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LEPROSY
THE CORRELATION OF ITS CLINICAL, PATHOLOGIC, IMMUNOLOGIC AND BACTERIOLOGIC ASPECTS*

by

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Leprosy affects the skin, the peripheral nervous system and the mucous membrane of the nose by preference, but other tissues and organs are also affected, often early in the disease, such as the testicles, the mammary glands, the lymphatic glands, the larynx and the eyes. Late manifestations of the liver, spleen and other internal organs may occur.

Lesions of the muscles, bones, skin, hair, nails and mucous membranes may not be directly due to the presence of *Mycobacterium leprae* but to trophic disturbances caused by nerve involvment.

The Correlation of the Pathology, Immunology and Bacteriology of Leprosy

	Pathology		Immunology Lepromin Test	Bacteriology
Leprosy of the skin	Lepromatous		Negative	Numerous bacilli
		Miliary	Positive	Rare bacilli
	Tuberculoid	Sarcoidal	Positive	Rare bacilli
		Lazarine	Positive	Abundant bacilli in necrotic areas; rare in tissues
	Nonspecific	Erythematous	Pos. or Neg. 50%	Few bacilli
		Pigmented	Pos. or Neg. 50%	Few bacilli
		Achromic	Pos. or Neg. 50%	Few bacilli

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Leprosy of the nerves	Lepromatous		Negative	Numerous bacilli
	Tuberculoid	Miliary	Positive	Rare bacilli
		Colliquative		
	Nonspecific		Pos. or Neg. 50%	Few bacilli
Leprosy of other tissues and organs	Lepromatous		Negative	Numerous bacilli
	Tuberculoid	Miliary	Positive	Rare bacilli
		Sarcoidal		
	Nonspecific ?		?	?

The preference of leprosy for the skin and peripheral nerves led to the classic conception of "cutaneous," "neural" and "mixed" types of leprosy. However, it is evident that the great majority of patients with leprosy present symptoms and signs of cutaneous, neural and visceral involvement and therefore most cases of leprosy would fall under the heading of "mixed leprosy."

On the other hand, the fact that the clinical manifestations of leprosy affect the skin, the peripheral nervous system and many other tissues and organs does not offer a definite foundation for the classification of the types of leprosy, especially as to their prognosis, epidemiology, pathology and immunology. Cutaneous lesions may be severe and of bad prognosis or may be slight and of good prognosis. Nerve involvement may be slight and chronic without much loss of function or may be severe, leading to rapid wasting and complete disability.

The leprosy congresses of Manila (1) in 1931 and of Cairo (2) in 1938 considered the classification of the clinical forms of leprosy, adhering to the old ideas and preserving the cutaneous, neural and mixed types. However, the South American dermatologists insist on the advisability of using a pathologic foundation for the classification of leprosy, following the suggestion made as early as 1936 by Eduardo Rabello Jr. (3) of Rio de Janeiro. This classification has been adopted by the South American dermatologists, among

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1. Report of the Leonard Wood Memorial Conference on Leprosy, Internat. J. Leprosy 2: 329 (July-Sept.) 1934.
2. Resolutions and Reports of the International Congress of Leprosy held in Cairo, Egyptian M. A. 21: 138 (March) 1938.
3. RABELLO, EDUARDO Jr. Una clasificação clinica-epidemiologica das formas da lepra, Rev. brasil. de leprol. 4: 375, 1936.

whom the contributions of the Rabellos, (4) Schujman, (5) N. V. Greco (6), Souza Lima, (7) Moura Costa, (8) Aguiar Pupo, (9) and Baliña and Basombrio (10) are prominent.

The pathologic changes found in leprosy are sufficiently definite and characteristic, corresponding with clearcut clinical aspects in the great majority of cases and with definite immunologic reactions and bacteriologic findings, making the correlation of these factors most important from the points of view of the prognosis and the sanitary control of the disease.

Whether leprosy affects the skin, the nervous system or the other tissues and organs, the pathologic changes may be grouped in three categories: lepromatous, tuberculoid and simple inflammatory, which we shall call nonspecific. To the trained eye these pathologic changes have clinical equivalents: the lepromatous, represented by the nodular infiltrative lesions, the tuberculoid, represented by flat infiltrated annular or ringlike, small nodular lesions and the nonspecific, represented by the macular manifestations of the skin and the simple dystrophic neural manifestations.

