"N-factor/Anergic Margin" of resistance / susceptibility to hanseniasis. II. The general acceptance of the theory

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ABSTRACT — In this second article of a series about the pathogenetical theory "N-factor/Anergic Margin" of hanseniasis, the first sympathethic editorial reactions (1938 -1940) and the general acceptance of the theory (1943-1977) are reviewed. Acceptance under modified terminology ("potential immunity", `inherited ability to destroy bacteria or form granuloma", etc. — for the N-factor"; "defect of cell-mediated immunity", "constitutional inaptitude to react", etc., for the "Anergic Margin"), will be reviewed in the third article of the series, together with the author's rebuttals to criticisms.

Key words: Hanseniasis. Immunity. Resistance. Predisposition. Heredity. Genetics. N-Factor Anergic Margin.

In the first article of this series (49), the foundations of the pathogenetical theory "N-factor/Anergic Margin" were given. Based on the observation of 2160 persons who had been tested. with Mitsuda's and, frequently, with other allergens, it was postulated (44, 45, 46, 47, 48) that all individuals are born Mitsuda-negative but gradually become Mitsuda-positive with age, after stimulation by Hansen's mycobacterium, *Myco. tuberculosis,* BCG or other unknown agents, *if they are capable of reacting, due to the presence of a constitutional, "natural" factor of resistance* ("N-factor"). The minority, in lack of "N-factor", remains Mitsuda-negative throughout life ("Anergic Margin") . If infection takes place, the Mitsuda-positive majority either does not show clinical signs or tuberculoid lesions appear in the skin and/or nerve — if "accessory factors" coadjuvate. From the infected "Anergic Margin' minority, Virchowian cases would spring out after similar coadjuvation. An extensive range of intermediate reactivities should be placed between both extremes of maximal reactivity and maximal anergy.

This theory contradicted the then prevalent ideas about predisposition to hanseniasis, which used to be attributed to a decrease of bodily vigor due to different diseases, alcoholism, etc. It also contradicted Mitsuda's own theory that the Mitsuda-negativity of the "nodular" (Virchowian) patients was the result of the "exhaustion" of reactivity after a "long fight against Hansen's bacillus".

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THE EARLY INTEREST

The first editorial comment of the International Journal of Leprosy (21) on the work presented at the Cairo Congress was not encouraging ("Dr. Rotberg draws rather sweeping conclusions regarding the [Mitsuda's] reaction") but soon afterwards the same Journal editorialized: "Whatever the cause of this unknown factor (N--factor) in leprosy, whether it is present at birth or comes into action later, there can be little doubt of its existence and of its importance" (34).

Two other editorials reported lengthily on the hypothesis of the "Unknown N--factor", speculated on its importance ("if substantiated by careful investigation in endemic and non-endemic countries") and pointed to its plausibility in accordance with experimental animal work. "Dr. Rotberg's article, an abstract of which we print, opens up interesting speculations If his hypothesis is confirmed that the majority of people are born with a definite 'N--factor', which renders them immune to leprosy, or at least to its lepromatous form, then methods of prophylaxis will call for revision" (11) . "His hypothesis supposes a natural factor (factor N) which is inherited by some children of a family but not by others. The individual inheriting factor N will, in contact with Hansen's bacillus, develop allergy, the individual without this factor remains anergic on contact with the bacillus, this latter group including all the bacillary or open cases of leprosy". (20).

"Recently, various workers in other countries, particularly Rotberg, have advanced views about the nature of the test which differ rather markedly from the views previously held. The truth of these views has to be proved by experiment and observation, but even if they are not proved it seems that there is a distinct possibility that the lepromin test is of more importance than has previously been recognized" (30).

Commenting on the theory, Rogers and Muir (42) state that "the applications of the Mitsuda test by Rotberg in South America in children of foreigners and natives did not show racial differences; but interesting results might be obtained by further extensive use of this test, if it is accepted as a criterion of individual immunity to leprosy."

A genetic factor is pointed out by Prasal & Mohamed Ali (36) from their epidemiological studies in South India and the "N-Factor" theory is quoted as the first suggestion of that possibility.

In the chapter of Cochrane's text--books about "Genetic Mechanisms", Spickett (61) states that "the constitutional N-factor suggested in 1937, anticipated Aycock's (1940-1948) theories about genetic factors in leprosy".

In a doctoral thesis, Hernandez Zurita points to the "undeniable facts" supporting the N-Factor theory and writes a chapter about the hypothesis which "would represent to leprosy what Lange's theory represented to tuberculosis" (18).

