

"N-Factor/Anergic Margin" or Resistance/Susceptibility to hanseniasis. 111. The general acceptance of the theory under other names, a few pending questions and the related researches ahead

A. ROTBERG (*)

ABSTRACT — In this third and final article of a series, the general acceptance of the "N-Factor/Anergic Margin" theory, under other names, is reported. "Constitutional capacity to react", "genetical aptitude" and "potential immunity" stand among the numerous synonyms for the old (1937) "natural" N-Factor; "lepromatous macrophage defect", "specific defect of cell-mediated immunity" are pathogenetical explanations for the "Anergic Margin" (AM). However, "depression" and "impairment" of immunity are not included among the synonyms for the AM, as, according to the theory, energy precedes and conditions Virchowian hanseniasis, is not caused by it.

Secondary unspecific depression of cell-mediated immunity possibly exists in moderately advanced cases of Virchowian hanseniasis, but has no relationship with the primary genetical incapacity to react to *Mycobacterium hansenii*, which characterizes the AM of the general population.

Studies with homozygotic twins and HL-A antigens support the theory of a genetical conditioning of types of hanseniasis. Many works on the immunogenetics of the disease were inconclusive, partly due to the fact that Mitsuda-negative persons were wrongly considered as a homogeneous group, not as a heterogeneous group ranging from total energy (the AM) to the highest grades of Mitsuda responsiveness (only needing the stimulation by mycobacteria, especially Hansen's and Koch's).

"N-Factor" bearers (reactors) and AM members (non-reactors) exist in the whole world, endemic and non-endemic, and constitute an ample field for research. Further investigations to clarify some of the pending questions are suggested.

Key words: Hanseniasis. Genetics. Immunology. Mitsuda test. N-Factor. Anergic Margin.

In the first article of this series (33) the observations that led to the hypothesis of a constitutional, "natural" factor of resistance against hanseniasis were summarized. In short, according

to the hypothesis (35, 32, 31, 30) all persons are born Mitsuda-negative, but become Mitsuda-positive after stimulation by *Mycobacterium hansenii* (**), *Muco. tuberculosis* (and BCG), possi-

(*) Professor of Dermatology. University of S. Paulo, Brazil. Chairman of the Committee on Hansenology, S. Paulo State Public Health Service, Brazil.

(**) Term suggested by Feldman (J.A.M.A. 183: 1041, 1953) to replace *Mycobacterium leprae*, which he considered "Ignominious". Arguments for a taxonomical revision were sympathetically considered by the Judicial Commission of the International Committee on Systematic Bacteriology but were not accepted on the grounds that the name *Mycobacterium leprae* does not cause terminological confusion. (Letter of Prof. P.H.A. Sneath to Dr. Rotberg, Jan. 10, 1974). Bearing in mind that a much more serious confusion exists with the Biblical "lepra" — which was not hanseniasis — and with the pejorative, stigmatizing and sensationalistic connotations of "lepra" in all epochs, the author of this article decided to adopt Feldman's term.

bly by other mycobacteria, *if they have a genetically conditioned, "natural" capacity to react* ("N-factor"). Those who do not, the "Anergic Margin" of the population (roughly 20%) remain Mitsuda-negative in spite of repeated stimuli. "Accessory factors" cooperating, the "N-factor" bearers will show tuberculoid lesions, the "anergic" will exhibit Virchowian aspects. Intermediate grades would eventually develop "borderline" lesions.

The hypothesis contradicted Mitsuda's own explanation for the Mitsuda

negativity of Virchowian patients (previously Mitsuda-positive persons "who became 'exhausted' in the long fight against the bacillus") and conflicted with the ideas, current at the time, that predisposition to hanseniasis depended on malaria, parasitic infestations, alcoholism and other debilitating conditions.

Criticized when postulated, the "N-factor/Anergic Margin" theory was later generally accepted, as reviewed in the second article of this series (34) (*).

The new terms for the old theory and the pending questions

Although not specifically referring to the terms "N-factor" and "Anergic Margin", many other authors have also agreed with the theory of "natural reactors" and "natural non-reactors" to Mitsuda antigen — and to *Myco. hansenii*. Terms like "constitutional capacity to react", "potential immunity", "natural resistance" and others are only variations of the original "N-factor"; "inherited capacity to form granuloma" and "inherent defect of cell-mediated immunity" are explanatory terms for the "N-factor" and for the "Anergic Margin", respectively. All authors who have written about an "immunological dichotomy" in hanseniasis have tacitly accepted the conclusions of the "N-Factor/Anergic Margin" hypothesis.