The fact that lepromatous lesions are extremely rich in Hansen bacilli, while the tuberculoid and nonspecific are paucibacillary and that the immunologic lepromin tests are negative in lepromatous and positive in tuberculoid types, adds strength to the practical importance of this classification.

The lepromatous and tuberculoid types are therefore definite clinical, pathologic, bacteriologic and immunologic forms of leprosy. The nonspecific types represent transitional stages and these cases may remain nonspecific for a long time or may develop into lepromatous cases or into tuberculoid cases. The tissues show only perivascular inflammation with lymphocytic infiltration. In some

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4. Rabello, Eduardo and Rabello, Eduardo, Jr. Une clasificación clinico-epidemiologique des formes de la lèpre, Rev. brasil. de leprol. 6: 229 (Sept.) 1938.
5. Schujman, S. A propósito de una nueva clasificación de la lepra, Rev. brasil. de leprol. 8: 111 (June) 1940.
6. Greco, Nicholas V. Clasificación de la lepra, Rev. brasil. de leprol. 8: 301 (Sept.) 1940.
7. Souza, Lima L. Classificação das leprides, Rev. brasil. de leprol. 6: 63, 1938.
8. Moura Costa, H. Letter to the editor, Rev. Brasil. de leprol. 8: 202 (June) 1940.
9. Aguiar Pupo, J. Das formas clinicas da lepra, Rev. brasil. de leprol. 7: 357 (Dec.) 1939.
10. Baliña, P. L. and Basombrio, G. Clasificación des formes cliniques de lèpre, Rev. brasil. de leprol. 6: 225 (Sept.) 1938.

cases a few bacilli are scattered in the tissues or are demonstrable in the lymph and mucous membranes, while in others few or rare bacilli are found. In 40 to 60 per cent of these nonspecific types the lepromin test is positive, while in the other 40 to 60 per cent the lepromin test is negative. Therefore the nonspecific types may progress to the severe lepromatous manifestations or slowly develop the more benign tuberculoid symptoms.

The accompanying table resumes the South American classification of leprosy modified by us, to make the clinical aspects more prominent and adding the lazarine type of tuberculoid leprosy.

THE LEPROMATOUS TYPES

When *Mycobacterium leprae* invades the skin, mucous membranes, peripheral nerves and other tissues and organs, finding little or no defensive reaction, the histologic features are those of a chronic infiltrating granuloma affecting the totality of the tissue. The cells are large histiocytes with special characteristics; some are vacuolated and badly stained and some are huge cells filled with mucous degenerated protoplasm and innumerable accumulations of acid-fast bacilli. The connective and elastic tissue disappear entirely and are supplanted by the cellular infiltrate. The glands and hair follicles are gradually choked and finally atrophy.

These infiltrations appear clinically as nodular formations, more or less lobulated, usually dark red, well defined from the adjacent parts and varying in diameter from a few millimeters to several centimeters. Others are diffuse infiltrations without definite outline, more or less flat and geographic in outline. In the peripheral nerves the infiltrations may be total, thickening the nerves to three or more times their normal size, or may be moniliform, like the beads of a large rosary along the trunk of the nerve. In other tissues such as the testicle and mammary gland the lepromas affect the form of hard nodules, absolutely painless and without apparent signs of inflammation. In the larynx, nose and other mucous membranes the lesions ulcerate early, and deformities and mutilations are extreme. In advanced cases lesions of the liver and other internal organs present the same diffuse lepromatous infiltrations or localized nodular formations.

This is the easiest type to diagnose, and the cutaneous lesions may be recognized even by the layman in countries where leprosy is common.

