



INTERNATIONAL JOURNAL OF LEPROSY

VOL. 8

JANUARY-MARCH, 1940

No. 1

THE EARLY REACTION INDUCED BY LEPROMIN

By JOSÉ M. M. FERNÁNDEZ, M.D.¹

*Department of Dermatology, Faculty of Medicine
Leprosy Department, Carrasco Hospital
Rosario, Argentina*

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¹Fellow of the Argentine Association for the Advancement of Science. The work for this paper was done in the Department of Leprosy Prophylaxis of the State of São Paulo, Brazil.

INTRODUCTION

All who have studied the intradermal reaction to lepromin, now known as Mitsuda's reaction because he first interpreted its significance,² agree that the positive reaction only begins to be perceptible a week after the injection, and that the definitive reading should be made between the third and fourth weeks, when the reaction has reached its highest intensity, when it is manifested by an evident papule or nodule which sometimes may ulcerate. It is also generally accepted that before the first week, between 48 and 72 hours, an early reaction may be observed which consists of an erythematous halo, sometimes infiltrated. This reaction is supposed to be nonspecific, probably due to the foreign protein, and to have no special significance. Hayashi (6), referring to this early reaction, states:

The filtrate of leper vaccine (leprolin) passed through a bacterial filter, only gives negative reactions. In certain cases of the neural type there is a reddening of 4 to 5 cm. in diameter one or two days after injection. This is a casual phenomenon which occurs sometimes with standard leprolin when the reddening appears in one or two days but is followed later by an extremely strong reaction with the formation of pus.

From this it is deduced the early erythema is caused by the filtrate. Its significance may be that of a protein reaction.

Rodriguez (9), in his recent report on the Mitsuda reaction, states with reference to the reading of the results:

Though the first reading is not made for a week, it must be noted that in most positive reactions there is an earlier, initial redness and edema, though usually it is not marked and may easily be missed unless specially looked for. Starting a few hours after the injection, this passing reaction is usually at its maximum intensity after 24 hours; thereafter it subsides rapidly and is usually gone by the fifth day. In some cases, however, this early reaction merges with the typical nodule formation, which becomes noticeable at about the end of the first week. The initial redness corresponds to the period of intensive edema, capillary hemorrhage, and microscopic abscess formation shown by biopsy during the first few days after injection.

My opinion regarding the reading of the reaction was stated in a previous work (3) as follows:

The reaction demonstrates itself generally in the first week, but it must be borne in mind there are positive reactions which develop late (2nd and 3rd weeks). On the other hand the local reaction, of traumatic origin, which develops a few hours after injection and is always transitory, should be discarded.

Cummins and Williams (2) studied comparatively, in a country where leprosy is not endemic, the intradermal reactions

²Gougerot (5) had previously employed a similar emulsion of nodular substances for diagnostic purposes.

to lepromin and to a suspension of dead tubercle bacilli, in a group of 25 psychopaths all of whom reacted positively to 1:2,000 tuberculin. They showed that the reactions could be classified into three types: Type A, maximum on the third day; Type B, maximum on the eighth day; Type C, negative on the third day but positive later, between the 3rd and 4th weeks. They observed the following results:

<i>Reaction type</i>	<i>Lepromin</i>	<i>Tubercle-bacillus suspension</i>
A	6 cases	21 cases
B	6 cases	2 cases
C	13 cases	2 cases

It must be noted these authors did not use the "standard" lepromin supplied by Muir for these experiments, but a dilution of 1 in 5. In spite of this, in 6 cases this dilute antigen induced early reactions of a tuberculin type; and, conversely, the suspension of Koch's bacillus produced in two cases a late reaction of a lepromin type. These authors concluded that there exists a group sensitization which explains these reactions brought about by acid-resistant bacilli.

Rabello, Jr. (8) notes that while tuberculin induces late reactions which arise after 72 hours, the Mitsuda antigen induces very late ones, between the third and fourth weeks. He also studied comparatively, in collaboration with J. C. Machado, the reactions induced by standard lepromin and an antigen prepared by the Mitsuda-Hayashi method from viscera of tuberculous guinea-pigs, in a group of lepers and contacts. They were able to show that the tuberculous antigen is capable of producing not only reactions of tuberculin type but also of lepromin type, that is to say extremely late ones. They also noted the appearance of slight transient local reactions in 24 hours. Rabello says that this fact gives rise to the hope that when Hansen's bacillus can be cultivated, we may obtain a "leprin" capable of inducing an earlier reaction of tuberculin type. He also deduces, from his experiments and those of Cummins and Williams, the existence of group sensitization.

Stein and Steperin (11) observed that the reaction to lepromin produces a rapid transitory inflammatory erythema which is followed by the late reaction. The symptoms of this early reaction, according to these authors, are similar to those of tuberculin reaction seen after 48 hours.

