8</sup>	Good
12	—	2+	2+	+	1+	—	Unkn.
13	—	+	1+	1+	1+	— <sup>5</sup> , <sup>6</sup>	Bad
14	—	1+	1+	—	1+	—	Good
15	—	—	2+	1+	—	—	Good
16	—	—	1+	2+	—	—	Good
17	—	—	1+	2+, +	1+, <sup>1</sup> , <sup>2</sup>	—	Unkn.
18	—	—	1+	—	1+	—	Good
19	—	—	2+	2+	—	—	Unkn.
20	—	—	2+	—	1+	—	Good
21	—	—	1+	—	1+	—	Good
22	—	—	2+	—	1+	—	Good
23	—	—	3+	—	1+	—	Unkn.
24	—	—	1+	1+	2+	—	Good

<sup>a</sup> The small figures, superior position, indicate in each instance the year after the acute infiltration reaction when the test was made.

<sup>b</sup> Unkn. = not known.

<sup>c</sup> This case was more reactive later—2+ in the 6th year, 3+ in the 7th year, and 2+ in the 8th year after the acute infiltration.

<sup>d</sup> In this case there was a relapse of the acute infiltration in the 4th year after the first one.

<sup>e</sup> This case was remarkable in that it had eight further tests after the third year one: 4th and 5th years, 1+; 6th year, 3+; 7th, 9th and 10th years, 2+; 17th and 19th years, 3+.

definition. Moreover, most of them had been proved to be negative before the reactional outbreak. In total, 17 had been tested beforehand, 10 of them within six months. In 13 of these 17 cases the result was

negative; 2 of them were 1+ (1 of the earlier group and 1 of later group), while 1 was 2+, two months before onset. One case in the less-than-six-months group was not entirely negative, but the reaction was of the doubtful ( $\pm$ ) grade.

During the period of the acute infiltration episode 11 of the 13 cases that previously had been negative, and the 1 that had been doubtful, became positive—5 of them 2+, the others 1+. As said, two remained negative at that time but one of them became positive later; the other was not tested again. The cases that were positive before the acute infiltration remained unchanged.

Out of these cases that had become positive, the reactions of three (Cases 8, 10 and 13) were later found to have turned negative again, in tests made 1, 4 and 5 years after the event. Those times do not, however, signify just when the reversal of reactivity occurred; more frequent tests would have been required to determine that.

On the other hand, the tests of several of the cases showed long-continued persistence of positivity, more than three years. The outstanding case is No. 18, which was under observation for about 20 years and tested repeatedly. After about five years the reactions became stronger, usually 3+ the case having become secondary neural. No. 11 was positive 8 years after the event, No. 13 6 years afterward, and No. 1 5 years afterward.

Generally speaking, it would seem that these cases are inclined to turn negative again after having been positive for a while. Yet fairly many of them did not do so, as we had rather expected they would. At least it can be said that most of the cases that turned positive after the onset of the acute infiltration episode continued to give positive Mitsuda reactions for from two to five years thereafter.

Case 9 is an interesting one. The Mitsuda reaction was negative at the time of the outbreak, was found positive (1+) two years afterward, and negative again in the third year. Then, in the fourth year, there was a second attack of acute infiltration, when the reaction was again 1+.

Two cases not included in the table may be mentioned. From their histories they were thought to have suffered from acute infiltration many years ago, and from the fact that their eyebrows remained absent it was thought they had been of the lepromatous type. They were found to give positive Mitsuda reactions (1+ and 2+, respectively), eight to seventeen years after the episode. It cannot, however, be said with certainty that this reactivity had any relation to the acute infiltration. No test was made at the time, and of course the Mitsuda reaction may turn positive without acute infiltration, when the resorption phase of lepromatous leprosy is prolonged.

With respect to prognosis in these cases, it will be seen from Table 2 that it proved to be good in 17 of the 24, for they got well. It was bad in only 3 of them, which got progressively worse, with reappearance of infiltrations and nodules. The outcome of 4 cases is not known.

## SUMMARY

Mitsuda (5) has written:

"Some cases of the lepromatous type of leprosy, with negative skin reactions, develop an acute condition on the face and extremities, but not with such high fever as occurs in erythema nodosum leprosum. This syndrome, which will be named "acute infiltration," is peculiar in that the skin reaction is usually positive, not negative as is the rule in the lepromatous type. Since the skin reaction is always negative in erythema nodosum leprosum, that condition is thereby distinguished from acute infiltration. This acute infiltration appeared in 19 cases, or 1.3 per cent, out of 1,463 cases of the lepromatous type. The intensities of their skin reactions were as follows: 1 case was 3+, 7 cases were 2+, and 9 cases were 1+; 2 gave doubtful ( $\pm$ ) reactions. The hyperemic swellings of this condition are gradually resorbed, but the positive skin reactions remained long after the attacks."

