

BOOK REVIEW

Experimental Tuberculosis, Bacillus and Host. With an Addendum on Leprosy. Edited for the Ciba Foundation by G. E. Wolstenholm *et al.* London: J. & A. Churchill Ltd., 1955, xii+396 pp., 42 shillings; Boston: Little Brown & Co., \$9.00.

In October 1954 an international group of chemists, pharmacologists, pathologists, bacteriologists, immunologists and tissue-culture experts engaged in tuberculosis research met in conference in London as guests of the Ciba Foundation. The meetings of this symposium on experimental tuberculosis and leprosy, at which 26 papers were read, lasted two and one-half days, the last half day being devoted to the four papers on leprosy. The publication of these papers and the discussions should be of immense value to all experimental workers in both diseases. Note will be made first of the four papers on leprosy.

LURIE, M. B. Pathogenetic relationship between tuberculosis and leprosy. Tuberculosis has a 'symbiotic phase' when there is an early diffuse accumulation of monocytes with coarsely vacuolated cytoplasm harboring many bacilli, which are in symbiosis with the uninjured host cells. This is followed by a "nodular phase" in which mature epitheloid cells with very finely vacuolated cytoplasm are collected in tubercles, and at the same time there is destruction of many intracellular bacilli. This latter phase is characterized by cell death and caseation, and tuberculin sensitivity. Lepromatous leprosy corresponds to the former of these phases, and tuberculoid leprosy to the latter. Thus the pattern of tissue response to different mycobacteria in different species, including those of human leprosy, appears as variations of a common theme. This theme varies with the predominating growth or destruction of the bacteria and the meagre or marked development of allergic sensitivity.

LOWE, J. The leprosy bacillus and the host reaction to it. The author mentions a "curious dichotomy" in the manifestations of leprosy infection. In one of the two main types there is sensitization and immunity, while in the other there is complete lack of these conditions. In tuberculosis there is an interplay of findings, some indicating the invasive powers of the infection and some indicating sensitization and resistance of the host tissue. In the lepromatous case with abundant bacilli but no cellular reaction to them, circulating antibodies are easily demonstrated but no sensitization, no cellular antibodies revealed by the lepromin test, and no resistance to infection. In the tuberculoid case, however, with limited lesions and very few bacilli but intense cellular reaction to these few bacilli, circulating antibodies are difficult to demonstrate and there is apparently a high degree of sensitization and immunity to the infection. Protein desensitization may be effected without impairing cellular response to the whole bacillus, as shown by the delayed Mitsuda reaction, so that the response to the whole bacillus and not to any fraction appears to be the main factor in immunity.

COCHRANE, R. G. Reaction of the host tissue to *Mycobacterium leprae*. The tissue reactions in the various types of leprosy are described, with particular discussion of two views regarding the nature of the lepromin reaction: (a) that the allergic response determines the type of leprosy, and (b) that the type of leprosy determines the allergic response. A permanent cure depends on the ability of macrophage cells to develop an environment which prevents re-multiplication after the number of bacilli has been sufficiently reduced by sulfone therapy.

HANKS, J. H. Immunological and physiological basis of immunization in tuberculosis and leprosy. Diseases like tuberculosis and leprosy are chiefly confined to persons in whom immunological response is slow and poor. Attempts at immunization should therefore be confined to identifying and immunizing the poor responders. The difficulty of the tuberculoid patient is not that he cannot make an immune response, but that he

achieves this response rather slowly. Had he been previously immunized he might not have had leprosy at all. The possibility of a mixed vaccine of BCG and dead *M. leprae* is mentioned. It is suggested hypothetically that when BCG is injected in a more resistant patient the bacilli may be more promptly destroyed; while in the more susceptible persons (requiring more antigen) the bacilli may not be destroyed so quickly and may thus produce more antigen.

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Among the papers and discussions on tuberculosis there are many points which may suggest lines of investigation in leprosy, according to the review from which the foregoing was taken [*Leprosy Review* 27 1956) 29-37], and the reader is referred to that review for the abstracts of the 21 papers on that subject that appear there. The following is the list of those papers.

