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EDITORIALS

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CROSS IMMUNITY IN LEPROSY AND TUBERCULOSIS

The relation of allergic and immunologic phenomena in leprosy and tuberculosis has been the subject of much speculation and intensive study. Since Fernandez,¹ in 1939, published his observations on the comparative study of the reactions to tuberculin and to lepromin in different subjects, many contributions to the subject have been made and great hopes have been entertained of the possibility of discovering a practical method of raising the defenses of the human body against infection with *Mycobacterium leprae*.

The original Mitsuda test, and later those performed with the purified bacillary antigens of Fernandez and of Dharmendra, showed that the human skin has a capacity to react against these antigens under certain conditions, and that in the case of persons infected with the leprosy bacillus who react positively the disease assumes the benign tuberculoid type. It is also believed by many, although it is still subject to actual proof, that normal persons who react positively are well protected against infection.

¹ FERNANDEZ, J. M. M. Estudio comparativo de la reacción de Mitsuda con las reacciones tuberculínicas. *Rev. Argentina Dermatosis*. **23** (1939) 425-453.

The high frequency of positive lepromin reactions in normal individuals, whether living in endemic areas or not, has given rise to numerous interpretations, especially as to the allergic or immunologic nature of the lepromin reaction. Furthermore, the view that there is a group sensitivity against all acid-fast bacteria has been offered as an explanation for this high index of positivity in the general population of practically all countries. Leprologists like Fernandez, Rabello and Souza Lima have favored this theory. Comparative studies of the results of the lepromin and tuberculin tests in patients with the lepromatous and tuberculoid types of leprosy have been discordant and unconvincing, the tuberculin reaction being positive in practically all cases of lepromatous as well as of tuberculoid leprosy. However, the early Fernandez lepromin reaction, assumed to be of allergic nature, seems to be positive in a high proportion of cases with cutaneous tuberculosis, which is not the case in the normal population of either leprosy or nonleprosy countries.

A most important contribution was made by Fernandez¹ when he showed that in 123 lepromin- and tuberculin-negative children, vaccination with BCG caused after 30 days reversal of the results, the tuberculin reaction being positive in all but one and the lepromin reaction positive in 92 per cent of the vaccinated subjects. These astonishing results seemed to confirm the suspicion entertained by some investigators of a cross immunity between leprosy and tuberculosis. If this were true, according to Fernandez, vaccination with BCG would not only protect against tuberculosis but would also raise the defenses against leprosy. Whether this immunity would be partial or complete, permanent or transitory, is still to be demonstrated. Would repeated vaccinations with lepromin raise the level of tissue defense and immunity to a point that would make the patient refractory to infection with leprosy for the rest of his life? Fernandez concluded that "...the Mitsuda reaction is specific in lepers and persons in contact with lepers; tuberculosis has no influence on this reaction. On the other hand, in persons uncontaminated with the Hansen bacillus the Mitsuda reaction is not specific and shows consensitization with tuberculosis." He was the first to suggest the "advisability of inoculation with BCG of persons in contact with lepers who do not react to lepromin." Whether this could be done with impunity in adults has been doubted by many, and considered dangerous by most observers.

The report of Convit, Azulay, Bermudez and Salgado² on the results of lepromin tests performed on 108 tuberculous patients in New York shows that 70 per cent of these patients reacted positively to the early lepromin test and 43 per cent gave positive late or Mitsuda reactions. These individuals were all tuberculin-positive living in a nonleprous community.

Harrell and Horne³ have reported that patients with sarcoidosis do not show special reactivity to lepromin, but they noted a high percentage of strongly positive lepromin reactions in persons strongly positive to tuberculin. This suggested the presence of common sensitizing antigens, and to explain these coincident reactions they suggested a possible mechanism based on the presence of polysaccharide antigens. David T. Smith, of Duke University (personal communication), has commented on the results of lepromin and tuberculin tests in 12 cases of Boeck sarcoid. The tuberculin-negative cases gave negative lepromin reactions, while on the other hand known cases of tuberculosis and cases of Boeck sarcoid which were tuberculin positive reacted positively to lepromin. Smith had gained the impression that the positive cases represented cross sensitivity with tuberculosis.

In 1944 Fernandez⁴ reported that of 4 nontuberculous patients—2 with psoriasis, 1 with rosacea and 1 with asthma—who had received repeated injections of BCG several months previously, all gave early and late lepromin reactions and all were positive to the Mantoux test. He concluded then that *M. tuberculosis* may, under certain conditions, produce an allergic state with regard to the lepromin antigen.