Bacteriologically the lepromatous lesions are so full of acid-fast bacilli that in the tissues they may be seen with the small dry objective in the form of bright red patches spread throughout the

microscopic field. Two methods may be employed to examine tissues for bacteriologic diagnosis: one may remove a piece of a leproma by means of small curved scissors, imprinting the tissue juices on several cover slides, or make a small incision in the mass of the leproma, scraping off the soft tissues in the bottom of the wound with the scalpel and spreading the juice thus obtained on a cover slide. When proper staining is done by the Ziehl-Neelsen method, the number of acid-fast bacilli in these preparations is enormous. It must be remarked that the specimens obtained from the mucous membranes of the nose should be taken by scraping the mucosa as deeply as possible without causing hemorrhage.

Immunologically lepromatous types show absolutely no reaction when tested with lepromin. Sometimes an early nonspecific reaction appears after the first or second day but disappears without leaving any trace. This absence of allergic response to lepromin means that the patient offers no defense to the infection. Therefore the prognosis of these cases is bad.

From a prophylactic point of view, lepromatous cases are dangerous, being open and literally oozing *Mycobacterium leprae* of the highest virulence. These are the cases that must be isolated from the community.

THE TUBERCULOID TYPES

The tuberculoid types show three different histopathologic variations: the typical miliary type with giant cells, the sarcoidal type with circumscribed collections of histiocytes of the foamy type in the form of round, oval or sausage shaped nests and a third type with peculiar features ending in necrosis, which we have described as "lazarine leprosy." (11) In the peripheral nerves the histologic changes are similar and there is a particular type reported by Eduardo Rabello Jr. (12) as "nodular colliquative neuritis" in which necrosis and abscess formation are the main features together with typical tuberculoid follicular structure. This last mentioned type may possibly be the neural equivalent of the "lazarine leprosy" of the skin.

Eduardo Rabello Jr. (13) has described tuberculoid changes of

11. PARDO-CASTELLO, V. and CABALLERO, G. M. Lazarine Leprosy: A Peculiar Monosymptomatic Form of Leprosy, Arch. Dermat. & Syph. 23: 1 (Jan.) 1931.
12. RABELLO, EDUARDO Jr. Etiologie générale et pathogénie de la lèpre tuberculoide, Rev. brasil. de leprol. 6: 291 (Sept.) 1938.
13. RABELLO, EDUARDO, Jr. Données nouvelles pour l'interprétation de l'affection de Besnier-Boeck: rôle de la lèpre, Ann. de Dermat. et Syph. 7: 571 (June) 1936.

the sarcoidal variety in the lymphatic glands and bones, a syndrome difficult to differentiate from lymphogranulomatosis benigna or Besnier-Boeck-Schaumann disease.

Clinically the tuberculoid lesions of the skin and peripheral nerves may be diagnosed by the expert. As a rule the lesions are few in number, sharply circumscribed, erythematous patches or flat infiltrations, often ring shaped or festooned, with macular center and elevated border, the latter being uniform or composed of small nodules arranged side by side.

Sometimes the lesions, which are first infiltrated and elevated patches of vivid red or purple, suffer a process of involution in the center and become atrophic with a ringlike border. The nerves more often affected are those of the upper extremities, particularly the ulnar, and also the superficial auricular branch of the cervical plexus. They appear as thick, pencil-like, lineal infiltrations under the skin but show no discoloration. The ulnar nerve may be palpated in the ulnar canal at the inner part of the elbow as a thick or moniliform cord. In the type described by Eduardo Rabello Jr., of which we have seen only 1 case, the painless abscess forms in the mass of the ulnar nerve and progresses toward the skin, adhering to the latter and finally causing superficial necrosis and ulceration.

Bacteriologically the lesions of tuberculoid leprosy show very few acid-fast bacilli. Often only one or two bacilli may be seen in a whole section of skin or nerve after painstaking search. Often no bacilli at all can be demonstrated, either in the sections or in the lymph, tissue scrapings or mucous membrane secretions.

Immunologically the tuberculoid types of leprosy show the maximum possible allergy of the skin in the form of strongly positive lepromin tests, varying from the nodular to the necrotic. This is a constant feature which shows the excellent defenses of the body and proves once more the law of Jadassohn-Lewandowsky.

From a prophylactic point of view, persons with tuberculoid leprosy are not dangerous and in some countries where leprosy is endemic these patients are not isolated but are allowed to remain at home under sanitary supervision. Some leprologists contend that these patients should not be treated but allowed to develop their immune reactions spontaneously.