We see, therefore, that although some workers mention the appearance of an early reaction, occurring within 48 hours after

the intradermal injection of lepromin, none accords to it any real value. Rabello, however, admits the possibility that an antigen prepared with cultures of the true leprosy bacillus may produce "early reactions of a tuberculin type."

PERSONAL INVESTIGATIONS

Agreeing with the unanimous opinion that Mitsuda's reaction is of late development, that is to say after the first week, I confess I had not paid much attention to its initial evolution. However, in the course of a comparative study of this reaction with that of tuberculin (4) an opportunity was had to observe carefully all of its phases from the beginning, and thus were seen certain features which seem to be of sufficient interest to merit this paper. These investigations were made on 250 contacts and 312 lepers (types L and N) using always the same lepromin prepared according to Muir's technique (7).

CLINICAL EVOLUTION OF THE REACTION

Initial stage (the early reaction).—Twenty-four hours after an intradermal injection of lepromin two things may have occurred. There may be either a slight traumatic lesion consisting of a simple blood-stained scab or a tiny papule (Plate 1, fig. 1), or an incipient inflammatory process manifested by an erythematous halo around the point of inoculation (Plate 1, fig. 2). Forty-eight hours after the injection the condition has either disappeared almost completely in the first case, or, in the second case, the erythematous halo has become intensified. That is to say, in certain cases the intradermal injection of lepromin produces an early reaction which can be seen already in 24 hours and which reaches its maximum after between 48 and 72 hours. This reaction is characterized by an erythematous halo, generally infiltrated, which surrounds the point of inoculation (Plate 1, fig. 3).

The intensity of this early reaction is judged according to the size of the halo and the degree of infiltration. In slight reactions its diameter varies around 10 mm., and there is very little or no infiltration. When the reaction is marked, the diameter is between 20 to 30 mm. and the infiltration is accentuated, sometimes with raised and well defined edges. The color is pale to deep red.

With regard to its ultimate evolution, as a rule this reaction starts to fade after 72 hours, losing its bright red color and becoming darker. At the end of the first week the erythematous

halo is replaced by a dark brown area, accompanied when the reaction has been intense by a folding of the skin and slight desquamation. This early reaction induced by lepromin resembles in its appearance and evolution the one that is induced by intradermal injection of tuberculin (Mantoux).

Final stage (the classical Mitsuda reaction).—After the first week a papule or nodular infiltration appears in the middle of the areola left by the 48-hour erythematous halo. This lesion increases progressively and reaches its maximum around the third week. In cases where the reaction is intense, ulceration of the nodule may occur (Plate 1, fig. 4).

HISTOPATHOLOGY OF THE REACTION

Schujman (10), who has studied the histology of the evolution of the lepromin reaction in the tuberculoid, neuro-macular and lepromatous forms of leprosy, draws attention to the fact that in the tuberculoid form there can be seen after 48 hours an acute inflammatory process with congestion and edema of the skin with marked infiltration of neutrophile and eosinophile leucocytes. On the fourth day the inflammatory process is less marked and tends to be localized round the vessels and glands. After eight days the acute inflammatory phenomena disappear and a chronic type of inflammation supervenes, containing lymphocytes, epithelioid cells and giant cells (tuberculoid granuloma).

Rodriguez (9) also describes the appearance at 48 hours of an acute inflammatory reaction affecting both dermis and epidermis, with intense polynuclear and lymphocytic infiltration and marked vascular congestion. He draws attention to the fact that during the first days the reactions to tuberculin and lepromin are almost identical in their histological structure, differing perhaps in the extent of the lesion. He adds:

Since the former is a protein reaction, being elicited by purified tuberculo-protein, it is suggested that the preliminary reddening in the leprolin test may also be due to a protein factor, but that the true leprolin reaction is produced by some other substance or substances, possibly partly derived from the waxy coating of the organism.

Büngeler and Fernández (1) have studied the Mitsuda reaction in its various stages, showing that 24 hours after the injection of the lepromin, and especially after 48 hours, specific alterations can be observed which show its allergic character. In this "early" stage of the reaction there are two types of phenomena, nonspecific and specific.

Nonspecific changes.—The nonspecific changes are of the type that produces purulent exudates (as described by Schujman and Rodriguez), characterized by marked edema of the papillae and corium, with vascular dilatation and congestion and evident increase and margination of the leucocytes in the capillaries. Around the small veins, hair follicles and sebaceous glands can be seen, besides diffuse hemorrhage due to diapedesis, an intense leucocytic infiltration and microabscesses with initial necrosis of the collagen fibers; among the leucocytes are found a fair number of eosinophiles. In some areas can be seen leucocytic emigration toward the cutaneous epithelium, producing at times tiny leucocytic pustules in the epithelium itself beneath the keratinized layer.

