

OUR IMMUNOLOGIC AND CLINICAL INTERPRETATION OF THE REACTIONS TO LEPROMIN¹

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The intradermal injection of lepromin, in man and reactive laboratory animals, is clinically manifested by four types of reactions, each of which has components of different clinical and immunologic significance. For the purpose of this report, these reactional types are designated by the letters, A, B, C and D.

The Type A reaction, which occurs in the hypersensitized individual, is manifested clinically, first by an infiltrated erythema of tuberculin type, which becomes perfectly individualized within 48 hours after the injection. This is the so-called "early reaction," or the reaction of Fernandez. Then, on the 7th day, there is observed the formation of a frankly inflammatory tubercle, usually surrounded by an erythematous and infiltrated halo. If the degree of hypersensitization is high, the tubercle may be visible as early as the 4th day, or even in 48 hours, always surrounded by a frankly inflammatory halo. This tubercle formation, which is accelerated in time in comparison with reactions in the nonhypersensitive individual, we call the "accelerated tubercle formation" or, as Fernandez has suggested, the "Olmos Castro phenomenon." Finally, in subsequent days the inflammatory halo tends to disappear, leaving a central inflammatory nodule. This constitutes the late lepromin reaction, or the Mitsuda reaction (or phenomenon).

The Type B reaction is characterized by negativity for the early reaction, but positivity for the accelerated tubercle formation and the late Mitsuda reaction.

The Type C reaction is characterized as being early negative, accelerated-tubercle negative, and late negative—i.e., a wholly negative reaction.

The Type D reaction is characterized as being early negative, accelerated-tubercle negative, but late positive. This late reaction is not regarded as of the same category as the late reaction in Types A and B.

CLINICAL AND IMMUNOLOGIC INTERPRETATIONS OF THE REACTION TYPES

TYPE A. *Immunologic interpretation.*—(a) The positive early reaction signifies hypersensitivity of the tuberculin type to the protein derivatives of *M. leprae*. (b) The positive accelerated tubercle reaction signifies tissue hypersensitivity to the leprosy bacillus or its integral

¹Translated from the Spanish.

²Dr. Olmos Castro died on December 31, 1962.—EDITOR.

TABLE 1.—Types of reactions to intradermal injections of lepromin.

Reaction type	Early reaction (2nd day)	Accelerated reaction (7th day)	Late reaction (21st day)
Type A	Positive	Positive	Positive
Type B	Negative	Positive	Positive
Type C	Negative	Negative	Negative
Type D	Negative	Negative	Positive

antigenic compounds. (c) The positive late nodular reaction is the final evolutive consequence of the accelerated formation of the tubercle, and therefore has the same immunologic significance.

This type of the lepromin reaction is seen in individuals possessing the tuberculin type of hypersensitivity to the protein derivative of *M. leprae*, and also hypersensitivity to the integral antigenic components of that microorganism. These may be either of monovalent specificity or group specificity.³

Clinical interpretation.—This type of reaction to lepromin is seen in tuberculoid patients, and in a few indeterminate cases; in healthy persons and dogs that have been previously injected intradermally with *M. leprae*; in healthy persons, dogs, and guinea-pigs recently injected intradermally with BCG, the Koch bacillus, the Stefansky bacillus, or other acid-fast bacilli with sensitizing capacity.

TYPE B. *Immunologic interpretation.*—(a) The negative early reaction signifies absence of the tuberculin type of hypersensitivity, or, if present, hypersensitivity of such low degree that it is not detectable by lepromin. (b) The accelerated tubercle formation, as before, signifies tissue hypersensitivity to *M. leprae* or its integral antigenic components. (c) The positive late reaction is the final evolutive effect of the accelerated formation of the tubercle.

This reactional type is seen in persons who, despite their lack of tuberculin-type hypersensitivity, exhibit a certain degree of tissue hypersensitivity to the integral antigenic component of *M. leprae*. This can be either monovalent or group specificity.