Table I is an incomplete list of terms and explanatory mechanisms which

have been found in the literature of the past four decades for the conditions previously identified as "N-factor" and "Anergic Margin". It must be remarked that the terms "depression", "impairment", "loss", "decline", "deterioration" and "degeneration" of the Mitsuda-reactivity are *not* tabulated. *According to that theory, the Mitsuda-negativity precedes Virchowian hanseniasis, is not determined by it.* It is one of the causes, not a consequence. There is neither "depression", nor "loss" of what, hypothetically, has not previously existed.

In spite of the present general admission of constitutional factors at the basis of resistance and susceptibility to hanseniasis, many unknowns remain. Some will be dealt with in the next items, and researches to clarify the subject will be suggested.

(*) Other authors who have accepted the "N-Factor/Anergic Margin" theory may be added to the references of article II of this series: Lines, A.R. (Arch. Urug. Med. Cl. y Esp. **43**: 21-26, 1953). Lines, A.R.; Poletti, J.G. (Bol. Of. Sanit. Panam., **25**: 884-888, 1946). Perez-Perez, B. (Rev. Leprol. Fontilles, **9**: 559, 1974). Randazzo, S.D.; Guarneri, B. & Giardina, A. (Università degli Studi di Catania, 1976, p. 34).

SOME NEW TERMS RELATED TO AN OLD THEORY

"N-Factor" (1937)	Intermediate area (1937)	"Anergic Margin" (1937)
The "immunological dichotomy"		
<p>Natural reactivity Constitutional immunity Constitutional resistance Constitutional aptitude Potential immunity Capability of developing an allergic state Native reactivity Monovalent hypersensitivity Latent immunity capability Natural capacity for immunization Unknown constitutional factor Host immunity resistance Specific immunologic responsiveness High responsiveness Genetical capability to develop resistance</p>	<p>Natural non-reactivity Constitutional anergy Constitutional susceptibility, predisposition Constitutional inaptitude Insufficient potential immunity Incapability of developing an allergic state Inherited incapacity for allergization Monovalent anergy Natural incapacity for immunization</p>	<p>Absence of unknown constitutional factors Host susceptibility Specific immunologic unresponsiveness Specific immunological incompetence Low responsiveness Genetical incapability to develop resistance Genetical defect Genetical unfitness; genetic deficiency, inability Genetical disfunction of the immunological response Inherent incapacity to react to Mitsuda Host determined incapacity to recognize Hansen's bacilli Inherited incapacity to disintegrate Hansen's bacilli and to form granuloma Lepromatous macrophage defect Defect of cell-mediated immunity (CMI) Primary cellular defect</p>
<p>Genetical fitness, ability Genetical immunological response Inherent capacity for immunization Host determined capability of recognizing Hansen's bacilli Inherited capacity to localize and destroy bacteria</p>	<p>Inherited capacity to localize and destroy bacteria</p>	<p>Inherited capacity to localize and destroy bacteria</p>
<p>Inherited granulomatous tendency Innate cell-mediated immunity (CMI)</p>	<p>Inherited granulomatous tendency</p>	<p>Inherited granulomatous tendency Defect of cell-mediated immunity (CMI) Primary cellular defect</p>

The "good" and "slow" reactors

The typical "good" reactor is the healthy child who, after a relatively short contact with a Virchowian patient and/or a single dose of BCG becomes Mitsuda-positive. On the opposite side, a group of "slow" reactors will only develop Mitsuda-positivity after very long contact with bacillary patients, sometimes long enough to allow erythematous and hypochromic macular lesions to develop. This recent Mitsuda-positivity will reflect on the macule, changing it into a reactional tuberculoid hansenide.

This seems to be an adequate explanation for the tuberculoid and "reversal" reactions accompanied by positive Mitsuda tests in previously Mitsuda-negative indifferenced (indetermined) patients — sometimes, with late Mitsuda reactions at the, precise site of formerly negative tests. It might be interesting to investigate whether some of these sudden clinical reactions with

Mitsuda-positivation are caused by intercurrent tuberculin-positivation.

"Slow reactors" might also be considered those children who develop Mitsuda-positivity only after many injections or series of orally administered BCG (39, 24, 25). Perez-Perez (25) considers as "slow reactors" those who need 2 or 3 doses of BCG to become Mitsuda-positive; "anergic" are those who remain Mitsuda-negative after the third dose. The Committee on Immunology of the 8th International Leprosy Congress (9) admitted the existence of "slow responders", the majority of whose lesions would tend toward self-healing.

