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EDITORIALS

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AGAMMAGLOBULINEMIA AND THE LEPROMIN REACTION?

This is the story of a fascinating recently-discovered aberrant condition and of a proposed inquiry based upon it. That proposal having met with frustration, it is passed on as a suggestion.

The condition is a remarkable chemical abnormality in which there is a deficiency of gamma-globulin synthesis, in some cases so complete as to justify the term agammaglobulinemia but usually more correctly called hypogammaglobulinemia. It was only in 1952 that the first case was reported,[1] but others soon came to light and material contributions have been made by, among others, Robert Good[2] in Minneapolis, and Nicholas Martin[3] in London, which places have become centers of study of the condition.

The deficiency, which may be congenital (seen only in males) or acquired (either sex), is an "immunological paralysis" which prevents the formation of common circulating antibodies and consequently renders the patients peculiarly susceptible to certain bacterial infections. On the other hand, it is said, there is usually no deficiency with respect to viruses because the immunity response to them depends on some mechanism not involving ordinary antibodies. A spectacular effect has been success with

[1] BRUTON, O. C. Agammaglobulinemia. Pediatrics **9** (1952) 722-727.

[2] GOOD, R. A. Agammaglobulinemia—a provocative experiment of nature. Bull. Univ. Minnesota Hosp. & Minnesota Med. Found. **26** (1954) 1-19. (At the December 1955 meeting of the A.A.A.S., Dr. Good was presented with the Theobald Smith Award for Medical Sciences for his work on the subject of congenital agammaglobulinemia and the contribution such diseases offer in elucidating the mode of action of immunological mechanisms [Science **123** (1965) 283].)

[3] MARTIN, N. H. Agammaglobulinemia; a congenital defect. Lancet **2** (1954) 1094-1095. [see also a review article in Triangle (Sandoz, Basle) **11** (1956) 297-305.]

homografts, at least in congenital cases, because of the absence of the usual antibody effect which leads to rejection.[4]

Only a few of the available reports reveal other than incidental interest in the influence which this condition may have with respect to the immunology of the common mycobacterial infection, tuberculosis. There are general statements like "total absence of circulating and fixed antibodies,"[5] or "negative skin tests,"[6] or "lack of cutaneous responses to antigens,"[7] and when the tuberculin test is mentioned the results are usually—not always—negative; but apparently that test has not been applied regularly. No mention has been seen of the BCG test, the skin test with tuberculosis bacillus bodies which would be of particular interest in the present connection.

There may perhaps be a difference in the matter of tuberculin reactivity between the congenital and the acquired forms. New antibodies are not formed in either variety, but there is no special tendency to destroy or eliminate antibodies that have already been formed. The few cases that have been found tuberculin positive may—in part, at least—have been that way before the hypogammaglobulinemia developed.

Elphinstone *et al.*[7] tell of a boy who developed tuberculosis in 1952, at the age of 7, after the symptoms of agammaglobulinemia were established. At first the Mantoux reaction was negative, but six weeks later it was positive (1/100 both times); and, although the patient responded well to antituberculosis treatment, he continued positive in 1954 and 1955 (then at 1/10,000). His younger brother was vaccinated with BCG (twice before tuberculin positivity was established) and remained reactive to tuberculin after he was found to have agammaglobulinemia. The authors mention a report by Kulneff *et al.*[8] who BCG-vaccinated—without harm—three agammaglobulinemia children two of whom became tuberculin positive.

Zinneman and Hall[9] studied an acquired case in an adult man with benign tuberculosis, strongly reactive to tuberculin. They point out that whereas an Arthus type of skin reaction could not be expected for lack of anaphylactic antibodies, the "delayed" type of bacterial hypersensitivity—which results from a different mechanism, the antibodies supposedly cell-bound—should not be abolished by the occurrence of hypogammaglobulinemia.

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[4] VARCO, R. L. MACLEAN, L. D., AUST, J. B. and GOOD, R. A. Agammaglobulinemia; an approach to homovital transplantation. Ann. Surg. **142** (1955) 334-345.

[5] YOUNG, I. I. and WOLFSON, W. Q. Idiopathic and acquired symptomatic agammaglobulinemia. J. Lab. & Clin. Med. **44** (1954) 959 (abstract).

[6] ROHN, R. J., BEHNKE, R. H. and BOND, W. H. Acquired agammaglobulinemia with hyperplenism; a case report. J. Lab. & Clin. Med. **44** (1954) 918 (abstract); American J. Med. Sci. **229** (1955) 406-412 (cited).

[7] ELPHINSTONE, R. H., WICKES, I. G. and ANDERSON, A. B. Familial agammaglobulinemia, British Med. J. **2** (1956) 336-338.

[8] KULNEFF, N., PEDERSON, K. O. and WALDENSTRÖM, J. Drei Fälle von Agammaglobulinämie; Ein klinischer, genetischer und physikal-chemischer Beitrag zur Kenntnis des Proteinstaffwechsels. Schweizter med-Wchnschr. **85** (1955) 363 (cited).

[9] ZINNEMAN, H. H. and HALL, W. H. Steatorrhea and probable tuberculosis with acquired hypogammaglobulinemia. American Rev. Tuberc. & Pulm. Dis. **74** (1956) 773-782.

Of interest, too are the findings of C. M. Martin and associates, who in an acquired case first passively transferred tuberculin positivity with intact leucocytes,[10] and then made homotransplants of lymph nodes from a tuberculin-positive donor with the result that the patient promptly became strongly positive and remained so—although less strongly—after the transplant had died and no longer could produce antibodies.[11]

Considering the peculiarities of agammaglobulinemia, it seemed possible that if the lepromin test could be applied to a number of the patients the results might produce new evidence concerning the mechanism of the late, or Mitsuda, reaction. The early, or Fernandez reaction is generally accepted as a typical one of "bacterial allergy" to the bacillary proteins (if not necessarily specific), but most students of the reactions to lepromin carefully avoid discussion of the *mechanism* of the late one, or any mention of allergy in connection with it, speaking only of its significance. The present writer, however, ventured an explanation some twenty years ago,[12-14] and has not seen reason to retract.