Clinical interpretation.—This reactional type occurs in tuberculoid leprosy patients, particularly those who have been healed for some years and have not been reinjected with lepromin; and in some cases of the indeterminate form. Experimentally, it is produced in dogs

³We understand, by the tuberculin type of protein hypersensitivity, a condition which results in an infiltrated erythema appearing within 48 hours after the intradermal injection of the antigen. This reaction can be either specific or nonspecific. Specific reactions to lepromin are provoked by *M. leprae* infection, or by injections of heat-killed *M. leprae* into organisms capable of being hypersensitized (monovalent specificity). Group specific reactions are those provoked by other acid-fast bacilli of sensitizing capability; nonspecific reactions are those provoked by other antigens possessing none of the antigenic components of acid-fast bacilli. We also hold the same criterion for the accelerated formation of the tubercle, which may be either specific (monovalent or group) or unspecific.

hypersensitized with lepromin under intensive and prolonged corticosteroid treatment; and in healthy persons and in dogs hypersensitized with BCG and retested with lepromin a year or more afterward.

TYPE C. *Immunologic interpretation.*—(a) and (b): The absence of the early and the accelerated tubercle formation have the same significance as before. (c) The negativity of the late reaction signifies potential lack of capability of becoming sensitized by *M. leprae*.

This reactional type is characterized therefore by complete negativity of all three phases of the reaction to lepromin.

Clinical interpretation.—This reactional type occurs in cases of the lepromatous form, and in healthy persons in early infancy; also in dogs during the first 3 months of age, and generally in other laboratory animals.

TYPE D. *Immunologic interpretation.*—(a) and (b): Absence of tuberculin type of protein hypersensitivity, and of tissue hypersensitivity to *M. leprae* or to its integral antigen components. (c) The positive late reaction signifies potential capability of sensitization by *M. leprae*.

Clinical interpretation.—This reactional type is seen in healthy persons, and in dogs, which had had no previous contact with *M. leprae* or with any other group of acid-fast bacilli but who possess potential capability of hypersensitization when injected intradermally with *M. leprae*. The absence of tuberculin-type protein hypersensitivity, and of tissue hypersensitivity to the bacillus, means that in the tested subjects there is no condition of previous hypersensitivity, contrary to that which occurs in Types A and B.

The formation of the late nodule has an immunologic significance entirely different from that ascribed to the nodules in Types A and B. While in those types the late development of the nodule is the effect of the final evolution of the accelerated formation of the tubercle, in Type D the nodule is the clinical expression of a new immunologic state created by the injection of *M. leprae* in a virgin organism, without previous hypersensitization.

These facts have compelled us to consider that the designation Mitsuda reaction given to this late tubercle is unsuitable, and we prefer the term suggested by Fernandez, who called it the "Wade phenomenon" in recognition of the fact that this investigator was the first to demonstrate this condition experimentally.

On the other hand, in view of the considerations involved we are of the opinion that this type of reaction should not be considered as a test for the lepromin reaction. This phenomenon is more closely related to the biologic procedures of sensitization or immunization.

DISCUSSION

1. The *lepromin* reaction, as we understand it, comprises the local clinical manifestations occurring in consequence of the intradermal in-

jection of *M. leprae*, or of its integral antigenic components, for the purpose of determining the existence or nonexistence of a state of altered reactivity to that antigen at the time of the test. The term *leprolin* reaction is applied to the test in which only the soluble protein derivatives of *M. leprae* are used, the purpose being to reveal only the state of protein hypersensitivity of the tuberculin type.

2. Of the four reactional types provoked by the intradermal injection of lepromin, two (Types A and B) express a state of altered reactivity to the integral antigenic components of *M. leprae*, and they should therefore be regarded as positive lepromin reactions. The reactional type A reveals both the state of hypersensitivity of the tuberculin type to the protein derivatives (the early reaction) and the state of altered tissue reactivity to *M. leprae* or to its integral antigenic components (the accelerated tubercle formation). The third component, which consists of the late nodule, or Mitsuda reaction, is in reality the final evolutive consequence of the second component and possesses the same immunologic significance. The reactional type B reveals an absence of the tuberculin-type protein hypersensitivity, but the existence, nevertheless, of an altered tissue reactivity to other antigenic components of *M. leprae* (positive accelerated tubercle formation). Its third component, the late reaction, has the same significance as that in the reactional type A. The reactional type C reveals a state of total absence of reactivity, characterizing the negative lepromin reaction.

As stated, we regard as positive lepromin reactions only Types A and B, and Type C as the negative reaction to lepromin. Each of these reactional types is characterized, clinically and immunologically, only by its first and second components.