Specific changes.—The specific changes occur in the midst of the infiltration and consist of small, clearly circumscribed nodules made up of a fibrinoid necrosis of the lax connective tissue fibers, principally the adventitious coats of the small vessels and the periglandular connective tissue. In the latter position can be recognized all of the stages of fibrinoid swelling leading to necrosis. It consists of lax, swollen, fibrous connective tissue the cells of which have lost their nuclei. The fibers become thickened and take the eosin stain more deeply than the rest of the tissue. After Weigert's method for staining fibrin these swollen fibers have a pale blue color; silver impregnation stains very fine fibers in the centers of these nodules. These changes, which attain a definite nodular character, are of the same nature as those observed in recent spontaneous leprous tuberculoid reaction lesions. In appearance and reaction to stains these foci of degeneration and fibrinoid necrosis are typical of the changes described by Klinge and others as the allergic connective tissue reaction. Later they behave as foreign bodies and bring about cellular reaction: conglomeration of histiocytes or epithelioid cells in the centers of the foci and, surrounding them, halos of lymphocytes (pretuberculoid foci of Wade). In the second and third weeks following the injection of lepromin these primitive foci become well organized nodules made up of epithelioid and giant cells bounded by a lymphocytic area, thus repeating exactly the characteristic nodules of typical tuberculoid leprosy (Plate 3, figs. 11-16).

RELATION BETWEEN THE EARLY AND LATE REACTIONS

Having become convinced that in certain cases intradermal injection of lepromin can produce, both clinically and histopa-

thologically, well-defined early reactions in 48 hours, I undertook to determine whether or not there exists any relation between this early reaction and the classical late one. Groups of patients with different types of leprosy, both children and adults, and also a group of contacts, were studied, careful note being made in each case of the reactions at 48 hours and during the third week. When there was a positive early reaction the diameter and the degree of infiltration of the erythematous halo were noted in order to classify the intensity of the reaction, these being the criteria employed in evaluating the Mantoux reaction.

The patients, 312 in number, comprising children and adults of both sexes with both the lepromatous and neural types of the disease, were inmates of the Padre Bento and Cocas leprosaria. The contacts were 251 children of lepers, mostly from 5 to 15 years of age, living in the Jacarehy preventorium. The results are shown in Table 1.

TABLE 1. *Early and late lepromin reactions in lepers and contacts (children of lepers).*

Reactions	Lepers (312 cases)	Contacts (251 cases)	Total (563 cases)	Correlation of results
Both positive.....	81 (26%)	160 (64%)	241 (43%)	Results in agreement
Both negative.....	218 (70%)	61 (24%)	279 (50%)	520 (92.4%)
One positive, other doubtful	11 (3.5%)	16 (6.4%)	27 (4.8%)	Results doubtful 27 (4.8%)
One positive, other negative	2 (0.6%)	14 (5.6%)	16 (2.8%)	Results in conflict 16 (2.8%)

Concerning the relation existing between the early and late reactions, it is to be said that in no case was there an absolute discrepancy between the two, as for example a definitely positive 48-hour reaction followed by a negative one in the third week, or vice versa. In the strongly positive cases both reactions always agreed; and in the absolutely negative cases, as in lepromatous cases, the agreement was also complete. The few cases in which there was a relative discrepancy were those which reacted only slightly to the antigen, that is to say when the response of the organism was not clear. It is a known fact that all workers do not agree regarding the reading of the classical Mitsuda reaction in these cases with only slight response.

RELATION BETWEEN THE EARLY REACTION AND THE TYPE OF THE DISEASE

The relation between the early reaction and the type of disease was studied in 339 cases of leprosy. The results are shown in Table 2.

TABLE 2.—Relation between the type of the disease and early reactions.

Type	No. of cases	Response at 48 hours	
		Positive	Negative
L.....	130	0	130
Ns. Na.....	138	36	102
Nt.....	71	63	8

Lepromatous (L) type.—In 130 patients of the lepromatous type of various grades the early reaction was always negative. At 48 hours there were to be seen only the traumatic changes mentioned; the erythematous infiltrated halo characteristic of this reaction never occurred. In some cases there was a small pustule, probably due to a simultaneous pyogenic infection, which disappeared quickly.

Simple neuro-macular (Ns) and pure neural (Na) forms.—In 138 cases of these varieties the early reaction was negative in 102 (74 percent), and positive in 36 (26 percent).

Tuberculoid (Nt) form.—Of a total of 71 tuberculoid cases, confirmed histologically, 63 (89 percent) gave positive reactions, only 8 being negative. In these 8 cases the reactions were also negative in the third week. These patients were all hospitalized, living with bacilliferous patients. In the tuberculoid group there frequently occurred a most intense early reaction, with a large and infiltrated erythematous halo.

The results of the early reaction thus observed approximate closely those obtained during the third week (Mitsuda classic reaction), which is usually negative in the lepromatous type, positive in the majority of tuberculoid cases, and variable in the simple neuro-macular forms.