Rotberg and Oliveira,⁵ in 1937, found that of 70 patients with tuberculosis 86 per cent gave positive lepromin reactions, and they called attention to the fact that the negative results occurred in far advanced cases of tuberculosis. However, these authors

² CONVIT, J., AZULAY, R. D., BERMUDEZ, D. and SALGADO, P. The lepromin test in tuberculous persons in a non-endemic area. *Internat. J. Leprosy* **12** (1944) 60-64.

³ HARRELL, G. T. and HORNE, S. F. The reaction to lepromin of patients with sarcoid or tuberculosis compared with that of patients in general hospitals, with a discussion of the mechanism of the reaction. *American J. Trop. Med.* **25** (1945) 523-535.

⁴ FERNANDEZ, J. M. M. Influencia del factor tuberculosis sobre la reacción a la lepromina. *Rev. Argentino-Norteamericana Cien. Med.* **1** (1943) 592-600.

⁵ ROTBERG, A. and DE OLIVEIRA, J. F. A reação da lepromina na tuberculose. *Rev. brasileira Leprol.* **5** (1937) Spec. No., pp. 287-291.

believed that there is no immunologic relationship between leprosy and tuberculosis, since the positivity rate they observed is equal to that found among normal persons in endemic areas.

Further interest in this subject has been raised lately through the contributions of Azulay⁶ in 1948 and of Souza Campos, Rosemberg and Aun⁷ in 1950, after Fernandez had suggested the possibility of raising the defensive powers of the human body against leprosy with one or more vaccinations with BCG. Azulay reported on 15 lepromin- and tuberculin-negative children born of leprous parents who had been removed from their environment immediately after birth, to whom he gave 100 mgm. of BCG by mouth. Two months later 10 of them proved positive for the early Fernandez reaction, and 12 gave positive late or Mitsuda responses. Children who had not been vaccinated remained lepromin-negative.

Souza Campos and associates, in a series of contributions, have thrown additional light on this subject of the immunologic relation between leprosy and tuberculosis. They found that the administration of a single dose of 100 mgm. of BCG to lepromin-negative children resulted in the change to positive in only two-thirds of the cases. Another group of previously lepromin-negative children who received daily progressive doses of BCG by mouth up to a total of 1.19 gm., all gave positive reactions after two months. Thus the ingestion of repeated and increasing amounts of BCG seems to have been directly related to the development of the positive lepromin reactions. These authors also call attention to the close concurrence of positive lepromin and Mantoux reactions in these patients.

There remains, however, an unexplained point, namely, the close parallelism between the reaction to tuberculin, which is an allergic proof of hypersensitivity to tuberculosis, and the lepromin reaction, which signifies a state of resistance, i.e., immunity. Nevertheless, the fact remains that BCG administered orally in repeated doses seems to be effective in turning the results of the tuberculin and lepromin tests to positive in patients who previ-

⁶ AZULAY, R. D. A ação do B.C.G. sobre a reação lepromínica. *Arq. Serv. Nac. Lep.* **6** (1948) 81-86; *also O Hospital* **34** (1948) 853-856.

⁷ SOUZA CAMPOS, N., ROSEMBERG, J. and AUN, J. N. Da relação imunobiológica entre tuberculose e lepra. *Rev. brasileira Leprol.* **18** (1950) 3-23. II. Da inter-relação entre as reações tuberculínicas e lepromínica em filhos de doentes de lepra. *Ibid.* **18** (1950) 117-127. III. A lepromino-reação em crianças de descendência não leprosa vacinadas com BCG por via oral. Dissociação entre alergia tuberculínica e reação de Mitsuda. *Ibid.* **18** (1950) 128-143.

ously had been negative to both tests. Souza Campos and associates recommended repeated BCG oral vaccinations for all children of leprosy parents during the first days of life as a prophylactic measure, and they suggest that the positive Mitsuda reaction brought about by the oral administration of BCG may be connected with the immunity process of tuberculosis and independent of the process of hypersensitivity.

The practical conclusion that we may draw from these interesting studies is that we are facing the possibility of mass immunization of children against leprosy in those countries highly affected by this disease, and that, although this immunity may not be absolute, the type of leprosy which might develop among some of these children would be of the tuberculoid type, i.e., of benign, practically noninfectious character. This may result in time in a great reduction of the incidence of leprosy and its eventual eradication.

There is food for thought in these contributions and experimental work. They seem to light a path of hope for the struggle against a scourge that man can trace during the whole historical period of his existence on the earth. —V. PARDO-CASTELLÓ