Positive reactions	Type A: early positive, accelerated positive
	Type B: early negative, accelerated positive
Negative reaction	Type C: early negative, accelerated negative

In short, we regard as pathognomonic of the positive lepromin reaction the occurrence of accelerated tubercle formation, whether or not that be preceded by a positive Fernandez reaction. The negative lepromin reaction is characterized by the absence of an accelerated formation of the tubercle.

With respect to the reactional type D, with its negative early reaction and its lack of altered tissue reactivity, followed by the late formation of the nodular reaction, we regard it as a biologic phenomenon of immunologic nature different from the reactional types (Types A and B), and therefore one that merits special consideration. This reactional type should not be regarded as a true lepromin reaction, because the late formation of the nodule does not reveal a state of previously altered reactivity but is rather an expression of a state of tissue hypersensitivity created by the lepromin injection itself. Its study would

better be considered as among the phenomena of vaccination, immunization or sensitization provoked by *M. leprae*.

SUMMARY AND CONCLUSIONS

1. The lepromin reaction is defined as the biologic test made with lepromins for the purpose of revealing the actual existence of states of altered reactivity to *M. leprae* or to its antigenic derivatives. Lepromin reactions are classified as positive or negative. The positive lepromin reaction is characterized clinically by the presence, on the 7th day after the intradermal injection of lepromin, of an erythematous tubercle whether or not surrounded by an infiltrated erythema (i.e., the accelerated tubercle formation). This reaction may or may not be preceded by an early, tuberculin-type reaction, the Fernandez reaction. The negative lepromin reaction is characterized by the absence of a nodule on the 7th day.

In the positive lepromin reactions, at the end of 21 days after the lepromin injection, there is observed the presence of an erythematous tubercle, which is called the Mitsuda reaction and which has the same immunologic significance as the 7th day tubercle. In negative lepromin reactions this late nodular reaction, or Mitsuda reaction, is absent.

2. The following immunologic interpretation is given to the lepromin reactions: In positive reactions, the formation of the tubercle on the 7th day expresses a condition of altered tissue reactivity to *M. leprae* or to its integral antigen components; when preceded by a positive Fernandez reaction it indicates, in addition, the presence of a tuberculin-type hypersensitivity to the bacterial proteins.

3. The states of altered reactivity revealed by the lepromin reaction are provoked by leprosy infection or by injection of killed *M. leprae* (monovalent specificity), or by infection or vaccination with other acid-fast bacilli (group specificity).

4. The negative lepromin reaction characterized by the absence of the 7th day tubercle, followed by formation of an erythematous tubercle in 21 days, is regarded as a different biologic phenomenon from the biologic tests made for the purpose of revealing states of altered reactivity to *M. leprae* or to other acid-fast bacilli. This phenomenon, consequently, should be excluded from the concept of the lepromin reaction.

Its study corresponds better to the techniques of sensitization, vaccination, or immunization with *M. leprae*. On the other hand, to designate this phenomenon as the "Mitsuda reaction" is not only incorrect but also unsuitable in the study of the lepromin reaction. These are the reasons that have induced us to sustain, with Fernandez, the designation of "Wade phenomenon" for this condition, in recognition of the fact that it was Wade who demonstrated experimentally its pathogenic significance.

RESUMEN Y CONCLUSIONES

1. Se define con el término de leprominorreacción, la prueba biológica, efectuada con leprominas, que tienen por finalidad revelar estados de reactividad alterada a *M. leprae* o sus derivados antigénicos. La leprominorreacción se clasifica en positiva y negativa. La leprominorreacción positiva, caracterízase clínicamente por la presencia al séptimo día, de un tubérculo eritematoso, rodeado o no de un eritema infiltrado; puede ir precedida o no de reacción tipo tuberculínica o reacción de Fernandez. La leprominorreacción negativa, se caracteriza por la ausencia de tubérculo al séptimo día. En las reacciones lepromínicas positivas, al cabo de 21 días de efectuado la intradermoinyección de lepromina se comprueba la presencia de un tubérculo eritematoso, conocido con el nombre de reacción de Mitsuda que posee el mismo significado inmunológico que el tubérculo del 7° día. En las reacciones lepromínicas negativas, está ausente esta reacción nodular tardía o reacción de Mitsuda.

