

## HANSENOLOGIA INTERNATIONALIS

(Hansen.Int.)

### The specific defect of immunity to hanseniasis ("Anergic Margin") — a 40-year old Brazilian theory

EDITORIAL

In 1937 the Revista Brasileira de Leprologia (10) published an article, subsequently read at the International Leprosy Conference of Cairo, 1938, and in abridged form at the Sixth Pacific Science Congress, Berkeley, California, 1939 (11,12). Its conclusions were drawn from the results of Mitsuda tests performed on 1529 persons:

1) Patients presenting different "elementary aspects" of hanseniasis ("erythematous" and/or "hypochromic", "bacillary" or "non-bacillary" macules; "leproma"; "clinically and/or pathologically tuberculoid" lesions, etc.), "aspects" which were adopted instead of the classical topographic "forms" of the disease ("neural", "cutaneous", "mixed") .

2) Contacts and non-contacts, of different age groups.

3) Patients of tuberculosis, blastomycosis and other debilitating conditions.

These conclusions widely differed from the previous epidemiological and pathogenetical theories admitted at the time, as they pointed out:

7) Hanseniasis could be far more contagious than it was thought.

8) Most of the infected contacts remain at the sub-clinical level due to

the development of a delayed "immuno allergic" skin reactivity to Mitsuda's antigen.

1) A fraction of those Mitsuda-positive contacts might reach the clinical stage, due to "accessory factors", and eventually manifest "tuberculoid" lesions in the skin or nerve trunks.

2) Of the minority of Mitsuda-negative contacts, a few might also reach the clinical stage and eventually manifest "bacillary macules", "diffuse", lesions, "lepromas", etc.

3) The capacity of the majority to react to Mitsuda's antigen and Hansen's mycobacterium *did not* depend on general health.

4) The capacity to react *did not* run parallel to the capacity of reacting to other skin tests.

5) The capacity to react *did not* have any relationship with age, sex or ethnic groups.

6) The capacity to react is specific for Hansen's mycobacterium and depended probably on an apparently constitutional unknown "natural" (N) factor.

9) The incapacity of the minority to react *did not* depend on a "general energy" to other skin tests of delayed reactivity.

10) Only that minority of the population genetically incapable to react (designated as the "Anergic Margin") should be the object of prophylactical attention.

Further studies with tuberculin in Brazil and with Mitsuda and tuberculin tests in a non-endemic country (1,14) partly altered the theory, which was adjusted to admit other stimulants of the Mitsuda-positivation in the "N-Factor" majority (Koch's and possibly other mycobacteria). However, none would have any appreciable reversal action on the Mitsuda-negativity of the "Anergic Margin", and the prophylactical value of BCG was thus put in doubt (15).

In a period when predisposition to hanseniasis was either correlated with childhood or attributed to a lowering of general resistance to bacteria, due to malnutrition, malaria, parasitic infestations, alcoholism and other debilitating conditions, all these views amounted to heresy. Moreover, stating that Mitsuda-negativity *preceded* and *prepared* for Virchowian ("nodular") hanseniasis, instead of being the result of a "long battle against the bacilli", lost by an "exhausted nodular host", Mitsuda's theory itself (5) was challenged. It was no wonder that they were labeled as "sweeping conclusions about the (Mitsuda) reaction" in an editorial of the International Journal of Leprosy covering the Cairo Conference (2).

True, soon afterwards the new theories were given a higher credit in other editorials (3,4), including the "Journal" itself (16). Even so, as late as 1948, the hypothesis of a "natural" factor of resistance and its reflections on the pathogenesis and classification of forms of the disease were considered "premature" by the majority of the Committee of Classification of the Havana Con-

gress, against the vote of Rabello, a member of the Committee (7).

Little by little, however, the theory took roots and was generally confirmed by facts observed in many areas. References to, or outright support of an "N-Factor" began to appear in articles and text-books, and the existence of "natural reactors and non-reactors" is no longer contested.

More recently, in many countries the "N-Factor" has been discovered and rebaptized under the names of "potential immunity", "constitutional capacity to react", "inherited ability to destroy bacteria" (or "to form granuloma"), "specific (or "monovalent") hypersensitivity" — and, on the negative side, as a "defect of cell-mediated immunity", "immunological unresponsiveness", "constitutional inaptitude" or "inherent inability to disintegrate Hansen's bacilli", and many other terms to express the state of non-reactivity originally and more simply designated as the "Anergic Margin".

Furthermore, the inconclusive prophylactical results of BCG in various parts of the world appeared as an undesired confirmation of the pessimistic forecast intrinsic to a theory of a gene-conditioned susceptibility.

In 1977, exactly 40 years after the "N-Factor/Anergic Margin" theory was proposed, its partial reinstatement is suggested by Rea & Levan (8), who quote Newell's sympathetic appreciation (6) and Dharmendra's confirmatory evidence in the field.

