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Emanuel Suter writes on "Some Aspects of Intracelluar Parasitism of Pathogenic Microorganisms.'

In this important review Suter, of Massachusetts, states that, in his studies of phagocytosis, Metchnikoff over-estimates the destructive effect of the phagocytes on pathogens. While his interpretation applies to acute infections it does not to the chronic ones where an intracellular parasitism lasting for a long time, often for the lifespan of the host, is apt to take place. In 1916 Rouse and Jones showed that typhoid bacilli when once phagocytised escaped the influence of antisera and antibacterial agents to which they are susceptible when not within the cells. Such infections in which the infective agents are able to survive, and even to multiply within the cells as well as extracellulary, are termed facultative intracellular parasitisms. Typical examples are brucellosis and tuberculosis. The study of this host-parasite relationship is particularly important in leprosy owing to the almost purely intracellular habits of human and murine leprosy bacilli.

Suter reviews the work that has been done on the intracellular parasitism of the tubercle bacilli. He says that it was found that streptomycin was unable to destroy all the tubercle bacilli in the body owing to this intracellular parasitism, and immediately treatment ceased, the bacilli began to multiply again. However, in animals that have been vaccinated with B.C.G. the macrophages have somehow been rendered inhospitable to the bacilli, and the bacilli become extracellular and susceptible to streptomycin. The latter restricts extracellular multiplication while the acquired state of the phagocytes limits intracellular multiplication. Isoniazid seems to retain its full activity against intracellular bacilli, so that in combination with streptomycin the bacilli within and without the cells gradually lose their vitality.

In order to study the action of drugs on the intracellular forms of the tubercle bacillus, Suter was able to prepare slides of cultivated macrophages to which streptomycin had been added so as to destroy the extracellular forms. He found that the virulence of the bacilli depended on their ability to multiply intracellularly, and their capacity to destroy the host cells. In normal animals, they multiplied freely within the macrophages, but when macrophages from B.C.G. vaccinated animals were used, bacillary proliferation was completely suppressed. That this inhibitory power resides in the macrophages and not in the serum was shown by adding serum from vaccinated animals. It was seen to have

no effect. Macrophages are therefore in a key position in regard to acquired immunity to tuberculosis. The possible application of these facts to the understanding of the problem of infection and treatment of leprosy is stressed.

John H. Hanks writes on "The Implications of Suter's Review of Intracellular Parasitism with respect to the Problem of Leprosy." Commenting on the above paper, Hanks writes:—

"Suter's demonstration that mild degrees of extracellular inhibition suffice to convert a cultivable mycobacterium into an intracellular parasite is an observation of prime importance to our clearer understanding of the pathogenesis of leprosy." "In our present views a notable combination of metabolic limitations and of inhibitions of extracellular fluids are main factors which force the fastidious and non-cultivated species toward seclusion in intracellular environment."

Hanks refers to his own work in Culion before the war and which unfortunately had to be given up because of it. In 1947 he had described how actively growing fibrocytes from tuberculoid skin lesions caused rapid reduction of M. leprae to acid-fast debris, whereas fibrocytes from lepromatous lesions grew normally when containing much higher numbers of bacilli, and were unable to bring about their prompt destruction. Thus the behaviour of cells from the two kinds of cases, even after prolonged cultivation in vitro, reflects certain of the well-known differences between the two polar types of leprosy. Later, cultures of blood macrophages were found to be more destructive to leprosy bacilli than fibrocytes. "We must be grateful to Dr. Suter for having again drawn our attention to cellular mechanisms which inhibit the intracellular growth of mycobacteria, and to the existence of physiological states which encompass their destruction. It is to this type of action that the mycobacteria are ultimately vulnerable."

Ng. Ph. Buu-Hoi writes on "The Selection of Drugs for Chemotherapy research in Leprosy."

In this paper the writer suggests certain empirical rules for the choice of drugs for the treatment of leprosy. They must be tuberculostatic and fungistatic. They must be relatively non-toxic for long term use and must be cheap and easily manufactured. He suggests that lipid solubility may increase activity against the leprosy bacillus. He suggests certain drugs for clinical assay, particularly D.D.S.O. (diaminodiphenyl sulfoxide).

Linda Nahas and Hans Rzeppa and Lauro de Souza Lima write on "Blood Picture in Sulfone Treatment of Leprosy."

Four groups of five patients were given: (1) Diasone 0.66 gms. daily (=D.D.S. 0.333 gm.); (2) Diasone 0.90 gms. daily (=D.D.S. 0.555 gm.); (3) D.D.S. 0.2 gm. three times weekly, and (4) 0.4 gm. daily; and the haemologic changes studied. The results showed that blood concentrations of over 0.6 mgm.% induced a moderate progressive anaemia, but that concentrations under that amount produced no anaemia. Daily doses of 0.333 gm. D.D.S. and 0.555 gm. D.D.S. in the form of Dapsone gave the same blood level, and so the larger dose presented no advantage. All patients receiving 0.4 gm. of pure D.D.S. daily showed a blood concentration of about 1 mgm., and showed toxic reactions and anaemia, but those receiving 0.555 gm. of D.D.S. daily as Dapsone showed no toxic reactions or anaemia. The detection of anaemia by haemogloblin determinations is held to be a safe index of the optimal individual dose to be given.