REACTIONS INDUCED BY STANDARD AND FILTERED LEPROMINS

Hayashi (6) and Muir (7) found that filtrates of lepromin suspensions always gave negative results, even in cases which reacted positively to the standard preparation. From this fact they deduced that the active part of the lepromin consists of toxins contained in the body of the bacillus. Hayashi also found that the filtrate could induce an early reaction, in 24 to 48 hours, consisting of a transitory erythema which he interpreted

as a protein reaction. To investigate this question I made a comparative study of the reactions induced by standard lepromin (L.S.) and a filtrate of the same preparation (L.F.). An L3 bacterial filter was used, and 0.1 cc. of the filtrate was injected intradermally in 55 persons, lepromatous and neural cases and contacts. The results are given in Table 3.

TABLE 3.—Early and late reactions induced by standard (L.S.) and filtered (L.F.) lepromins.

Antigens and results	Type of reaction	
	Early reactions (48 hours)	Late reactions (3 weeks)
L. S. negative } L. F. negative }	29 cases	29 cases
L. S. positive } L. F. positive }	21 cases	3 cases
L. S. positive } L. F. negative }	5 cases	23 cases

Early reactions.—In 29 cases there was no early reaction with either antigen. In 21 cases both antigens induced definite early reactions, which generally were more intense to the standard than to the filtrate (Plate 1, fig. 5). In 5 cases the standard antigen induced slightly positive reactions and the other doubtful ones, which were considered negative. The results were therefore in agreement in 51 cases, and there was a slight discrepancy in 5 cases.

Late reactions.—All cases in which the standard antigen induced positive 48-hour reactions were also positive in the third week, presenting either the nodule or ulceration characterizing the classical Mitsuda reaction. On the other hand, of 21 cases with positive early reactions to the filtrate all but 3 were completely negative in the third week (Plate 1, fig. 6). The three that were not negative showed a small papule at the injection point. These three cases had reacted violently to the standard antigen.

These results lead to the conclusion that the early lepromin reaction is due in great part, though not exclusively, to soluble substances or toxins of the bacillus (exotoxins), while the late reaction is induced by substances or toxins contained in the bacillary body (endotoxins).

Observations made by Stein and Steperin (11) have shown

that the constituents of the skin cells have no action in the mechanism of the Mitsuda reaction, since an "extract" or "suspension" prepared with normal skin does not induce any reaction in subjects positive to lepromin. Hayashi (5) and Fernández (3) have also shown that the activity of lepromin is in direct relation to its bacillary content.

THE EARLY LEPROMIN AND THE TUBERCULIN REACTIONS

In this connection a comparative study was made of the lepromin and tuberculin reactions in a group of 131 leprous children at the Sanatorio Padre Bento (aged from 4 to 16, including both lepromatous and neural cases), and in 262 contacts, both children and adults, in the Jacarehy preventorium. The tuberculin tests were made in each case by the Mantoux, von Pirquet and epicutaneous techniques. For the Mantoux reaction a freshly prepared 1:10,000 saline solution of crude tuberculin from the Pasteur Institute of Paris, was used, and for the von Pirquet and epicutaneous reactions the same tuberculin undiluted. In order to be considered positive at the 48-hour reading the intradermal reaction had to show as a minimum a 10 mm. inflammatory halo; positive cutaneous and epicutaneous reactions showed erythema and infiltration, and vesiculation, respectively. The results are shown in Table 4.

TABLE 4.—Comparison of the early lepromin and the tuberculin reactions (both after 48 hours) in leprous children and contacts.

Reactions		Number of cases (and percentages)	Correlation of results
Lepromin	Tuberculin		
Leprous patients (131 cases)			
+	+	21 (16.0)	Results in agree- ment 79 (60.3%)
—	—	58 (44.3)	
+	—	37 (28.2)	Results in conflict 52 (39.7%)
—	+	15 (11.4)	
Contacts (262 cases)			
+	+	69 (26.3)	Results in agree- ment 129 (49.2%)
—	—	60 (22.9)	
+	—	107 (40.8)	Results in conflict 133 (50.8%)
—	+	26 (9.9)	

Even though the early reaction to lepromin is both clinically and histologically similar to the intradermal reaction to tuberculin (Mantoux), the two reactions were not in agreement in

a high percentage of both lepers and contacts. It was frequently observed that cases strongly allergic to tuberculin were not so to lepromin, and vice versa (Plate 2, figs. 8 and 9).