In "lazarine leprosy" the clinical lesions consist of plaques of cutaneous gangrene developing at the site of bullae; these necrotic manifestations are few in number but extremely destructive, causing deep, foul ulcers usually in the extremities, which disorganize

the muscles, tendons and joints. These ulcers are painless and as a rule heal, leaving irregular scars in which there is absence of thermic and painful sensations. Recurrent crops of bullae may occur after healing. These are the only clinical manifestations, there being no other cutaneous or neural lesions of tuberculoid type. The peculiar feature of this type of tuberculoid leprosy is that in spite of the tuberculoid structure of the affected tissue the gangrenous parts and the contents of the bullae are extremely rich in Hansen bacilli but not the tissue. The lepromin test is strongly positive, showing a high allergic reaction indicative of excellent defenses. In our opinion the "lazarine" type of leprosy is the result of a massive infection with Hansen bacilli of patients with high immunologic defenses and the clinical symptoms represent the typical Koch phenomenon, with the throwing off of huge numbers of Hansen bacilli by the defensive mechanism of the body. Lazarine leprosy, although highly destructive, is of good prognosis and most patients recover spontaneously.

THE NONSPECIFIC TYPES

Clinically the nonspecific types of leprosy are characterized by the presence of macular erythematous, achromic or pigmented skin lesions and by slight enlargement of the peripheral nerves with areas of apparently healthy skin in which the thermic and painful sensations are abolished. These types are at times exclusively neural and then the sole manifestations may be those due to trophic disturbances, such as areas of anesthesia, muscular atrophies, retraction of the fingers and toes, paralysis of the muscles of the face, bone reabsorptions, mal perforans plantaris, disturbances of the sweat and sebaceous secretions and falling of the hair. More often neural disturbances and cutaneous erythematous or dyschromic lesions are present together. Pathologically the tissues show only perivascular and perineural simple inflammatory changes consisting of cuffs of lymphocytes around the larger vessels of the upper cutis or the small trunks of the cutaneous nerves. In the cutaneous dyschromic or erythematous manifestations often called "leprids" there is also pronounced vascular dilatation and passive congestion. The basal cells are often devoid of pigment, and chromatophores may be very abundant in the upper cutis in the pigmented lesions.

Bacteriologically these lesions, whether of the skin or of the nerves, are poor in acid-fast bacilli. As a rule direct examinations of lymph result in negative findings.

The lepromin test is negative in some cases and positive in oth-

ers, about 50 per cent of each, although some investigators claim the numbers of positive much higher.

In reality cases of "nonspecific" leprosy are transitional types, some of which progress toward the "lepromatous" type and others toward the "tuberculoid" types. At times the transition is quite rapid, and a patient who showed only macular lesions will suddenly develop crops of lepromas in an acute outbreak of "lepra reaction."

The prognosis of these transitional types may be foretold by the results of the lepromin test. Those who show positive tests will probably remain as nonspecific types or will develop tuberculoid lesions. Those showing a negative lepromin reaction will in all probability develop lepromatous lesions.

THE MIXED TYPES

These transitions naturally result in types in which both lepromatous or tuberculoid and nonspecific "leprids" coexist until the patient finally develops the definite type which the disease will follow in his particular case. Therefore in these cases the presence of leproma establishes the type as "lepromatous" in spite of the presence of numerous erythematous or dyschromic lesions. Likewise the presence of tuberculoid lesions establishes the type as "tuberculoid" in spite of the presence of erythematous or dyschromic manifestations. In many cases the clinical appraisal may be difficult and resort must be had to pathologic and bacteriologic examinations and even to the lepromin test in order to classify a case in the proper type.

The presence of lepromatous and tuberculoid lesions in the same patient has not been observed by us. The transformation of a lepromatous type into a tuberculoid type or *vice versa* has been reported by several investigators, but we have not seen this phenomenon.

LEPRA REACTION

In sharp contrast with the usual slow and insidious evolution of leprosy there is sometimes observed an acute inflammatory phase which very frequently interrupts its chronic course or is the first clinical manifestation of the disease.