H. Gass and M. Balasubrahmanyan write on "Changes in the Cutaneous Nerves in Leprosy."

The authors made a study of the cutaneous nerves in different types of leprosy and attempted to correlate the clinical observations with the histological findings. In estimating tactile sensation they found that hairs played an important part in the reception of tactile stimuli, and shaving the skin reduced sensitivity very markedly. After shaving they found that maculo-anaesthetic, tuberculoid and lepromatous lesions were all completely insensitve to light touch.

Sections 20-30 microns thick were made from 30 cases of leprosy and were fixed and stained by a silver impregnation method for nerve fibres and then counterstained. It was found that the damage to the nerves in different kinds of lesions was of the same kind, but of different degrees, and was influenced by the nature and age of the lesions. They found fusiform swellings and "bubbles" along the course of the axons, and twisting, flattening and fragmentation of axis cylingers which could be accounted for by Wallerian degeneration consequent to damage by pressure in the deeper nerve fibres.

Seitaro Okada writes on "Studies on Tuberculoid Visceral Leprosy. Tuberculoid Granuloma in the Liver revealed by puncture biopsy."

In order to determine whether tuberculoid granuloma occurred in the liver in cases of tuberculoid leprosy, the author examined specimens obtained by liver puncture from 5 patients. In one case several well defined tuberculoid granuloma were found, and in three of the others incomplete tuberculoid lesions were seen.

S. Miguel, A. Roldan, J. Guillen, J. Terencio and J. Ponciani write on "Plasma proteins in Leprosy." A translation of the authors' own summary is as follows:—

"In our study of the serum proteins of leprosy patients by electrophoresis, the examinations were indiscriminately made by the cell method (Kern apparatus) and the paper technique (Macheboeuf-Rebeyorette apparatus), ascertaining first in both instances the mean value in normal subjects for a point of reference. The findings in the patient were as follows: Total proteins were usually about normal in values, although they were increased in more cases than decreased. The albumin-globulin ratio was generally below unity. The globulin fractions were increased, especially the gamma fraction, there being a decrease of the alpha globulin in the cases where the gamma showed the most marked increase. These changes were most pronounced in the more advanced lepromatous patients, especially those with manifest visceral amyloidosis. In the phases of lepra reaction the disturbances of the globulins were pronounced, but they partly subsided when the lepra reaction disappeared.

"For the evaluation of the Weltman band reaction, the cadmium reaction, the Takata-Ara reaction, and the erythrocyte sedimentation, these tests were made at the same time that the electrophoresis studies were performed. The sedimentation rate was found to be the most sensitive, and to be more in accord with the albumin-globulin ratio and with the gamma globulin increase than the others. In second ranks are the cadmium and the Weltman band tests. We found the Weltman band abnormal (either dimininshed or prolonged) in 78 per cent of the patients, indicating especially the protein disturbances in lepra reactions, in which the band was constantly shortened. In toxic disturbances of the liver caused by the medication, the band was always prolonged, while the Takata-Ara reaction was positive in all cases."

J. Mauzé and G. Arnaud write on "Electrophoresis of Leprosy Serum." The authors' own summary is as follows:—

"The authors hold that electrophoresis, whether by the classical technique or by the paper method, is at present the best and most precise method of investigating sera. They have tested the sera of 100 patients, of various types and grades, most of whom have been under sulphone treatment. The paper method of Machebouef was used in this work.

"It was found that, whatever the clinical form of the case, the albumin fraction is diminished, while the γ globulin, the α globulin, and the β globulin are constantly increased. When the γ fraction reaches $K=2.0$, the patient is in a bad condition and reacts poorly to treatment. The nearer it is to 1.0, the more stable is the case and the more amenable to treatment. Increase of α_2 and β together or separately, to 1.8 or more signifies important intestinal parasitism or microfilaria.

"The authors believe that electrophoresis of the serum is an excellent means of determining the patients' response to treatment, that the γ fraction is the most interesting, and that the sulphones do not cure the disease."

R. D. Azulay writes on "The Protective Role of B.C.G. in Murine Leprosy."

Fifty-seven rats were inoculated with B.C.G. subcutaneously or peritoneally and 115 days later inoculated with M. leprae murium and compared with 20 controls. Clinically the unvaccinated animals showed earlier and larger lesions, and although bacteriologiclly there were no alterations in the bacilli either in shape or in staining, the percentage of positivity in the visceral organs was higher in the unvaccinated than in the vaccinated animals. The writer considers that B.C.G. has a definitely protective effect against leprosy infection in rats, and that this experiment will serve to strengthen the view that B.C.G. may be useful in the prevention of leprosy.

In an editorial in this issue Wade discusses the above papers of Suter and of Hanks, and suggests that macrophage cultures from patients with different forms of leprosy, and patients vaccinated with B.C.G. should be studied, particularly in the matter of their reaction to M. leprae obtained from lepromas.

In this issue is printed Part I of a translation into English by G. L. Fite, of Virchow's chapter on Leprosy from his book Die Frankhaften Geschwülste 1864, said not to have been previously translated into English. This writing of Virchow, of an era before the leprosy bacillus had been discovered, is of considerable interest.

G. O. TEICHMANN.