In the last few years, suggestions to revive the older and simpler Brazilian terminology have been received. Their number augmented since the publication of Rea & Levan's paper.

Accordingly, a series of articles about the "N-Factor/Anergic Margin", to appear in future numbers of "Hansenologia Internationalis", will summa-

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alize the foundations and the acceptance of the theory, under its original or substitute names, as well as its still difficult and controversial points. Their aim will not be only to evade the confusing multiplicity of new names, but also to call attention to terms which are not in agreement with the old theory. In fact, expressions like specific "depression" - or "impairment" of cell mediated immunity sound very much like the rebirth of the unproved Mitsuda's hypothesis of "exhaustion";

the idea of a "general depression" - or "impairment" is equally questionable and was criticized even before the "Anergic Margin" was postulated (9).

It appears, therefore, that the publication of the 40-year old theory and its appraisal by modern methods and techniques will contribute to a better knowledge of the immunology of hanseniasis and to suggest further investigation on the subject.

A. ROTBERG

REFERÊNCIAS/REFERENCES

1. AZULAY, R. D. & CONVIT, J. The Mitsuda test in non-leprous persons in a non-endemic country. *Int. J. Lepr.*, 15: 264-266, 1947.
2. THE CAIRO Congress Number. *Int. J. Lepr.*, 6: 371-376, 1938 (Editorial)
3. EDITORIAL. *Lepr. Rev.*, 10: 104-105, 1939.
4. THE LEPROMIN test. *Lepr. India*, 12: 115-116, 1940 (Editorial Note)
5. MITSUDA, K. Les lépreux maculo-nerveux, d'une part, les tuberculeux d'autre part, se comportent différemment à la suite d'une inoculation d'émulsion de tubercule lépreux. In: CONFERENCE INTERNATIONALE DE LA LEPRE, 3, Strasbourg, 1923, p. 219-220.
6. NEWELL, K W. An epidemiologist's view of leprosy. *Bull. WHO*, 34: 827-857, 1966.
7. RABELLO, F. E. A doutrina da hanseníase na concepção dos hansenólogos de formação latina (1938-1974): um retrospecto com vistas ao futuro Congresso Internacional-México 1978. (*The Latin American conception of hanseniasis - 1938/1974: a retrospect having in view the International Congress, Mexico, 1978*). *Med. Cut. Ib. Lat. Amer.*, 4: 217-226, 1976.
8. REA, T. H. & LEVAN, N. E. Current concepts in the immunology of leprosy. *Arch. Dermatol.*, 113: 345-352, 1977.
9. ROTBERG, A. *Contribuição para o estudo das cuti-reações alérgicas na lepra. Reação de Mitsuda-Hayashi. (Contribution to the study of the allergic skin tests in leprosy. Mitsuda - Hayashi's test)*. S. Paulo, Brazil, 1933. (Thesis - Fac. Med.)
10. ROTBERG, A. Some aspects of immunity in leprosy and their importance in epidemiology, pathogenesis and classification of forms of the disease. Based on 1529 lepromin-tested cases. *Rev. Bras. Leprol.*, 5 (n.º esp.): 45-97, 1937.
11. ROTBERG, A. Modern trends in the study of the epidemiology of leprosy. In: PACIFIC SCIENCE CONGRESS, 6th, Berkeley, California, 1939. *Proceedings*. v.5, p. 939-945.
12. ROTBERG, A. The influence of allergic factors in the pathogenesis of leprosy. In: PACIFIC SCIENCE CONGRESS, 6th, Berkeley, California, 1939. *Proceedings*. v.5, p. 977-982.
13. ROTBERG, A.; BECHELLI, L. M.; KEIL, H. Reação de Mitsuda em área não leprogênica. (*The Mitsuda reaction in a non-leprous area*) In: CONGRESSO INTERNACIONAL DE LA LEPROA, 5.º, Havana, 1948. *Memórias*. Habana, Editorial Cenit, 1949. p. 586-594.
14. ROTBERG, A.; BECHELLI, L. M.; KEIL, H. The Mitsuda reaction in a non-leprous area. *Int. J. Lepr.*, 18: 209-220, 1950.
15. ROTBERG, A. Fator: "N" de resistência à lepra e relações com a reatividade lepromínica e tuberculínica. Valor duvidoso do BCG na imunização anti-leprosa. (*"N-Factor" of resistance to leprosy and its relationships with reactivity to lepromin and tuberculin. Doubtful value of BCG in anti-leprous immunization*). *Rev. Bras. Leprol.*, 25: 85-106, 1957. -
16. THE UNKNOWN factor in leprosy. *Int. J. Lepr.*, 7: 269-272, 1939.