The major characteristic of the lepra reaction is its acuteness, more or less accentuated in different cases. It is probably a manifestation of allergy or hypersensitivity of the body to the pathogenic agent. Sometimes the outbreak of the lepra reaction can be ascribed to a definite cause: complicating diseases, alimentary or alcoholic excesses, too intensive antileprotic treatment, and so on.

Frequently it is impossible to determine its cause. The clinical picture and evolution of lepra reaction differ in lepromatous and tuberculoid cases.

In lepromatous leprosy it generally begins suddenly with fever (39 to 40 C., or 102.2 to 104 F.), rigors, arthralgias, headache or prostration, followed in several hours by an eruption of erythema multiforme or erythema nodosum type and the exacerbation of preexisting lesions. In some cases there are extracutaneous symptoms: adenitis, orchitis, splenic and hepatic enlargement, neuritis and keratitis. The fever, of remitting type, and the other symptoms persist during several days, ten to fifteen, rarely more, and then disappear in lysis. Relapses are frequent. The lepromin test is negative. The erythrosedimentation index is greatly augmented. Short, acute reactions are of good prognostic significance.

Long or relapsing reactions aggravate the course of leprosy.

The first therapeutic measure is the cessation of all antileprotic treatment and the administration of a mild saline laxative and a bland diet.

Injections of antimony and potassium tartrate 1 per cent solution, calcium salts, vitamin B_1 and diphtheria toxoid are useful agents.

Exacerbations in tuberculoid leprosy are not accompanied by any general symptoms or fever. They are characterized by the turgescence of preexisting lesions, the appearance of new wine red, infiltrated patches mostly located on the face and extremities, by a protracted course, never less than three months, and frequently more than a year in length. The lepromin test is positive. The erythrosedimentation index is always low and prognosis is always good.

THE HISTAMINE TEST

The early manifestations of leprosy of the nonspecific or simple inflammatory type may be difficult to diagnose, although, if thermal and pain anesthesia are present, matters are simplified. However, many patients, especially children, do not cooperate or they find it difficult to express their sensations, in which event the performance of the "histamine test" is very valuable.

When a drop of a 1 : 1,000 solution of a histamine salt is placed on the normal skin and a needle prick is made through the liquid, a small wheal surrounded by an erythematous halo develops within a few seconds and persists for five minutes or more. When the sensitive nerve endings are paralyzed or destroyed, the phenomenon occurs as far as whealing, but no erythematous halo develops

around the wheal. The normal response to histamine is called the "positive test"; the absence of erythematous reaction around the wheal characterizes the "negative test." Therefore in the cutaneous lesions of leprosy the histamine test is always negative. We have found occasion to do this test in numerous cases in which erythematous or dyschromic lesions were suspected of being early manifestations of leprosy. The superficial, erythematonodular, cutaneous syphilids have been the subject of differential diagnosis with early lesions of leprosy in several cases, and in these the "histamine test" has proved of definite help. The serologic reactions may be positive in the presence of leprosy, and the changes in cutaneous sensations may be difficult to appraise when patients are not cooperative.

THE LEPROMIN TEST (MITSUDA REACTION)

The lepromin test consists essentially in the intradermal injection of an antigen prepared from lepromatous tissues rich in Hansen bacilli.

Skin tests in leprosy were originally intended to find a diagnostic procedure similar to the tuberculin test in tuberculosis. No results were obtained in this direction, and investigations were given up until 1923, when Mitsuda (14) reported that, when an emulsion prepared with lepromatous skin was inoculated, healthy persons gave positive results, maculoanesthetic patients presented a late, nodular, persistent inflammation and tuberous patients gave a negative local reaction. He deduced from his experiences that persons without leprosy and maculoanesthetic patients had a special immunity to the infection, while tuberous patients had no immunity. These findings and conclusions were later fully confirmed by many investigators.

All attempts to consider the test of any value in diagnosis are definitely abandoned. Its great importance in the classification of cases of leprosy and its immunity and prognostic value are actually recognized by all.