To summarize, acute infiltration may occur in an early stage of lepromatous leprosy, or late in the long-continuing absorption phase, especially when the lepromatous nodules or infiltrations are resorbed rapidly because of treatment. Like the other forms of reaction, it may be precipitated by various factors, but it does not occur at the stage of the disease when erythema nodosum leprosum or the acute lepromatous infiltration may occur.

The eruption appears acutely, in extreme cases causing, overnight, erysipelas-like swelling on the face, the extremities, or the trunk. In its general appearance it has some resemblance to that of the reactional tuberculoid condition (*akuter Schub*), and it is often difficult to distinguish it from that condition.

As for the histological findings in the eruptive skin lesions, the most numerous elements are small round cells, with a few mast cells and plasma cells, but the significant element is more or less abundant epithelioid cells, and sometimes Langhan's giant cells or cells that resemble them. Foamy lepra cells, specific to the lepromatous type, are not present in the round-cell infiltrations; if they exist they are at the boundary, as if they had been pushed aside by the infiltrations. The epithelioid and Langhan's cells stain faintly with Sudan III. Lepra bacilli are scattered; some are phagocytosed by the epithelioid and other cells, while others are found extracellularly. Aggregates of the cigarette-bundle type are never found.

The Mitsuda reaction at the time of the episode was positive in 22 of 24 cases or 92 per cent. Although the proportion of positives is high, the degree of reactivity is far less than in the tuberculoid type, especially in so-called *akuter Schub*.

Positivity of the Mitsuda reaction usually continues long after absorption of acute infiltration, and may last for more than ten years, or even twenty years. Cases may turn negative again, but that apparently does not happen until some time after the acute infiltration clears up.

As might be expected from the Mitsuda reactions, it seems that attacks of acute infiltration seldom make the prognosis worse. On the

contrary, the course of the disease ordinarily becomes more favorable. Acute infiltration is a turning point at which the Mitsuda reaction usually reverts to positive. Since the results of the Mitsuda test differ according to the immunological status of the individual, it follows that if this acute infiltration is brought about by some medical treatment or irritation (Promin, iodine, etc.) it is to be expected that that effect may be a means of obtaining desirable results in the cure of leprosy.

#### CONCLUSION

The "acute infiltration" of lepromatous leprosy is an abruptly developing but transitory syndrome which sometimes appears in an early stage of that type, but more often after the case has been for a considerably long time in the prolonged absorption stage. Clinically it presents an appearance of erysipelas-like redness, infiltration and edema and is accompanied by fever (37° to 39°C) and joint pains. It has to be distinguished from a rather similar reactional condition of tuberculoid leprosy called *akuter Schub*.

Histologically, the lesions are like those of reactional tuberculoid leprosy. Lepra bacilli are more numerous than in the lesions of that condition, but much less in number than in the acute lepromatous reactivation (ordinary "lepra reaction"). In this respect the histological findings are quite different from those of any other acute condition that might be confused with acute infiltration.

The Mitsuda reaction usually turns positive, and the positivity last for a fairly long time. Some cases have given positive reactions as long as twenty years after the eruptive episode.

In many cases this condition is favorable for prognosis, not only temporarily; improvement may be permanent, as if the acute infiltration had been a turning point in the course of the disease. Finally there may be only the condition known as secondary neural.

Considering the features enumerated, acute infiltration can be differentiated from the *akuter Schub* ("reactional tuberculoid leprosy") of the neuro-tuberculoid type, the erythema nodosum leprosum of the lepromatous type, and the acute relapse reaction of that type ("acute lepromatous reactivation").

#### ACKNOWLEDGMENT

I gratefully offer this article to my respected teacher, Dr. Kensuke Mitsuda.

#### ADDENDUM

Leprosy cases are to be classified into two main types, lepromatous and tuberculoid. There remain, however, a few cases which are difficult to assign to either of these groups, and these include the acute infiltration condition. Originally they were lepromatous, but they have become tuberculoid from the histological point of view. Furthermore, the Mitsuda



reaction reverts from negative to positive. On the other hand, as regards their bacteriology, the bacilli are numerous, contrary to the findings in tuberculoid cases. These being the facts, this condition presents a problem for discussion.