THE GENERAL ACCEPTANCE OF THE "N-FACTOR-ANERGIC MARGIN" THEORY — 1955-1965

Little by little the theory was found to agree with many facts of clinico--pathological and epidemiological observation and was accepted by many authors.

Ignacio *et* al. (19) admit the possibility of an inherent factor which is essential to the development of a strong (Mitsuda) positive reaction." "This is

what Rotberg called the 'N-factor'. "It seems quite probable that this inherent factor is responsible for the apparent freedom from manifestations of disease of many children of leprous parents living under conditions of constant exposure." "This factor, obviously, is of basic importance in resistance to the disease, and the lepromin reaction is only an indicator of its presence in the individual."

Rosenberg *et al.* (43) explain the positive Mitsuda reaction as a resultant of the equation "N-Factor + sensitizing agent". Souza-Campos (59) accepts the N-Factor, "which no one could challenge", but suggests another constitutional factor for predisposition ("P--Factor"). In 1957, Souza-Campos *et al.* (60) write that "the capacity to react is congenital, and may be revealed either positively, thereby creating a state of resistance (presence of the N-factor) or negatively, i.e., as a lack of capacity of antibody formation, which constitutes a state of susceptibility to infection."

Ramos e Silva (39) presents a Mitsuda and Mantoux-negative case of bacteriologically positive "roseolar leprosy", despite repeated doses of BCG prior to the onset of the disease, and explains this "constitutional anergy" to Mycobacteria as a "total absence of the hypothetic factor-N of resistance."

Bechelli *et al.* (2) think that the positivity of the Mitsuda tests in Dutch immigrants living in Brazil might have been explained "by sensitization to the injected lepromin, of people who possess capacity of defense against leprosy (factor N)."

Kinnear Brown and Stone (24) refer to the N-factor and state that their observation of identical tuberculoid twins confirms the hypothesis of a constitutional factor genetically transmitted. In a later work Kinnear Brown (23) referring to the N-factor admits that susceptibility is genetically conditioned ("a race inside a race").

Tuma (63) states that no known condition except age, influences the Mitsuda-type reactivity, a fact which favors the hypothesis of a progressive stimulation of individuals possessing the congenital N-factor.

Leiker (29) writes that the hypothesis that an endogenous factor ("N--factor") is necessary to enable an individual to develop resistance to *M. leprae* "would explain much about the epidemiology of leprosy, if this factor is a quantitative and hereditary one." "In addition to this factor one has to assume one or more local tissue factors to explain such clinical findings as the "immune area of Wade". "Theoretically it is improbable that tuberculosis contact or BCG vaccination has any effect on the N-factor."

Diaz (10) and Saul & Diaz (52) accept the heredity of a N-factor of natural resistance, but add a P- factor of predisposition.

Silva (57) suggests a profound study of the Mitsuda test, based on the genetical N-factor, "the most logical explanation" for many facts observed in hansenology.

According to Miguez Alonso (32), a positive Mitsuda-test may be induced and intensified by unspecific agents, like BCG, "but only on those constitutionally capable to react that way, for having something called N-factor."

According to Seabra Santos (55), the N-factor is due to the clone of immunological competent' cells to antigen T (from Hansen's bacillus) and the "Anergic Margin" to an immunological tolerance to it. A similar interpretation is given by Giordanelli (17).

Fernandez (13) agrees with the theory when he outlines the evolutive

possibilities of hanseniasis: "A-without the N-factor (anergic leprous infection, anergic indeterminate leprosy, anergic lepromatous leprosy), B-with the N--factor (allergic leprous infection, allergic indeterminate infection, allergic dimorphous leprosy, allergic tuberculoid leprosy)".

1966 — 1970

Silva (58) states that all epidemiological observations made after the theory "N-factor" had been suggested have confirmed its validity, although their intimate mechanism' remain obscure.

Newell (35) states that "the Anergic-Factor-N hypothesis is the one most consistent with known occurrences. "Factor-N is a supposititious and possibly hereditarily transmissible constitutional capacity to react specifically against *M. leprae* on challenge." "The Factor-N hypothesis appears to be the most promising, and if substantiated it is unlikely that the BCG vaccination can be a very useful tool for prevention."

Newell's views about the Factor-N and other aspects of hanseniasis were considered a "fresh look at leprosy" by a Lancet editorial (15).

According to Dharmendra (8), the N-factor hypothesis is "an interesting one." It "receives support from the observations that a certain proportion of population continue to remain lepromin negative, in spite of repeated inducements by different methods, and that these persons are found to be highly susceptible, and potentially liable to developing the lepromatous (the more severe) form of leprosy." "The findings from a study of contacts in West Bengal (India) have a bearing on the point under discussion." "These findings revealed that a certain proportion of contacts living in an endemic area remained lepromin negative, in spite of repeated testing; and that these individuals developed leprosy particularly in the lepromatous form, to a greater extent than the initially lepromin negative contacts who became lepromin positive by repeated testing."