REACTIONS IN LEPERS TO INTRADERMAL INJECTIONS OF TUBERCULIN
AND OF A TUBERCLE-BACILLUS SUSPENSION

In connection with the observations made in the comparison of reactions induced by the entire toxins of Hansen's bacillus (standard lepromin) and the filterable toxins (filtered lepromin), a similar experiment was made to ascertain what differences there might be between the reactions induced by the complete toxins of Koch's bacillus and its filterable toxins. The bacillary suspension used was of human-type tubercle bacillus from an 11-day culture on potato-glycerin, diluted in a phenol solution to contain 100,000,000 bacilli per cc. and sterilized at 95°C. for one hour.³ The tuberculin used was a 1:10,000 solution in saline of crude tuberculin from the Pasteur Institute.

These two substances were injected intradermally, 0.1 cc. doses, in a group of 24 adult lepers (14 of lepromatous type and 10 neural). The results were observed after 48 hours and in the third week, the same criteria being used in the readings as in the previous work. The following results were observed:

Forty-eight hour reactions.—In 11 cases neither antigen gave any reaction at all. In 9 cases both substances induced definite positive reactions, most of them consisting of an erythematous infiltrated halo of more than 10 mm., more intense in the case of the suspension than the solution. In 3 cases the tuberculin induced a doubtful (\pm) reaction and the suspension a positive one, while in one case the reaction to the tuberculin was negative and to the suspension positive (see Table 5).

Reactions in the third week.—All the cases which gave positive 48-hour reactions with the suspension were also positive in the third week, showing a papule or nodule and sometimes an ulceration (Plate 2, fig. 10). The cases which were negative at 48 hours with the suspension were also negative in the third week.

These results show that the entire substances or toxins of Koch's bacillus can induce intradermally not only a 48-hour reaction of "tuberculin type" but also a late or "lepromin

³Prepared for this study by Dr. Moacyr de Souza Lima, bacteriologist in the Conde Lara Institute, São Paulo.

type" reaction, either nodular or ulcerated, in the third week. This observation has also been proved by Cummins and Williams and by Rabello Jr. and Machado.

TABLE 5.—Forty-eight hour reactions to tuberculin and a tubercle-bacillus suspension.

Reaction	Number of cases
Tuberculin + } Suspension + }	5 cases
Tuberculin — } Suspension — }	11 cases
Tuberculin — } Suspension + }	4 cases

SUMMARY

The intradermal reaction to lepromin has been studied in a total of 563 persons, cases of leprosy and contacts. Observation of its clinical and histopathologic development has shown the following facts:

(a) In allergic cases intradermal injection of lepromin induces an "early" reaction which is well defined, both clinically and histologically, beginning a few hours after injection and reaching its maximum between 48 and 72 hours, thereafter decreasing until it disappears completely during the first week.

(b) This early reaction, which is manifested clinically by an erythematous halo, usually infiltrated, is not of nonspecific character since it has the histologic structure common to allergic reactions and is only seen in those cases which offer resistance to the infection (i.e., neural forms of the disease, particularly the tuberculoid form) and does not occur in cases which are considered anergic, as in the lepromatous type.

(c) In 95 percent of cases the early reaction coincides with the late nodular reaction in the 3rd week (the classical Mitsuda reaction).

(d) The early and late reactions are probably brought about by different substances or toxins of the Hansen bacillus, since a filtrate of lepromin always gives the early reaction in allergic cases whereas only exceptionally does it cause a faint late reaction.

(e) When the filterable toxins of the Koch bacillus (tuberculin) and the total toxins of the same (suspension of the bacillus

killed by heat) are injected intradermally into lepers, the former only induces an early reaction whereas the latter induces both this reaction and a late one, consisting of a nodule or papule, in the third week.

(f) The previous experiment gives rise to the supposition that, like the Koch bacillus, that of Hansen contains soluble toxins which can be separated from the bacillary organism and insoluble toxins which cannot be thus disassociated, both being capable of producing allergic reactions in sensitized individuals.

(g) The early reaction induced by lepromin resembles, clinically and histologically, the Mantoux reaction. Nevertheless, in a comparative study of both reactions in a group of lepers and contacts, the results did not agree in 45 percent of cases.

CONCLUSIONS

1. The intradermal reaction to lepromin is clinically and histologically evident in 48 hours.

2. This early reaction is allergic in character.

3. The early reaction coincides in its results with the classical Mitsuda reaction of the third week in the majority of cases.

4. From the practical point of view this early reaction has the same value as the classical Mitsuda reaction, it being positive in the allergic forms of leprosy and negative in its anergic forms.

For their valuable cooperation I wish to express my gratitude to Doctors Francisco Salles Gomes Jr., director of the Serviço de Prophylaxia da Lepra do Estado de São Paulo; Nelson de Souza Campos, sub-director; Lauro de Souza Lima, director of the Sanatorio "Padre Bento"; Luis M. Bechelli, physician at the Asilo-Colônia "Cocães"; Argemiro Rodríguez de Souza, physician at the Asilo-Colônia "Pirapitinguy"; Moacyr de Souza Lima, bacteriologist of the Serviço de Prophylaxia da Lepra; and also to my wife, María Inés Frazzini de Fernández.