- STACEY, M. The proteins of the tubercle bacillus.
 ASSELINEAU, J. and LEDERER, E. The structure and activity of fycolic acids.
 ROSE, F. L. and SNOW, G. A. Mycobacteria; a growth factor for acid-fast bacilli.
 STACEY, M. Polysaccharide components of the tubercle bacillus.
 UNGAR, J. Granuloma-producing properties of synthetic fatty acids.
 MILES, A. A. Early tissue reactions to tubercle bacilli and their products.
 HIRSH, J. G. Biochemical factors which may influence the fate of tubercle bacilli.
 BLOCH, H. Bacterial components concerned in the early phase of infection.
 BOYDEN, S. V. and SORKIN, E. Serological activity of various fractions of culture filtrates of the tubercle bacillus.
 ILAND, C. N. and PEACOCK, D. B. Serology of tubercle polysaccharides.
 RAFFEL, S., ASSELINEAU, J. and LEDERER, E. The chemical nature of the lipoidal factor of the tubercle bacillus responsible for the induction of tuberculous hypersensitivity.
 MEYER, R. L. Tubercle bacilli as immunological adjuvants.
 SUTER, E. Relation between growth inhibitory property of the monocytes for tubercle bacilli and hypersensitivity to tuberculin; an *in vitro* study.
 BROWNLEE, G. and MADIGAN, D. G. Tuberculous hypersensitivity and desensitization.
 BRIEGER, E. M. Tubercle bacilli in infective tissues grown on tissue culture.
 BLOCH, M. The role of bacterial multiplication in the establishment of immunity to tuberculosis.
 LURIE, M. B. and ZAPPARODI, P. The mode of action of cortisone on the pathogenesis of tuberculosis and its implications for the nature of genetic resistance to the disease.
 RAFFEL, S. The mechanism involved in acquired immunity to tuberculosis.
 CANETTI, G. Human lung tissue reactions to the tubercle bacillus in relation to chemotherapy.
 HART, P. D'ARCY and WEES, R. J. Influence of certain surface-active agents on the host-parasite relationship in experimental tuberculosis.
 MIDDLEBROOK, G. The relationship between the growth requirements and the pathogenicity of isoniazid-resistant mutants of tubercle bacilli; a study of the role of host physiology in susceptibility to infectious disease.

An Attempt to Control Leprosy by B.C.G. Vaccine in the Loyalty Islands. By Médecin-Capitaine des Troupes Coloniales LACOUR, directeur de l'Institut Pasteur de Nouméa, Nouvelle Calédonie. Sydney: South Pacific Commission, 15 pp. + 18 annexes; mimeographed.

In the introduction reference is made to French leprologists who have written in favor of trials of BCG as a possible prophylactic in leprosy, and also to a contrary opinion. The WHO Expert Committee took a cautious attitude, and recommended that studies on the matter should be undertaken. The Loyalty Islands was considered

a particularly suitable area for such a trial because of the stability and homogeneity of the population, and because there was already accurate knowledge of the situation and records of annual case-findings. The total population of the three islands—Maré, Lifou and Ouvea—was counted as 12,612. The 1953 census showed 358 leprosy cases (nearly 27 per thousand), and in October 1954—the year this work was done (March to December)—there were 319, of which 98 were considered contagious and were isolated while the remaining 221 were under supervision in the villages.

The procedure in the field work was to inject lepromin on the 1st day, read the results and make the tuberculin tests on the 21st day, and record the results of that test and if necessary make BCG vaccinations on the 25th day. The BCG vaccine, prepared from a freeze-dried stock from the Institut Pasteur in Paris, was applied in parallel skin scarifications on the forearm. In total, it was possible to apply the lepromin test to 8,985 persons and the tuberculin test to 9,101, of whom 3,412 were vaccinated with BCG. The persons seen constituted about 72% of the total inhabitants counted in the census, but around 90% of those actually present on the islands when they were visited; some were absent fishing and on other employment. The results of skin tests and other data are given in tabular form in some 16 annexes.

Inspection of the curves which show, for each district of each island (no totals for the islands individually or as a whole), the positive reactions to the two antigens reveals certain interesting features. Whereas the percentages of the lepromin positives usually reach into the 90's in the older age groups, those for tuberculin positives—much smaller in the younger groups, as is usual—attain practically the same height and in some instances are slightly higher. The report contains no discussion of findings, and so no explanation of the extremely high tuberculin rates is offered. The tuberculin used was an OT product from the Institut Pasteur in Paris, the dose only 1/40 cc. of 1/100 dilution (= 1/10 cc of 1/400).

Most peculiar results with the lepromin test are shown for 5 of the 7 districts of Maré, where the percentages of positives are extraordinarily low, ranging in the over-40 age groups between 27 and 53; in 2 of the districts they were higher, but only 74 and 83. This is in sharp contrast with the records for Lifou and Ouvea, where 7 of the 9 districts had lepromin maxima of 98-100%. (In 2 of the Maré districts even the tuberculin rates had low maxima, 43% and 52%.)