Jonquières (22) admits an unknown natural factor (N-Factor) as one of the explanations for immunization to hanseniasis.

Bergel (3) says that the importance of genetics in hanseniasis, suggested long ago in Brazil — the N-factor hypothesis — "only now (1967) is being accepted by specialists of the whole world."

Schuppli (54) cites the N-factor as an explanation for "the natural immunity against lepromatous infection."

Although stating that the N-factor theory was not as yet confirmed, Lechat (28) notes that many studies in genetics agree with it, and that "the hypothesis of a genetic susceptibility to lepromatous leprosy explains some epidemiological observations."

Miranda (33) accepts the N-Factor but suggests that the "Anergic Margin" would not depend on a lack of N-factor but rather on the activity of a "factor-A" (for "anergy"). The relative quantity of each factor would determine the degree of resistance.

Languillon and Carayon (26) admit that there is a natural factor of resistance against the bacillus : "this "N"--factor is congenital and probably hereditary". "It must be 'awakened' to act and to materialize as a positive Lepromin-reaction". The conditions which cause that awakening are contacts with Hansen's bacillus, with Koch's bacillus, perhaps the lepromin test itself, and finally vaccination by BCG." All the pathogenetical develop-

ment of the forms of the disease, of Languillon and Carayon's "Precis", agree with the original N-factor theory.

Accordingly, Languillon (25) casts doubts about the efficiency of BCG and quotes Lechat who said at the Conference of Hammamet (1967) that "BCG seems to protect those who do not need protection, and does not protect those who do".

Estrada-Silos (12) admits the "N--Factor" teory, "as do most writers" although an acquired, non-constitutional capacity to react should also be investigated.

Saul (51) states that the inherited "N-Factor" of resistance to hanseniasis "is already accepted by all", to explain the relatively low prevalence of the disease among those exposed to contagious patients.

Terencio de las Aguas (62) admits that there must be a genetic factor of resistance (N-factor) and of predisposition (P-factor of Saul & Diaz) which should be added to the "bacillus factor" and support a "dualistic pathogenesis of leprosy".

According to Castellazzi (7), the constitutional N-Factor hypothesis is the one which better agrees with known facts, so that a method to disclose its absence should be thought of.

Schujman (53) writes that "the biological ground in leprosy is everything or almost that". "It rules the clinical form and under its dependence are the evolution and prognosis of each case". "Taking in account the very great importance of the ground. it is necessary to orientate and intensify new research to confirm some hypothesis regarding the nature of the above mentioned ground, namely the N-factor (Rotberg) ; the defect of cellular immunity (Goihman-Yahr) ; the delay of cutaneous hypersensitivity (Mayama) ; the deficiency in the control of auto-oxidation of fats (Bergel) ".

1971 — 1977

According to Gay-Prieto (16) there is an anergic group of the population in whom "neither natural causes, nor BCG, nor lepromin could induce the positivity of the Mitsuda reaction". "This fact, universally accepted, justifies Rotberg's hypothesis of an unknown constitutional and possibly hereditary factor — the N-factor".

Santos Silva (50) writes that "the N-Factor concept is intimately bound to the practice of the Mitsuda test, one of the strongest pillars of modern hansenology".

Série *et al.* (56) deduct from their clinico-epidemiological observations in French Guyana that constitution is of primary importance, which induced them to research immunologic, genetic, enzymatic and endocrine factors "in accordance with the N-factor theory".

In a doctoral thesis, Diabate (9), studying the Australia antigen in 593 patients of different types and 3011 controls admits the N-factor theory but does not think that the absence of the factor by itself would explain susceptibility to Virchowian hanseniasis (lepromatous leprosy in the original). "This type of disease depends on absence of N-Factor and presence of one or more factors of susceptibility. Australia antigen is one of these factors".

Languillon *et al.* (27) also conclude from their investigation on 194 African patients and 42 controls that the Australia antigen might be considered

as one of the several factors of susceptibility to Virchowian hanseniasis, by reference to the hypothesis of a natural factor resistance" (N-factor).

Rasi writes (40) that the "N-Factor is receiving more support year by year because it is the one which better explains the constant rates of L form in the general population of different foci and numerous other unknowns of leprosy, an interesting and almost sole model of immunological disease".