Therefore, Mitsuda-negative indifferenced patients should not be considered as anergic and as candidates to the Virchowian type of hanseniasis unless that negativity co-exists with a tuberculin-positive reaction or persists after repeated doses of BCG.

The "width" of the "Anergic Margin"

The fraction of the healthy population who do not react to Mitsuda tests was roughly and schematically estimated at 20%. This percentage was suggested by the averages of Mitsuda-positivity observed by various authors on adults of endemic and non-endemic countries and was unaffected after BCG was introduced for the reversal of Mitsuda-negative reactions and after new studies on tuberculin (26, 4) were published. A review of articles published up to 1957 (30) had shown

suda-negativity after BCG administration persisted in percentages varying between 12.5% and 25% in most cases. A "margin" of "non-reactors", of about the same "width", may be observed in the epidemiological studies by Del Favero (11) and Martinez-Dominguez (21), in endemic countries.

Criticizing the "N-factor" theory, Doull *et al* (12) stated that "if such persons exist (the "Anergic Margin") on Mactan (Philippines) they must be

very uncommon; in our studies 95 per cent of persons of 20 years and over, not known to have lived in household association with leprosy, showed lepromin reactivity of the Mitsuda type".

It seems that the existence of such persons, i.e., the "nonreactors", can not be denied anymore. However, the criticism brings attention to the necessity of a more exact determination of the "width" of the "Anergic Margin". How many in a population present what is now called "specific defect of cell-mediated immunity" against hanseniasis might be determined by:

a) Mitsuda tests in tuberculin-positive adults, presumably also stimu-

lated by other mycobacteria, in addition to Koch's.

- b) Mitsuda tests in tuberculin-positive contacts of all ages, stimulated by, at least, *Myco. hansenii* and *Myco. tuberculosis*.
- c) Mitsuda tests in children, contacts of Virchowian patients, after injection of BCG, which might have to be repeated in order to stimulate the "slow reactors".

Investigations with standard materials and reading criteria might determine the approximate "width" of the "Anergic Margin" and perhaps detect regional differences.

The members of the "N-factor" majority and of the "Anergic Margin"

For any program of research in the field of "reactors" and "non-reactors", "who is who" must be considered. *Many works on the immunology and the genetics of hanseniasis have been handicapped and are inconclusive for the fact that those classes have not been properly identified.*

- 1) There is no difficulty as regards the "reactors". All Mitsuda-positive individuals, non-hansenic or showing the tuberculoid type of hanseniasis, are "reactors". For investigative purposes, reactions which do not progress to ulceration should be biopsied in order to separate the strong (tuberculoid structures) from doubtful or weak reactors (5).
- 2) *Mitsuda-negative individuals are not necessarily "non-reactors". According to the "N-factor" theo-*

ry, the Mitsuda-positive reaction is the result of the stimulation by mycobacteria, especially *Myco. hansenii* and *Myco. tuberculosis*, of previously Mitsuda-negative persons possessing the N-Factor. Therefore :

- a) Mitsuda-negative Virchowian patients are "non-reactors";
- b) Mitsuda-negative indifferntiated (indetermined) patients, if tuberculin-positive, are "non-reactors" ;
- c) Mitsuda-negative indifferntiated patients, if also tuberculin-negative are *probably* "non-reactors", but due to a possible "slow reactivity", this cannot be affirmed unless repeated BCG injections fail to change that Mitsuda negativity; Mitsuda-negative healthy individuals, if tuberculin-positive, are "non-reactors" ;

- e) Mitsuda-negative tuberculin-negative healthy persons who remain Mitsuda negative after repeated injections of BCG should be considered "non-reactors".

By stating that "no special significance is attached to negative Mitsuda

reactions in healthy non-contacts, except when tuberculin tests are positive and BCG immunization has been conducted", the Committee on Immunology of the 8th International Leprosy Congress (9) has accepted the principles of the N-Factor theory.

The specific anergy to hanseniasis

The typical member of the healthy "Anergic Margin" is the tuberculin-positive hanseniasis contact who shows a Mitsuda-negative reaction in spite of that double stimulation by *Myc. hansenii* and *Myc. tuberculosis*, perhaps by other unknown stimuli. However, he reacts "normergically" to other stimuli. Reactivity to the smallpox virus, trichophytin, candidin, leishmanin and other agents will develop in the "Anergic Margin" as regularly as in the "N-Factor" majority.