There are tables showing the correlation of the two reactions, by percentages, there being totals by islands as follows, but no over-all total.

| | Mitsuda positive | | Mitsuda negative | |
|-------|------------------|----------|------------------|----------|
| | Mantoux+ | Mantoux— | Mantoux+ | Mantoux— |
| Lifou | 58 | 17 | 4 | 21 |
| Ouvea | 68 | 17 | 3 | 11 |
| Maré | 19 | 6 | 24 | 50 |

Thus the Mitsuda positives totalled: on Lifou, 75%; on Ouvea, 85%; on Maré, only 25%. The tuberculin positives totalled: on Lifou, 62%; on Ouvea 71%; on Maré, only 43%—and a majority of them in cases recorded as Mitsuda negative. In view of these findings, BCG vaccination—intended for all tuberculin negatives—was applied: on Lifou, to 34.3% of the persons tested (1,673 of 4,853); on Ouvea, to 25.6% (418 of 1,637); while for Maré the figure was 50.5% (1,321 of 2,611).

As for the effects of the BCG vaccination on the skin reactions, nothing could be said. It had been intended to make retests after a proper interval, but that could not be done by the staff available. No conclusions are formulated. It is pointed out that none with respect to the value of the measure will be possible until after a long period of observation.—[In part from review in *Trop. Dis. Bull.* 53 (1956) 68, and *American J. Trop. Med. & Hyg.* 5 (1956) 578, details of data added.]

Second Report, 1955 Campaign. This further report, also by Lacour, also mimeographed but more informal (6 pp. + 7 sheets of tables), tells of the activities in 1955

in furtherance of the campaign started the year before. The number of currently registered leprosy cases was lowered from the previous 319 to 303, and the number in isolation was decreased from 98 to 74 largely because of release to their villages of patients who had fulfilled the then required two years of bacteriologic negativity (now reduced to one year). Only 6 new cases were found during the year, one-half the number found in each of the preceding two years, which in turn had a similar relation to those found in the two years before that (specifically: 1951, 30 (11 L); 1952, 24 (3 L); 1953, 12 (2 L); 1954, 13 (2 L); 1955, 6 (1 L). [In other words, the BCG campaign was started at a time of decreasing incidence, with lepromatous cases in relatively small proportion—about 15%, 1952-1955.]

Retests of the people who had been BCG vaccinated in 1954 because they were tuberculin negative gave the following results:

| | Vaccinated | Lepromin 1955 ^a | | Tuberculin 1955 | |
|-------|------------|----------------------------|----------------|-----------------|----------|
| | 1954 | No. | Positive | No. | Positive |
| Ouvea | 418 | 317 | 92.7 % | 296 | 92.5 % |
| Maré | 1,321 | 1,212 | 89.4 % | 1,242 | 84.7 % |
| Lifou | 1,672 | 1,374 | 57.7 % | 1,400 | 90.1 % |
| | 3,411 | 2,903 | — ^a | 2,938 | 88.7 % |

It is thus seen that the tuberculin positive rates are high for all the islands, with nothing peculiar—this time—about Maré. The lepromin positive rates are equally high except for Lifou, where about 75% of the tests were made with a 1/750 dilution of lepromin. As shown in the tabulation for 1954 in the preceding review, among the Mantoux negatives (who were therefore vaccinated) there were more Mitsuda negatives than positives. There is of course no way of telling whether the high rates of lepromin conversion (where actual lepromin was used) were due to the BCG vaccinations made a year before or were "spontaneous" changes due to "natural" influences.

The results in the group which in 1954 had been negative to both tests is regarded as "particularly significant," but the main thing about it is the very high proportions that became positive to both tests—except the lepromin test on Lifou. It is of some interest that 6.1% of this class on Ouvea, and 7.1% on Maré (41.8% on Lifou!) had become positive to tuberculin but had nevertheless remained negative to lepromin—or at least were found to be negative a year after the vaccination.

Tests were made of unstated numbers of persons missed in 1954 and of children born in the interim (898 tuberculin tests and 790 lepromin tests). Also, 453 persons were vaccinated or revaccinated with BCG. It is stated in the conclusions that 90-95% of persons resident in the Loyalty Islands had been examined and tested, and that 85-90% at present are positive to tuberculin and lepromin. —H. W. W.

^aOn Ouvea and Maré the same regular lepromin was used as in 1954; on Lifou about 75% of the tests were made with the antigene diluted to 1/750.