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DESCRIPTION OF PLATES

PLATE I

1. Intradermal reaction to lepromin, 48 hours after injection. Titu-
pule, no erythematous halo. Result: negative.
- FIG. 2. Intradermal reaction to lepromin, 24 hours after injection in a
case of tuberculoid leprosy. Erythematous halo, slightly infiltrated. Result:
positive.
- FIG. 3. Intradermal reaction to lepromin, 48 hours after injection in a
case of tuberculoid leprosy. Marked infiltrated, erythematous halo. Result:
positive. The upper test was made with lepromin prepared according to
Muir's technique, the lower with a lot prepared by the Mitsuda-Hayashi
technique.
- FIG. 4. The same case as in Fig. 3, observed in the third week. Ulcer-
ated nodules characteristic of the very strong Mitsuda reaction.
- FIG. 5. Upper lesion (L.S.), reaction produced by "standard" lepromin.
Lower lesion (L.F.), reaction produced by lepromin filtrate. Observation 24
hours after injection.
- FIG. 6. Upper lesion (L.S.), ulcerated nodule produced by standard lep-
romin. Lower lesion (L.F.), residual macule produced by filtered lepromin.
Observation 3 weeks after injection.

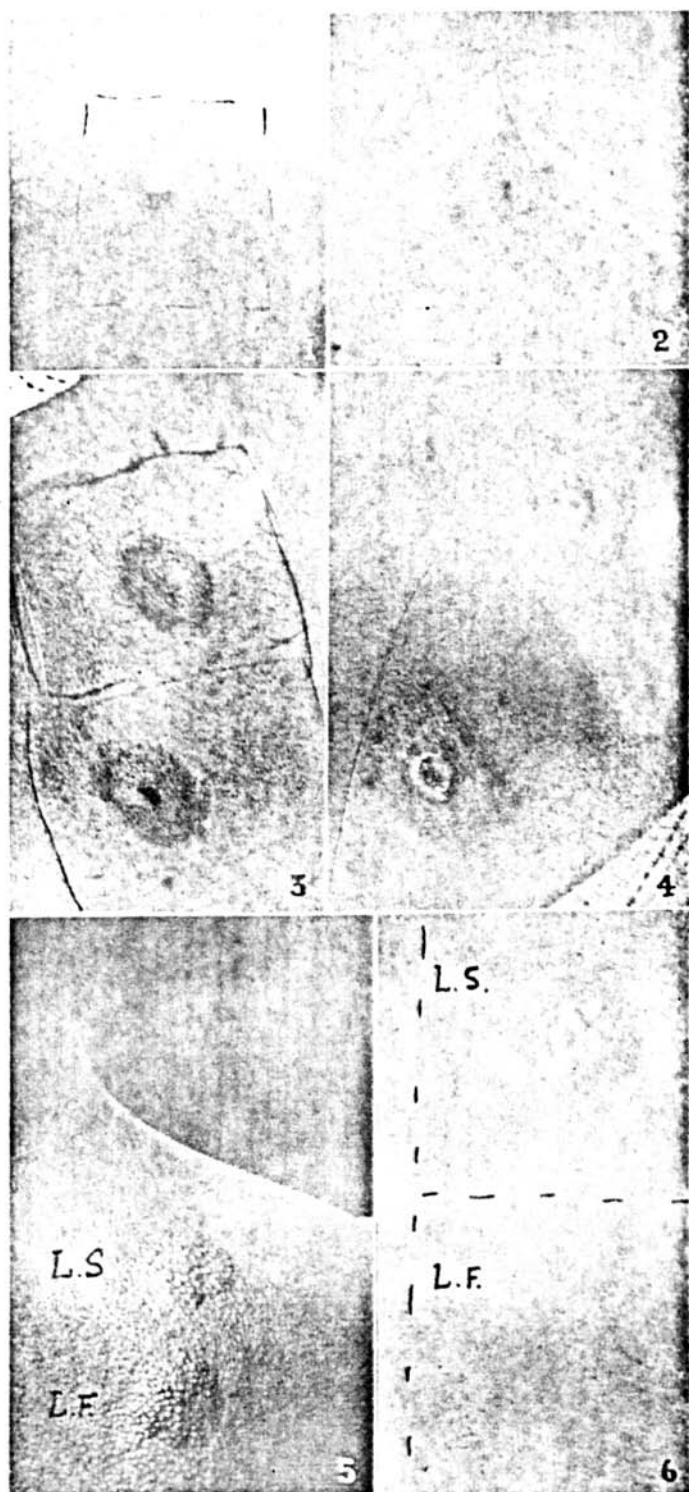


PLATE 1

PLATE 2.

FIG. 7. (1) Mantoux reaction, (2) von Pirquet reaction, both positive (3) lepromin reaction, slightly positive (\pm). Observation 48 hours after injection, in a case of tuberculoid leprosy.