Lepromin is prepared by boiling lepromatous tissues in isotonic solution of sodium chloride for one hour. The mass is then ground up in a mortar, and 20 cc. of isotonic solution of sodium chloride is added for each gram of ground up tissue. After thorough mixing and grinding again, the supernatant fluid is pipetted off, filtered

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14. MITSUDA, K. Troisième Conference internationale de la lèpre, Communications et Debats, Paris, J. B. Baillière et Fils, 1924, p. 219.

through gauze and stored in a sterile container, the remaining tissue being discarded. (15)

The liquid is autoclaved at 120 C. for fifteen minutes, phenolized at 0.5 per cent and distributed in insulin type vials ready for use. It is a cloudy, milky emulsion containing numerous bacilli and globi plus all the tissue elements of the leproma. Kept in a dark, cool place, it retains its activity for a long time. No easy standardization of lepromin is possible, being as it is such a complex suspension of bacilli and tissue material, but this does not interfere with the accuracy of results, as wide variations in the concentration of the antigen do not give correspondingly different reactions. A nonreacting patient to the usual lepromin will not react to an antigen two or three times stronger. A reacting patient will do so to dilutions as high as 1 : 3,000 of lepromin, although with less intensity.

The presence of bacilli is essential to the activity of lepromin. Filtered antigens are inactive. Lepromins prepared with tuberculoid tissues (paucibacillary) produce attenuated reactions and then only in patients with strong reactions to the usual lepromin. Antigens prepared with normal skin are inactive.

The test is performed by injecting into the cutis 0.1 cc. of lepromin. The most common sites used are the arms, the dorsum and the anterior surface of the thigh. At the end of twenty-four to forty-eight hours an erythematous halo may be observed, with at times some infiltration; but these manifestations disappear quickly, usually after the fifth day, leaving a dark brown discoloration and some wrinkling of the skin. On the seventh to the tenth day a small papule begins to form in the positive cases, gradually increasing in size and reaching its acme about the third to the fourth week, when it may be a nodule of as much as 1 cm. in diameter. Occasionally the center sloughs off and a small ulcer forms which requires several weeks to heal. In most cases the nodule regresses gradually after the fourth week, but in some cases of positive reaction some scarring is left. Rarely a positive reaction may not show until the third or fourth week and then follow the usual regressive course.

The erythematous reaction of the first few days is considered nonspecific. The reading of the test should be done about the thirtieth day after the intradermal injection. If there is no reaction or only a small (less than 5 mm.) infiltration the test is negative. A

Microscopic examination when the Mitsuda reaction is positive

15. ROTBERG, A. Some Aspects of Immunity in Leprosy and Their Importance in Epidemiology, Pathogenesis and Classification of Forms of the Disease, Rev. brasil. de leprol. 5: 45 (special number) 1937.

well-formed nodule more than 5 mm. in diameter with or without a necrotic center characterizes the positive test.
shows in specimens removed at its acme a collection of histiocytes, lymphocytes and at times giant cells, with an aspect very similar to that of tuberculoid leprosy. In specimens removed forty-eight hours after inoculation acute inflammatory phenomena may be observed without any specific changes, but in some of our specimens a decided perivascular histiocytic infiltration was present, resembling even at this early date the tissue changes of tuberculoid leprosy. However, we do not believe this is of diagnostic significance, as we have observed similar changes in lepromin tests of forty-eight hours' duration which later proved to be negative. The injected bacilli are not demonstrable in the lepromin reacting tissues. In negative tests, after the initial inflammatory reaction biopsies performed after eight, fifteen and twenty-eight days showed a return of the tissues to normal.

COMMENT

1. The classification of the types of leprosy on a histopathologic foundation into "lepromatous," "tuberculoid" and "nonspecific" is the result of studies made by dermatologists of Brazil and Argentina, and accepted by Latin American dermatology. In this article an attempt is made to correlate these pathologic forms with the clinical, immunologic, bacteriologic and public health aspects of the disease.

The lepromin test is given an important place among the immunologic reactions of the skin and reports are made based on many tests performed by the authors, corroborating for the most part the findings of other investigators.

The histamine test is studied as a diagnostic procedure in early cases of leprosy with lesions of the "nonspecific" type.