This view is that the reaction results—in normal people as well as leprosy patients and presumably infected contacts—because of some sort of allergic change induced in the body after the test dose of killed bacilli is injected, rather than from pre-existent allergy; that it demonstrates the *capability of the individual to react* to the antigenic complex of the bacilli—the "bacillus-body reaction"[15]—and not previous allergic sensitization in the ordinary sense of that term.

The bacilli in lepromin cannot be regarded as inert, nonantigenic bodies, as tuberculin is antigenically inert, and experiments in dogs reveal that they can be so highly antigenic as to make possible on reinjection the production of an accelerated (Koch type) reaction.[14] In man, however, the leprosy bacillus exhibits its most

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[10] MARTIN, C. M., GORDON, R. S. and MCCULLOUGH, N. B. Acquired hypogammaglobulinemia in an adult. Report of a case, with clinical and experimental studies. New England J. Med. **254** (1956) 449-456.

[11] MARTIN, C. M., WAITE, J. B. and MCCULLOUGH, N. B. Antibody protein synthesis by lymph nodes homotransplanted to a hypogammaglobulinemic adult. J. Clin. Invest. **36** (1957) 405-421.

[12] WADE, H. W. Problems of allergy in leprosy. Festschr. Bernard Nocht, 1937; Hamburg: J. J. Augustin, 1937, pp. 652-655. "The reaction, obviously, is not due to a pre-existent hypersensitiveness of infected persons, but to an ability to react to the presence of (dead) bacilli which is shared alike by healthy persons and neural-type lepers. The slow evolution of the papule indicates that the state of the tissue which is responsible for it occurs after the test material has been introduced."

[13] (WADE, H. W.) The immunology problem. Internat. J. Leprosy **6** (1938) 95-101 (editorial, unsigned). "In other words, the test appears to be one of capability to react to the presence of the killed bacilli and not [one] of the actual existence of specific hypersensitiveness, or allergy."

[14] WADE, H. W. The lepromin reaction in normal dogs; preliminary report. Internat. J. Leprosy **9** (1941) 39-56. "It is concluded that this reaction, while undoubtedly one of allergic nature, is not a test of the existence of allergic hypersensitiveness, but rather one of capability of developing an allergic state after the introduction of the antigen."

[15] USTVEDT, H. J. The BCG-test. WHO Expert Committee on Vaccination Against Tuberculosis, **6**, 20 Nov. 1953, mimeogr. 26 pp.

conspicuous antigenic peculiarity, namely, an inability to establish the type of hypersensitivity manifested in tuberculosis by the Koch reaction. If that were not the case (i.e., if the situation paralleled that in tuberculosis), injection of lepromin into the skin of a tuberculoid patient would cause a prompt and violent reaction.

Considering this thesis together with the evident fact that many individuals may not be sufficiently prepared, or "conditioned," to give any evident reaction on first testing, or only a slight one read as doubtful, it is understandable how the below-threshold effects of the first test may make many such individuals react positively on second test.[16, 17] When Ustvedt[15] called the BCG test a "microvaccination," he employed a term which is equally applicable to the lepromin test. In line with the idea of "conditioning" expressed are the "positivizing" effects of (1) exposure to leprosy infection in contacts, (2) infection with tuberculosis in "natural" tuberculin reactors and the changes induced by BCG vaccination, and (3) conditions of the environment and the individual's experience which in one way or another contribute to immunobiologic maturation.

By what means the lepromin-induced immunologic changes are mediated to produce the local effect (which cannot be simply a foreign-body effect) is quite unknown, except that presumably there are involved some kind of "antibodies"—a widely-inclusive term. Because, as said, it seemed possible that much-needed light might be thrown on this matter if a number of individuals with agammaglobulinemia could be tested with lepromin, the proposition—with endorsement—was submitted to the entities in Minneapolis and London which are responsible for studies of agammaglobulinemia. No response was received from the former. From London, Dr. Nicholas H. Martin responded cordially, but his reply closed the door:

I raised your problem informally at the Working Party on Agammagloublinemia [of the Medical Research Council.] Everyone was very sympathetic but there are so many direct questions to be answered about this interesting condition, and the Working Party was already so heavily committed in attempting to answer some of them, that no one felt that they could set aside patients for the study you suggested.

This proposition is passed on in the hope that someone so fortunately situated as to have access to cases of agammaglobulinemia—preferably, perhaps, the adult acquired form—may be led to study the reactions of such patients to lepromin. Or, if that should not be feasible, such tests might be made with killed tubercle bacilli. In either case, the purpose would be to secure further evidence regarding the mechanism of the "bacillus-body" reaction elicited by the pathogenic mycobacteria. Reports of results in even single cases would, in the long run, be contributory.

—H. H. WADE

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[16] DE PAULA SOUZA, R., DE TOLEDO FERRAZ, N. and BECHELLI, L. M. Influencia do BCG vivo o morto sôbre a reação de Mitsuda. (Observações preliminares.) Rev. brasileira Leprol. **21** (1953) 43-50.

[17] SILVA, C. O., RABELO NETO, A. and DE CASTRO, I. Ação do BCG sôbre a leprimino-reação em comunicantes de casos de lepra. Bol. Serv. Nac. Lepra **14** (1955) 123-135. (There will be a comprehensive abstract of this article in the next issue of THE JOURNAL.)