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EDITORIALS

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INTERRELATIONSHIPS AMONG MYCOBACTERIA

Among the original articles and other papers published in this issue of *THE JOURNAL* are several bearing on a matter of increasing interest in medical meetings and scientific journals, viz., antigenic interrelationships among the mycobacteria.

The paper by Rao, Nadkarni and Khanolkar illustrates the trend, and indicates some of the principal immunologic methods used today in demonstrating the presence of antigens or antibodies, possessed in common, among chemically complex mixtures, such as culture filtrates from growing microorganisms, and the serum of animals immunized by disease or artificial inoculation. One of the most fruitful techniques described is that of double (or multiple) diffusion of antigens and antibodies from separate locales in agar plates, with the production of lines or concentric rings of precipitin reaction, giving visible evidence of antigen-antibody union.

Numerous other methods are available, which in essence yield similar data. Rao and her associates have reported results with several of these procedures. Only time will tell if the cultivable organism with which the report deals is truly closely related to leprosy. One element brought out in the paper is the difficulty, in any such experiments, of eliminating antibodies to other substances than the mycobacterial antigens, and particularly to the blood and tissue components almost invariably adhering to bacilli grown in living tissues, cells, and media derived from them. Reference will be made to this phenomenon a few paragraphs hence.

Another paper of important significance in the same respect is the one by Convit, Lapenta and Ilukevich, in which the bold and imaginative concept is presented that the numerous cultivable, fast-growing mycobacteria isolated occasionally from lepromatous lesions may not represent saprophytes living as secondary invaders in leprotic tissues, as often supposed, but actually be new species derived from the true leprosy bacilli in the lesions by genetic interchange of factors possibly concerned in growth on artificial media. A great deal of work will be required to test the validity of this cautiously ad-

vanced hypothesis. It is a demonstrated fact, however, that the nature of some mycobacteria can be modified by the introduction of genetic material from outside sources. What might be called the "Southern California bacteriophage school" has shown on numerous occasions that phage desoxyribonucleic acid can be added to mycobacteria, including tubercle bacilli and saprophytes such as *M. smegmatis*, a procedure that might lead to permanent genetic change. Definite, persisting genetic modifications have been brought about in many other microorganisms in the years following the classic experiments of Avery, MacLeod and McCarty in 1943 on the transformation of pneumococcal types through the interchange of their respective desoxyribonucleic acids. There appears to be reason to expect the discovery of similar phenomena in mycobacteria.

The subject is stimulating increasing attention in international meetings. Several papers touched upon it at the recent Rio de Janeiro Congress. Studies are going on all over the world. The Editor, not unnaturally, is more familiar with those in the United States than elsewhere, and it is possible that a greater effort has been made thus far in the United States to classify and codify the mycobacteria. The wide use of the group-classification of Ernest Runyon supports this view. So much interest has been displayed that a number of investigators in the United States have combined in a loosely knit "antigen study group" for a concentrated investigation of mycobacterial antigens.

This movement led, in its early stages, to a small international gathering in April 1963 of experts in the field at the Airlie House in Warrenton, Virginia, where the experience of qualified workers from Europe, Asia and the Americas was set forth. The symposium was sponsored by the George Washington University of Washington, D.C. and the National Tuberculosis Association of the United States, with the generous support of a pharmaceutical supply house. Not surprisingly the discussions were based in considerable measure on chemical and immunologic procedures developed over many years in studies of the tubercle bacillus. It is of interest in this connection to note a remark of one of the evening speakers at the symposium, Dr. James Watt, Assistant Surgeon General for International Affairs, U.S. Public Health Service, who referred to tuberculosis and leprosy as "country cousins." This is a term probably not widely known outside of English-speaking countries. It refers in an imprecise way to relatives who visit each other infrequently and are not well informed on each other's environment and activities. It is used particularly to designate country-resident kin visiting relatives in the busy big cities. The analogy is not wholly far-fetched. The moral is, of course, that to mutual advantage, they might know each other better. Dr. Watt implied that leprosy investigators and students of tuberculosis should have more contact.

Technics discussed on that occasion, which have proved fruitful thus far in studying the overlapping antigenic relationships among mycobacteria, included differential chemical fractionation, electrophoresis, ion-exchange chromatography and other "ultra" procedures, for the preparation and purification of mycobacterial antigens, and a variety of immunologic testing procedures, including skin-testing of the tuberculin type and a number of the newer technics for recognition of antibodies, such as the Ouchterlony and similar diffusion technics for demonstration of multiple antigens and antibodies.

Leprosy was represented in this assemblage of experts by R. J. W. Rees, who outlined his experiments on *M. leprae*, *M. lepraemurium* and other mycobacteria. In the experiments he reported, *M. leprae* antigen was obtained from human leprosy lesions, and *M. lepraemurium* antigen from culture filtrates from tissue culture of that organism. Rabbits were used for the production of antisera, and agar diffusion methods, among others, were employed in immunologic tests. These results, like others in this symposium, will be published in the near future, but advance examination of the transcribed record indicates that Rees found a significant extent of cross reactions in the case of leprosy bacilli and other mycobacteria and to somewhat less extent in the case of rat leprosy organisms and the other bacteria tested. Leprosy bacilli stimulated the production of antibodies causing precipitation with the homologous antigen, and other mycobacteria as well, including the tubercle bacillus. Rigid precautions were taken through antibody absorption technics to exclude reactions to animal or human constituents.

Much work may be expected in this general field in the months to come. In the world's leading tuberculosis journals the trend is clearly visible. Readers will recall articles of comparable import in the INTERNATIONAL JOURNAL OF LEPROSY. The subject has many ramifications, including, particularly: cross, and therefore undesirable, skin reactions in epidemiologic surveys for tuberculosis; the possibility of using other than homologous organisms in artificial immunization, e.g., BCG in leprosy; and specific and nonspecific elements in chemotherapy. A mutual partial susceptibility to some of the tuberculostatic drugs is evident in tuberculosis and leprosy, but extraordinary variations occur in the sensitivity of the various other mycobacteria.

The cross relationship appears established, but it must be admitted that insufficient attempt has been made to learn of cross reactions among mycobacteria and other nonacid-fast bacteria. It would be impossible even to direct attention to the many investigations underway. Without some other relationships, such as overlapping antigenic components, the unity of mycobacteria as a group would hang chiefly on a rather slender thread, viz., their capacity, once stained, to resist acid and alcohol decolorization. As it is, however, not only do antigenic relationships come into play, but others as well, in-

cluding chemotherapy. In a review, in THE JOURNAL (**32** (1964) 100-101) of a thought provoking Japanese monograph entitled "*Studies of Leprosy Based upon Fundamental Investigation into Tuberculosis*," attention was called to a statement by K. Tanioku, who considered it unlikely that anything as simple as constitutional make-up, as revealed by acid-fastness, could be responsible for the success of some of the antituberculosis drugs in leprosy. His view is probably shared by many, viz., that other factors in pathogenesis, e.g., the phenomena of allergy, are concerned.

All in all, much attention is being given to the problem. Nearly sixty years ago, in 1905, it was recognized as an old one, but considered closed. Two competent investigators in Robert Koch's Division of Tuberculosis in the Department of Health in Berlin, A. F. Weber and Max Taute, after exhaustive study, were satisfied that the mycobacteria were well fixed in type. Not a few investigators today, however, have become seriously doubtful of their nonmutability.

—ESMOND R. LONG