FIG. 8. (1) Mantoux reaction, (2) reaction to a suspension of human tubercle bacilli killed by heat. Observation 48 hours after injection, in a case of lepromatous leprosy.

FIG. 9. The same case as in Fig. 8, 3 weeks after injection. (2) Ulcerated nodule produced by the tubercle-bacillus suspension, similar to that produced by standard leprosin.

FIG. 10. (1) Mantoux reaction, (2) reaction to a tubercle-bacillus suspension. Observation 3 weeks after injection, in a patient of tuberculoid leprosy.

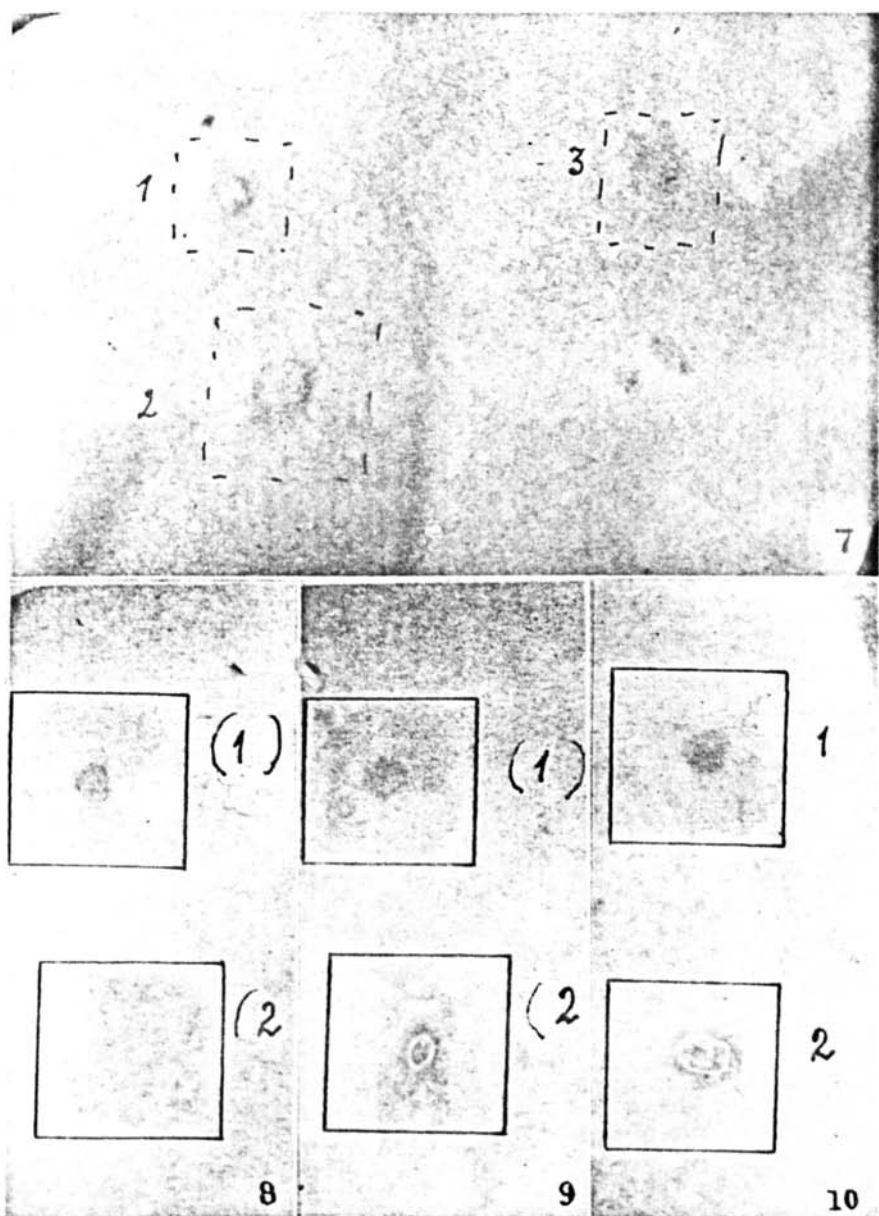


PLATE 2

PLATE 3.

FIG. 11. Reaction to lepromin, 24 hours after injection. Marked lymphocytic and leucocytic infiltration, with numerous eosinophiles, around a sebaceous gland and a hair follicle. Edema of the lax periglandular fibrous connective tissue.

FIG. 12. Reaction to lepromin, 48 hours after injection. Nonspecific alterations in an early reaction. Diffuse inflammatory leucocytic infiltration, with formation of small abscesses and necrosis of the collagenous bundles in the corium.

FIG. 13. Reaction to lepromin, 24 hours after injection. Fibrinoid tumefaction of the lax connective tissue around a small vein of the corium, lymphocytic infiltration, discrete eosinophilia.