In recent discussions of type classification among leprologists in other countries, a new form has gained recognition, namely, the "borderline group," regarded as an intermediate form between the two polar types, tuberculoid and lepromatous. This group was adopted by the WHO Expert Committee in 1952, and then by the Madrid congress in 1953. Having read the report of that congress since the publication of my recent articles on which the present one is based, I find that I had misunderstandings about that form.

Characteristics of the borderline group are (a) numerous lepra bacilli, (b) negative Mitsuda reaction, and (c) unfavorable prognosis. Wade and other workers hold that some cases of the tuberculoid type undergo transformation as a result of repeated *akuter Schub* reactions,<sup>6</sup> that beyond a certain point these cases fail to recover and return to the original tuberculoid condition as ordinarily occurs after *akuter Schub*, and that they then acquire some of the characteristics of the lepromatous type while still showing stigmata of the original tuberculoid condition; and this is the stage called borderline. They hold, finally, that some proportion of these cases will go on to become actually lepromatous. This I now understand. In short, the borderline form is a transitional stage (or at least potentially transitional) in a progression from tuberculoid to lepromatous, a malign development in a benign type.

The acute infiltration that I have described is a contrary process. It is a benign development in the malign, lepromatous type. The acute eruption appears, for some one of various reasons, at a time when immunity is being gradually restored, usually long after the lepromatous infiltration or nodules have been resorbed. Histologically the eruption resembles the tuberculoid condition rather than the lepromatous condition. Bacilli are found in larger numbers than in tuberculoid lesions, but not as many as in lepromatous lesions. The acute infiltration lesion, therefore, is not properly classified as of the borderline group.

I wish to emphasize the fact that although the acute infiltration syndrome occurs in lepromatous cases, yet it has special features that clearly distinguish it from the "acute lepromatous activation" (ordinary "lepra reaction"), which is simply an exacerbation of the lepromas and has corresponding lepromatous histology.

It is my desire that the facts about this condition be made widely known, so that cases may be studied by workers in other countries and a general understanding about it may be reached. As for the name, "acute

<sup>6</sup> The definition of the borderline group in the report of the Madrid congress includes the following statement: "Such cases may arise from the tuberculoid type as a result of repeated reactions, and sometimes they evolve to the lepromatous type."

infiltration" is used only tentatively. This is the literal translation of a Japanese term. I would accept some other name which would identify the condition more satisfactorily.

I have studied and written about the syndrome since 1935, but nobody even in Japan regarded it as important until recently. Since the sulfones have come into general use, however, such cases have appeared more frequently and the condition is gradually gaining recognition.

#### CONCLUSIONES

La "infiltración aguda" de la lepra lepromatosa es un síndrome que se presenta bruscamente, pero pasajero, que aparece algunas veces en un período incipiente de dicha forma, pero más a menudo después que el caso ha permanecido durante un espacio considerablemente largo de tiempo en la prolongada etapa de absorción. Clínicamente, toma aspecto de enrojecimiento erisipelatoideo e infiltración, yendo acompañada de fiebre ( $37^{\circ}$  a  $39^{\circ}$  C.) y dolores articulares. Tiene que ser diferenciada de un fenómeno de reacción algo semejante de la lepra tuberculoidea llamado *skuter Schub*.

Histológicamente, las lesiones son semejantes a las de la lepra tuberculoidea reaccional. Los bacilos leprosoes son más numerosos que en las lesiones de dicha dolencia, pero mucho menores en número que en la activación lepromatosa aguda (la ordinaria "reacción leprosa"). En este respecto, los hallazgos histológicos son bastante distintos de los de cualquier otra dolencia aguda que podría confundirse con infiltración aguda.

La reacción de Mitsuda suele volverse positiva, durando esta positividad bastante tiempo. Algunos casos han acusado reacciones positivas hasta veinte años después del episodio eruptivo.

En muchos casos, este estado es favorable para el pronóstico, no tan sólo temporalmente; la mejoría puede ser permanente, como si la infiltración aguda hubiera sido el punto decisivo en la evolución de la enfermedad. Al fin, tal vez sólo reste el estado denominado neural secundario.

Considerando las características enumeradas, cabe diferenciar la infiltración aguda de la *skuter Schub* ("lepra tuberculoidea reaccional") de la forma neurotuberculoidea, del eritema nudoso leproso de la forma lepromatosa y de la reacción recidivante aguda de dicha forma ("activación lepromatosa aguda").

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#### DESCRIPTION OF PLATES

##### PLATE (10)

FIGS. 1-4. Photographs of Cases 6, 18, 13 and 24, respectively, illustrating the lesions of the acute infiltration reaction.



PLATE 10



PLATE (11)

Photomicrographs illustrating the histopathology of the acute infiltration lesions.