This is a fact of common observation in the endemic countries and no study has yet shown in this healthy "Anergic Margin" any general or unspecific depression to agents of infection, or to chemicals (dinitrochlorobenzene, picryl chloride, etc.) or any incapacity to act on mitogens "in vitro" or to reject skin grafts. The subject should be investigated, but it is improbable that the still conflicting observations in Mitsuda-negative individuals already affected by Virchowian hanseniasis will be more conclusive in the non-affected "Anergic Margin".

"Accessory factors" cooperating members of the "Anergic Margin" infected with *Myc. hansenii* will devel

op the signs and symptoms of Virchowian hanseniasis. Previously existent positive reactions to tuberculin or leishmanin were not shown to be affected. One of the arguments which led to the theory of a specific incapacity to adequately react against *Myc. hansenii* was the observation of Virchowian patients strongly reacting to tuberculin (29) and to suspensions of other mycobacteria. The general reactivity of Virchowian patients to these suspensions is so well known that it even became a method for differentiating pseudo-cultures of *M. hansenii* from the real agent, which never causes a positive reaction in this type of disease (17).

Arantes (1) reported that 3 out of 97 Virchowian patients reacted strongly to leishmanin and that all of those reactors referred clinico-epidemiological histories of leishmaniasis, the typical scars of which were evident. More recently, Convit *et al* (10) inoculated Virchowian patients with live *Leishmania braziliensis* and produced typical localized lesions accompanied by positive Montenegro tests. Similar observations have been made by Saint. André and Bueno (38) with *Leishmania tropica*.

A possible secondary (and moderate) unspecific depression in Virchowian hanseniasis

In 1968 Bullock (7) reported that the percentages of positive reactions of hanseniasis patients to PPD, trichophytin and candidin, and their capacity to become sensitized to picryl chloride were lower than in control subjects. Many other articles have appeared since, suggesting or concluding that the Virchowian patients respond less intensely and/or less frequently to a variety of chemicals and biological substances, such as dinitrochlorobenzene, picryl chloride, keyhole limpet hemocyanin, tuberculin (and PPD), candidin, trichophytin, streptococcin, staphylococcin, mycobacterial suspensions and phytohemagglutinin. Also impaired would be the Virchowian patients' capacity to reject allografts of normal skin and that of their lymphocytes to transform in vitro under the blastogenic action of phytohemagglutinin. Decreased percentages of T lymphocytes in their peripheral blood, reduction of lymphokine production in vitro as well as failure to respond to the leukocyte migratory inhibition and the indirect macrophage migration tests have also been reported.

The observations of different authors are often conflicting and do not lead to a definite conclusion. There is a possibility that the Virchowian patients' capacity to respond to various stimuli is somewhat depressed when compared with that of the tuberculoid patients and of the normal population. What seems certain is that this depression has no relationship with the fundamental, inborn capacity to react to Mitsuda antigen and to destroy live *Mycobacterium hansenii*. This incapacity, which is

characteristic of the Virchowian patient and of the "Anergic Margin" of the general population, is practically absolute and is uniformly observed by all authors. That depression is moderate, not uniformly observed and not always evident except by statistical methods. Moreover, as stated above, not enough researches have been conducted in the healthy "Anergic Margin" of the population, in which that unspecific depression would probably be even less apparent. (However, studies by Fliess *et al* (13) and Baliria *et al* (3) with lymphocyte cultures and PHA suggest some similarity between Virchowian patients and their Mitsuda-negative consanguineous contacts.).

Many authors have concluded that this moderate unspecific depression is not the primary predisposing cause but a consequence of the disease (22, 28). This would be due to an impairment of the structure and functions of the paracortical area of lymph nodes (40) and of other antibody-forming tissues. Rea *et al* (27) stated that epicutaneous sensitization to haptens might be influenced by diffuse Virchowian infiltration of the skin.

In fact, that depression has been found more often in advanced cases (37) and is less evident in treated patients (7, 37, 14).

It is possible, therefore, that some of the discrepancies between results of different authors might be attributed to the diverse composition of the groups studied. A study of unspecific depression on patients divided according to

growing states of severity within the Virchowian type may clarify the subject.