FIG. 14. Reaction to lepromin, 24 hours after injection. Specific alteration in the middle of an inflammatory infiltration at the site of the injection. A well-defined nodule can be seen in the center. The nuclei of the connective-tissue cells are swollen and faintly stained, the protoplasm is slightly basophilic. At the periphery lymphocytic infiltration and eosinophiles. Marked edema.

FIG. 15. Reaction to lepromin, 48 hours after injection. Specific alterations in an early reaction. Marked edema throughout. In the center is a glandular lobe with marked edema and lymphocytic infiltration of the lax fibrous connective tissue. A small, typical nodule can be seen, with fibrinoid swelling of the connective-tissue bundles and incipient fibrinoid necrosis. These alterations are similar to those described by Wade as "pretuberculoid."

FIG. 16. A detail of Fig. 15, seen with greater magnification.

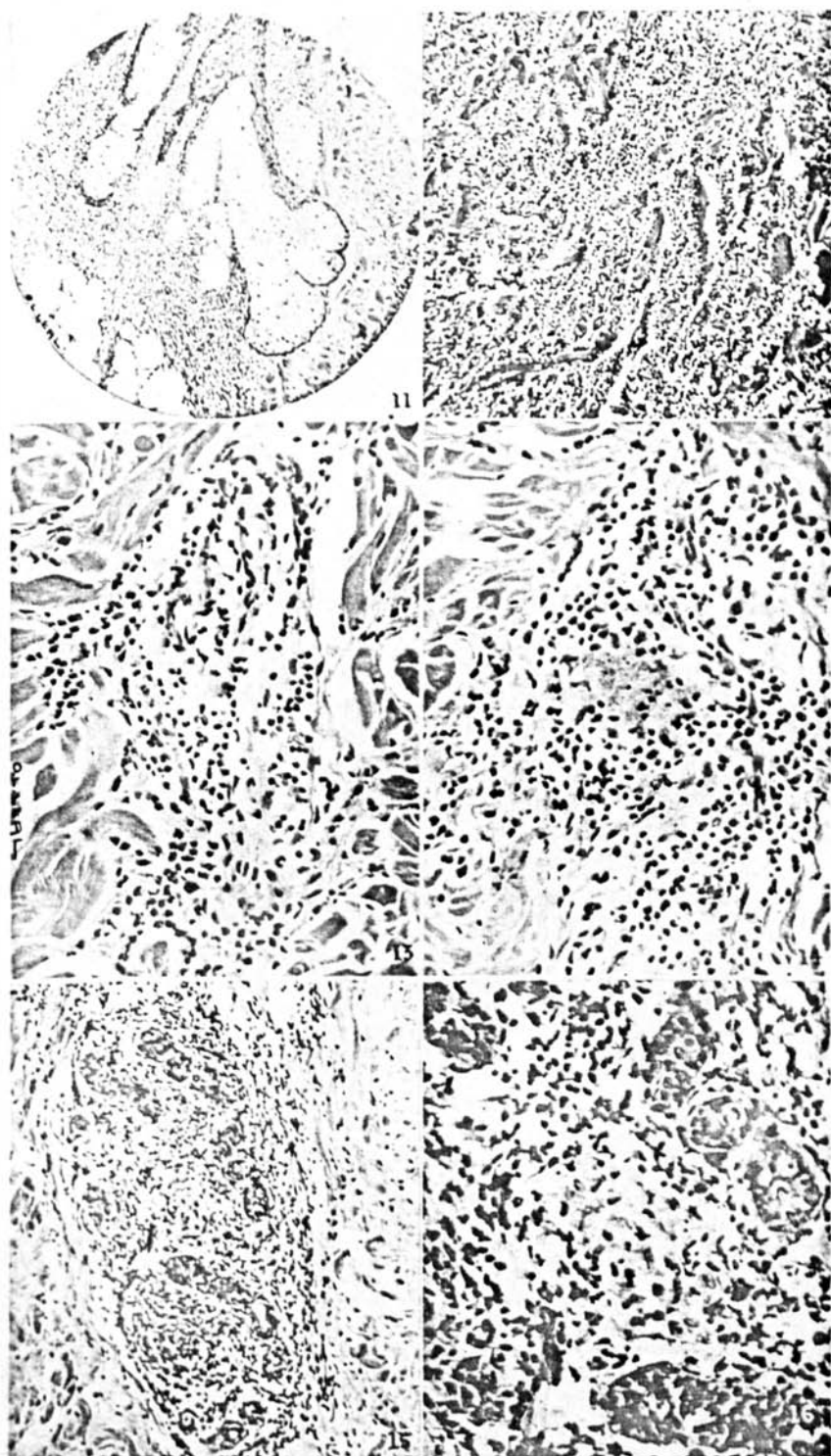


PLATE 3