2. Se da la siguiente interpretación inmunológica a las leprominorreacciones: en las reacciones positivas, la formación del tubérculo al séptimo día, expresa el estado de reactividad hística alterada a *M. leprae* o sus componentes antigénicos integrales; cuando vá precedida de reacción de Fernández positiva, acusa además la presencia de hipersensibilidad proteica tipo tuberculínico.

3. Los estados de reactividad alterada, que revela la leprominorreacción son provocados por infección leprosa o por inyección de *M. leprae* muerto (especificidad monovalente) o bien infección o vacunación con otros ácido alcohol resistentes de grupo (especificidad de grupo).

4. Las leprominorreacciones negativas, ausencia del tubérculo al séptimo día, seguida a los 21 días por la formación de un tubérculo eritematoso, se lo considera como un fenómeno biológico distinto a las pruebas biológicas que tienen por finalidad revelar estados de reactividad alterada a *M. leprae* u otros ácido resistentes y por lo tanto este fenómeno debe ser excluido del concepto de leprominorreacción.

Su estudio correspondería más bien a las técnicas de sensibilización, vacunación o inmunización con *M. leprae*. Por otra parte la designación de reacción de Mitsuda para fenómeno, no solo resulta incorrecta, sino también inconveniente en el estudio de la leprominorreacción. Estas razones nos inducen a sostener con Fernández, la designación de fenómeno de Wade, para este fenómeno, en mérito de haber sido Wade quien demostró experimentalmente su significado patogénico.

RESUMÉ

1. La réaction à la lépromine est définie comme l'épreuve biologique qui, au moyen de lépromines, se propose de révéler l'existence réelle d'états où la réactivité à *M. leprae* ou à ses constituants antigéniques est altérée. Les réactions à la lépromine sont classées en positives et négatives. La réaction positive à la lépromine est caractérisée cliniquement par l'apparition, au septième jour qui suit l'injection intra-dermique de lépromine, d'un tubercule érythémateux entouré ou non d'une zone érythémateuse infiltrée (traduisant la formation accélérée du tubercule). Cette réaction peut être ou non précédée par une réaction précoce, de type tuberculinique, la réaction de Fernandez. La réaction négative à la lépromine est caractérisée par l'absence de nodule au septième jour.

Lors de réactions positives à la lépromine, on observe au bout de 21 jours après l'injection de lépromine, la présence d'un tubercule érythémateux, nommé réaction de Mitsuda, qui revêt la même signification immunologique que le tubercule du 7^{ème} jour. Dans les réactions négatives à la lépromine, cette réaction nodulaire tardive, ou Mitsuda-réaction, est absente.

2. L'interprétation immunologique suivante est fournie pour les réactions à la lépromine. Dans les réactions positives, la formation du tubercule au 7^{ème} jour exprime une condition de réactivité tissulaire altérée à l'égard de *M. leprae* ou de ses constituants antigéniques intégraux; lorsqu'elle est précédée d'une réaction de Fernandez positive,

elle indique de plus la présence d'une hypersensibilité de type tuberculinique aux protéines bactériennes.

3. Les états pour lesquels la lépromine révèle une réactivité modifiée sont provoqués par l'infection lépreuse ou par l'injection de *M. leprae* tués (spécificité monovalente), ou encore par l'infection ou par la vaccination par d'autres bacilles acido-résistants (spécificité de groupe).

4. Les réactions à la lépromine qui sont caractérisées par l'absence de nodule au 7^{ème} jour et par la formation subséquente d'un tubercule érythémateux après 21 jours, sont considérées comme un phénomène biologique différent des épreuves biologiques pratiquées dans le but de révéler des états de réactivité altérée à l'égard de *M. leprae* ou à l'égard d'autres bacilles acido-résistants. Ce phénomène, dès lors, devrait être exclu du concept de lépromine-réaction.

Son étude se prête davantage à des techniques de sensibilisation, de vaccination et d'immunisation avec *M. leprae*. D'autre part, il est non seulement incorrect de désigner ce phénomène par le terme de réaction de Mitsuda, cela est également inadéquat pour l'étude de la réaction à la lépromine. Telles sont les raisons qui nous ont portés à maintenir, avec Fernandez, l'appellation de "phénomène de Wade" pour désigner cette condition, en reconnaissance du fait que c'est Wade qui démontra expérimentalement sa signification pathogénique.