Rabello (38) writes (circa 1974) that "everything we know today about the Mitsuda test we owe to Hayashi (1933) — and principally to Rotberg (1934-1937). "It behove to Rotberg to explain: a) that the negative response'precedes bacillary hanseniasis — is not conditioned by it' ; hence, Mitsuda's viewpoint that negative cases had 'lost' their immunity was erroneous); b) that negative reactions in childhood might be 'accidental', if the child was not yet infected, or genuine, when infection had already taken place, typified by strong reaction in small children (against the then current opinion that children were more 'susceptible', also against Muir, 1933) ; c) finally that cases of neural leprosy were not necessarily resistant, as thought by Jadassohn (1928), because they may be Mitsuda-negative (with invasive structures) or Mitsuda-positive (with structures of resistance) ". "Above all we owe to Rotberg the statement that, except for the 'accidentally' Mitsuda-negative reactions in non-infected individuals, the Mitsuda-negativity of 'nodular' and bacillary patients reflected their 'congenital anergy', a congenital incapacity to react positively". "The opposite capacity to react positively was attributed to a 'natural factor of resistance', which he called 'N-factor'."

Basset *et al.* (1) observing aggravations of hanseniasis due to corticoids, state that only in the "grande lèpre lepromateuse" is the N-factor of natural resistance really absent.

Margarido and Belda (31) fully accept the "Factor-N-Anergic Margin" theory in their work about oral BCG vaccination of newborn.

Writing about the pathogenesis of the different aspects of hanseniasis, Bourée (5) states that "if an individual present some natural resistance against Hansen's bacillus ('N-factor of resistance') , the disease becomes clinically limited and without bacilli, the Mitsuda test is positive and the tuberculoid type is formed. "If, on the contrary, there is no such natural resistance factor, a diffuse, bacteriologically positive, Mitsuda-negative form will develop : lepromatous leprosy". Biot (4) outlines the pathogenesis of hanseniasis along the same principles.

Price *et al.* (37) write that "the Factor-N hypothesis, cited by Newell, proposes that a certain proportion of the population is constitutionally incapable of reacting to *M. leprae* and that from this group lepromatous leprosy cases are derived". "This hypothesis is supported by the data of Dharmendra and Chatterjee which indicated that lepromin negative individuals were much more likely to develop the lepromatous form of leprosy than were positive reactors".

Fliess *et al.* (14) think that experiments in mice and armadillos give support to the hypothesis of a genetical origin of the cell-mediated immunity, advocated by various authors, since the N-factor theory was postulated.

The last known article referring to the theory is that of Rea & Levan (41) who state that "the N-factor has three virtues: (1) it is consistent with lepromin reactivity in the absence of

exposure or tuberculin reactivity; (2) it is consistent with Dharmendra's epidemiologic findings; (3) it is consistent with the seemingly paradoxical, always low incidence of LL but extremely variable incidence of TT through BB". "The N-factor hypothesis can be partially reinstated immunologically as the failure or disfunction of an immune-response gene". "However, seven studies of HL-A antigens have demonstrated no consistent relationship between leprosy and HL-A antigen distribution, and thus provide no support for the immune--response gene hypothesis". This last statement by Rea & Levan will be discussed in a further article of this series about "the pending questions".

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The above review of the literature includes only those textbooks and articles known to the author, which specifically mention the "N-factor", agreeing with the theory, totally or in part. It neither includes "neutral" references, like the one of Browne (6) and others, nor those which have antagonized it. (*)

The following article of this series will review (a) the papers which have accepted the theory under a variety of names ("potential immunity", "inherited ability to destroy bacteria or form granuloma", etc. — for the "N-factor" ; "defect of cell-mediated immunity", "constitutional inaptitude", etc. — for the "Anergic Margin") and (b) the papers which are antagonistic to the theory followed by author's rebuttals.

RESUMO

Neste segundo artigo da série sobre a teoria patogenética "Fator-N/Margem Anérgica" da hanseníase, são revistas as primeiras reações editoriais favoráveis (1938-1940) e a aceitação geral da teoria (1940-1977). A aceitação sob terminologia modificada ("imunidade potencial", "capacidade herdada de destruir bactérias ou formar granuloma", etc. — para o "Fator-N"; "defeito da imunidade celular", "inaptidão constitucional para reagir", etc., para a "Margem Anérgica") será revista no 3.° artigo da série, juntamente com a réplica do autor às criticas.

Termos índice: Hanseniase. Imunidade. Resistência. Predisposição. Hereditariedade. Genética Fator-N. Margem Anérgica.

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(*) The author would appreciate being informed about other favorable, neutral or unfavorable references to the "N-factor"/Anergic Margin" theory, to eventually appear in an "addendum" at the end of this series.

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