It might be presumed that an untreated contact of the "Anergic Margin", Mitsuda-negative due to a "primary and specific" defect of cell-mediated immunity against *Myco. hansenii* develops a Virchowian type of hanseniasis, with the cooperation of "accessory factors". Paralelly to the aggravation of the disease, to the impairment of

antibody forming tissues and to lesions of the skin itself, a "secondary and general" depression occurs which makes the Virchowian patient gradually less able to reject allografts of normal skin and to react to a coterie of biological and chemical products.

The Mitsuda reaction, however, is neither "depressed" nor "impaired" because it has never been positive. This is a biological observation with reflections on a correct semantics.

The assessment of the epidemiological aspects of the "N-Factor" theory
by modern methods

It was suggested in 1937-1939 (35, 32, 31) that the transmission of hanseniasis is much more frequent than it was generally admitted at the time and that, as in tuberculosis, the infection, in endemic countries, would spread to most of the population but would not be recognizable except by the positivity to Mitsuda. The defense "of the human organism against leprosy infection is assured by a ready and efficient immunitary response, which will restrict leprosy within the reduced limits of its present known incidence" (35).

Twenty years later (30) that statement was amended. Studies in non-endemic countries (12, 36) and with BCG had shown that a Mitsuda-positive test could no longer be considered as exclusively determined by *Myco. hansenii*. The "general infection, of the population, as in tuberculosis", was an exaggeration. Even so, the concept that hanseniasis is more infectious than it was presumed — also more immunizing — has been supported by modern methods. Using the lymphocyte transformation and the leucocyte migration

inhibition tests in contacts of hanseniasis patients including medical personnel, Godal *et al* (16) and Godal (15) suggested that "sub-clinical infection commonly follows exposure to *M. leprae* and therefore indicate that leprosy is more highly infectious than denoted by prevalence and incidence rates", and that "the low prevalence of disease among such contacts appears to be due to the development of effective immunity in a great majority of those who become exposed". Similar statements have been made by Myrvang (23) Fliess *et al* (13) and others.

Louvet *et al* (20) ask whether the recent advances in epidemiology could change the strategy of the fight against hanseniasis. "The systematic practice of the LTT has shown that infection by Hansen's bacillus is much more frequent than was believed, but that the contacts either develop an unapparent form — which is the most more common case — or a Virchowian type, reflecting their immunitary condition — "a natural resistance which might be modified by supervenient factors".

All the above statements are practically a confirmation of what has been postulated 40 years previously (35, 32, 31). However, it might be interesting to speculate now on what would be the results of the lymphocyte transformation test and other modern methods in the general population of endemic

and non-endemic countries, considering their Mitsuda and tuberculin reactions, as well as in Mitsuda-negative groups, prior and after administration of BCG.

Those results might well cast new light on the epidemiology of hanseniasis — or on the validity and specificity of the tests themselves.

The field for immunogeneticists

By having dismissed to a second plane of "Accessory Factors" the former predisposing causes represented by malnutrition, alcoholism, malaria and other debilitating diseases, and by having given emphasis to a genetical, "natural" resistance — a constitutional capacity to react at skin level to *Myco. hansenii* — the "N-Factor/Anergic Margin" theory has attracted the attention of geneticists. Articles trying to correlate genetical markers with that theory have been reviewed in the second article of this series (34). Many others have investigated the hereditary background of "reactors" and "non-reactors", represented by tuberculoid and Virchowian cases of hanseniasis, respectively. A few have concentrated on the genetical aspects of the Mitsuda reaction itself.

In a review of the subject, Beiguelman (6) cites 17 genetical markers which have already been studied, from taste sensitivity to phenylthiourea to HL-A antigens. According to Beiguelman, most articles have been analyzed, leading to negative or controversial results "probably because almost all genetical polymorphisms studied in relation to hanseniasis were chosen at random by the researchers."

Another cause of difficulties and conflicts might be perhaps added. It is found in many genetical studies which have dealt with Mitsuda-negative consanguineous relatives of hanseniasis patients, without having considered that this Mitsuda-negative group is, in fact, a conglomerate of persons ranging from total anergy (as in tuberculin-positive or BCG treated hanseniasis contacts) to the highest grades of immunity (as the Mitsuda-negative "N-Factor" bearer who only needs the necessary stimulation by *Myco. hansenii* and/or *Myco. tuberculosis* to be converted to the highest grades of Mitsuda-positivity).

