CORRESPONDENCE

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Fiftieth Anniversary of the "N-Factor/Hansen-anergic Fringe" Hypothesis for Hanseniasis

TO THE EDITOR:

The "N-Factor/Hansen-anergic fringe" (NF/HAF) hypothesis for hanseniasis was postulated in Brazil in 1937 ([10]), and internationally reported at the Cairo Congress in 1938 ([3]) and the Sixth Pacific Science Congress (San Francisco) in 1939 ([12, 13]). Differing from the then prevailing notions that predisposition to hanseniasis depended principally on age and/or debilitation due to malnutrition and various diseases, the hypothesis maintained that it was probably related to genetic factors. Stimulated by Hansen's bacillus, the majority of the population (75%–80%) would react in various degrees to the Mitsuda test due to the presence of a "natural" (N) factor of resistance that would protect them against the development of the disease or, at most, permit the organization of nonbacillary sarcoid or tuberculoid-like lesions in the skin and/or nerves. The minority, the "anergic fringe"—a term later changed to "Hansen-anergic fringe" in order to stress its specificity—would not react and, with the cooperation of "accessory factors" (malnutrition, diseases, etc.), would eventually develop bacillary, Virchow's cell-loaded lesions. "Intermediate" aspects could appear between those extremes of reactivity. The different degrees of reactivity might help in establishing a new classification of forms of the disease.

The NF/HAF hypothesis was sympathetically accepted in editorials of the INTERNATIONAL JOURNAL OF LEPROSY ([5]) and other periodicals ([11, 18]), and was entirely or partially accepted in many articles and textbooks. It is practically incorporated in modern hansenology, in spite of the fact that its genetic foundation is not yet fully confirmed. After a study of the influence of *Mycobacterium tuberculosis* and BCG on the Mitsuda reactivity, the hypothesis was completed in 1957 ([14]) to admit their stimulating capacity for Mitsuda-positivation in the NF majority. However, since the HAF was not reduced, the failure of BCG as a preventive vaccine was forecast 12 years before the practically negative value of the vaccination experiments in Burma were reported by the World Health Organization (WHO). The same forecast has been made ([16]) for other vaccines as well if they do not change the reactivity of the HAF.

Curiously, the origin, authorship and terminology of the 50-year-old hypothesis gradually faded away and many other authors—with as many new terms—have been credited with its postulation. At least 24 pairs of synonyms have replaced the term NF/HAF, of which the more commonly used are "innate cell-mediated immunity/defect of cell-mediated immunity," "natural reactivity/natural nonreactivity," "constitutional immunity/constitutional anergy," and others ([15]).

Professor Newell ([7]) is the author most

often credited with the etiopathogenetical and epidemiological viewpoints of the NF/HAF hypothesis after he wrote that ". . . From the epidemiological standpoint the 'anergic' or factor N hypothesis describing the lepromin reactions and lepromatous leprosy appears to be the most acceptable . . . ." adding new facts favoring the hypothesis, which "seems to be the one most consistent with known occurrences." However, certainly unaware of the original articles of 1937–1939 ([10, 12, 13]), he also wrote that "one of the leading advocates of this hypothesis is Rotberg. 1957)" emphasis added). These underlined inexactitudes were aggravated by a favorable appreciation of Prof. Newell's article by WHO ([19]) in which the original papers and dates of publication were omitted, easily leading the reader to attribute the NF/HAF hypothesis to Prof. Newell.

One of the results is that in the INTERNATIONAL JOURNAL OF LEPROSY from 1975 to 1988, 12 articles cite Prof. Newell as the author of the etiopathogenetical and epidemiological viewpoints of the NF/HAF hypothesis. For instance, Nakajima, *et al.* ([6]) write that a "special depression of cell-mediated immunity in the lepromatous form is a host-dependent characteristic which probably is genetically determined." Harboe ([2]) editorializes that "Epidemiological studies indicate that susceptibility to lepromatous leprosy is, at least partly, genetically determined." and Chirmule, *et al.* ([1]) refer to the ". . . lepromin-negative healthy subjects who represent a high-risk group in leprosy-endemic areas." All these statements are attributed to Prof. Newell, in spite of having been clearly postulated 50 years ago at the Cairo and San Francisco Congresses ([10, 12, 13]).

With whichever authorship of terminology, what is important is that, at its 50th anniversary, the NF/HAF hypothesis appears to be well implanted, although more confirmatory genetical evidence is necessary. However, in spite of the fact that recent works such as those of Languillon ([4]), Price, *et al.* ([8]), and Rea and Levan ([9]), and Stoner ([17]) have given credit to the original author, it seems that the Brazilian contribution to this advance could soon be forgotten.

—Abrahão Rotberg

Professor of Dermatology (1958–1973)
Escola Paulista de Medicina
São Paulo
Associate Prof. of Dermatology
Faculty of Medicine
São Paulo, Brazil

Rua Pedroso Alvarenga 125/74
São Paulo 04531, Brazil

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