FIG. 5. Low power photograph showing four areas of predominantly lymphocytic infiltration.

FIG. 6. Low power photograph of a more massive lesion, containing several giant cells in the predominantly lymphocyte infiltration.

FIG. 7. In the upper center an accumulation of epithelioids, surrounded by lymphocyte infiltration.

FIG. 8. Showing a group of Langhans giant cells, and around them and to the left epithelioid cells.

FIG. 9. In the upper part of the infiltrate two Langhans giant cells in an area of epithelioid cells.

FIG. 10. Leprosy bacilli in the acute infiltration, demonstrated by fluorescence microscopy.

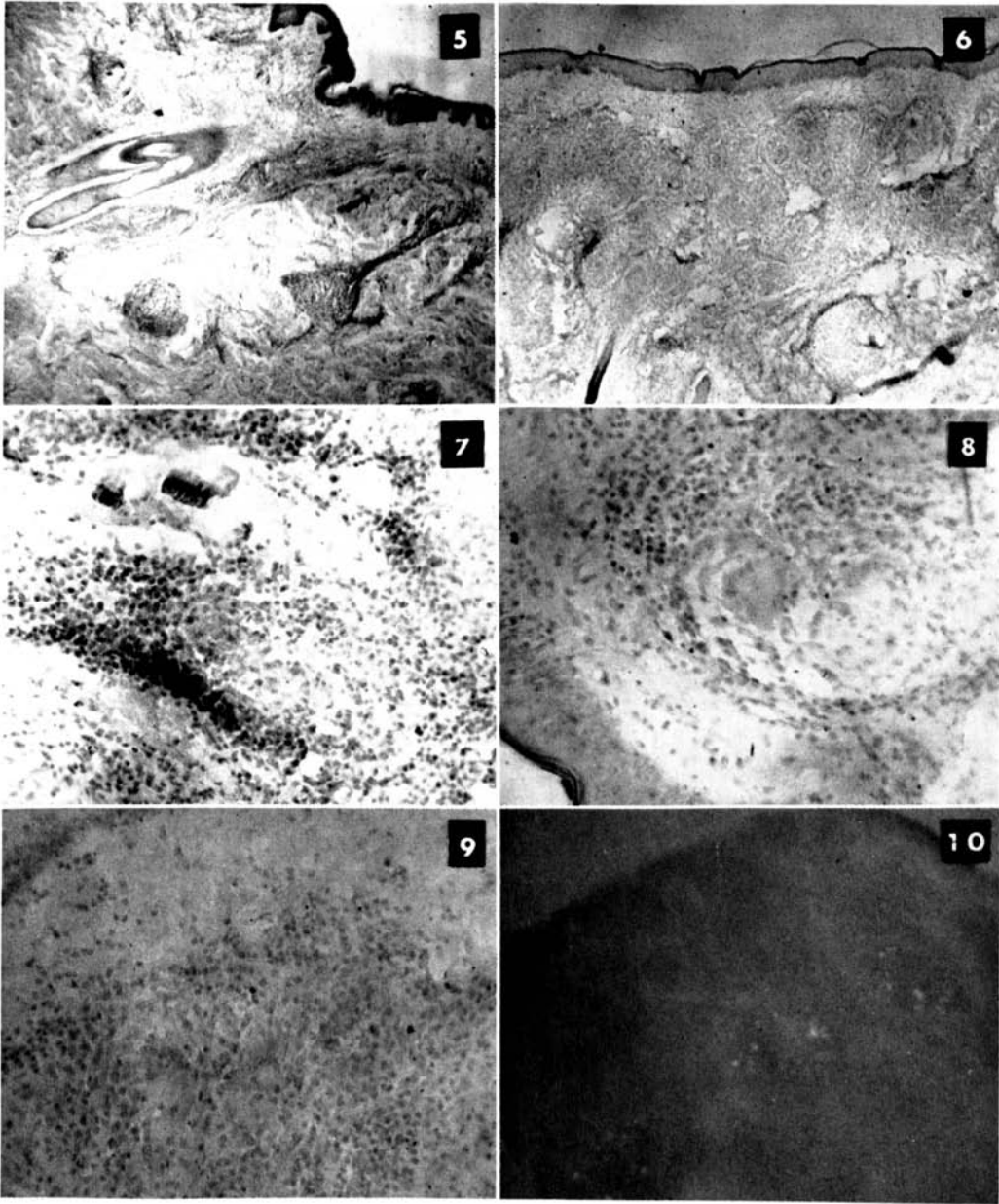


PLATE 11