Other articles have favored the hypothesis of genetical factors influencing the type of hanseniasis. Chakravarti & Vogal (8) report their observations of 62 monozygotic and 40 dizygotic twins and conclude that "there is a definite genetic variability in susceptibility to leprosy infection in the population investigated". This conclusion and other observations that monozygotic twin brothers are on the same pole of reactivity shows that there is an ample field for research ahead.

Levinson *et al* (19) state that "the notion of a genetic defect in the lepromatous type is supported by the recent observation (by Kreisler *et al* 18) of increased frequency of two HL-A specificities in those with this type."

A line of investigations as much as possible free from the seriously disturbing post-natal influences may be suggested — the capacity of Mitsuda and tuberculin negative homozygotic twins to develop a Mitsuda positive

reaction through a single intradermal injection of a standard suspension of BCG. This basic study might be extended to include a) more than one injection (to verify the "slow reactors") b) heterozygotic brethren c) parents and other consanguineous members of the family. (As emphasized above, Mitsuda-negativity of the family should not be considered "anergy" unless it persists after stimulation by *Myc. hansenii* and/or *Myc. tuberculosis*) d) genetical markers.

Immunological and genetical research in non-endemic countries

"N-Factor" bearers (i.e. Mitsuda-positive persons resistant to hanseniasis) live in the whole world, side by side with the "Anergic Margin" (2, 36, 41). From observations in non-endemic areas of the United-States (36) it might be suggested that the Mitsuda-positivity of 228 persons was caused by cross-reaction with *Mycotuberculosis*, considering that 164 of them (71,9%) were also tuberculin-positive and that BCG is an efficient instrument for Mitsuda-positivation. The Mitsuda-positivity in the absence of tuberculin positivity (i.e. 28,1%) can not be explained but by the action of unknown agents, possibly other mycobacteria. It seems, however, that the role of these unknown agents may be more important than it was thought of. Waters (41) found 43% of Mitsuda-positivity among 65 tuberculin-negative persons who had never received BCG and never had been resident at any time in endemic areas.

Out of the 84 tuberculin-positive adults in New York and Cleveland 9 were Mitsuda-negative (36). These 10.7% constitute the local "Anergic Margin". It would be interesting to know how many of the Mitsuda-negative/tuberculin-negative persons observed by Waters would remain Mitsuda-negative after administration of BCG.

The purpose of these considerations is to show that many investigations could be conducted in non-endemic countries. Most of the working hypotheses of this article depend only on the presence of Mitsuda-reactors and non-reactors. Both classes are ubiquitous. Therefore, immunopathologists and geneticists of the non-endemic world should not feel hindered by not working in direct contact with patients or for not having co-workers in the endemic countries.

RESUMO

Este terceiro e último artigo de uma série refere-se à aceitação de hipótese "Fator-N/Margem Anérgica", sob terminologia diversa. "Capacidade constitucional de reagir", "aptidão genética" e "imunidade potencial" estão entre os numerosos sinônimos do antigo (1937) Fator- N ("natural"); "defeito específico da imunidade celular" e "defeito macrofágico lepromatoso" são interpretações patogênicas da "Margem Anérgica" (MA). Entretanto, a "depressão" e "deterioração" da imunidade não são incluídas entre os sinônimos da MA, já que, de acordo com a hipótese, **a anergia precede e condiciona** a hanseníase virchowiana, não é causada por esta.

Em casos da hanseníase virchowiana relativamente avançada existe, possivelmente, depressão inespecífica e secundária da imunidade celular, não relacionada com a incapacidade genética primária de reação ao **Mycobacterium Hansenii**, que caracteriza a MA da população geral.

Estudos com os antígenos HL-A e gêmeos homocigóticos reforçam a teoria do condicionamento genético dos tipos de hanseníase. Muitos trabalhos sobre a imunogenética da doença foram inconclusivos, em parte devido ao fato de que indivíduos Mitsuda-negativos foram considerados como grupo homogêneo, não como grupo heterogêneo, partindo da anergia total (a MA) até os mais fortes graus de reatividade ao Mitsuda (necessitando apenas do estímulo por micobactérias, principalmente as de Hansen e Koch).

Portadores do Fator-N ("reatores") e membros da MA ("não-reatores") existem em todo o mundo, endêmico ou não, constituindo amplo campo para investigação. Sugerem-se novas pesquisas para esclarecimento de algumas das questões pendentes.

Termos índice: Hanseníase. Genética. Imunologia. Reação de Mitsuda. Fator N. Margem Anérgica

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