The Pathogenesis of Tuberculosis

Research on the pathogenesis of tuberculosis is being undertaken at the Institute of Orthopaedics, as this is not only a major orthopaedic infection but biopsy material may be obtained earlier and more frequently than in chest hospitals. The first task has been to determine the morphological variability of the organism. Koch described spores, and several bacteriologists have worked out complex life cycles (Kahn, 1929; Grigoraki, 1950). This perennial question has become pertinent in view of the recent discovery of the 'L cycle' of some other genera (Klineberger-Nobel, 1951), and phase contrast microscopy provides us with the means of making continuous observations on living cultures under variable conditions. During the past two years, using a hot box and phase contrast (Lack, 1952), the tubercle bacillus has been cultured and observed in over a hundred experiments covering a wide range of media. No true 'life cycle' has been observed but it has been noted that starvation and antibiotics such as streptomycin, penicillin, P.A.S., and isoniazid lead to a progressive diminution of size until the cells are coccal rather than bacillary. These coccal forms are often still viable and may grow back to bacillary forms when nutrition is restored (Lack and Tanner, 1953).

This reduction in size is more than quantitative; there are qualitative differences which affect the pathogenicity of these organisms. Virulent bacillary forms grow in cords (Middlebrook et al., 1947); they appeared to be stuck together by a substance, the cord factor, which Bloch has identified as a lipid and shown to be a factor of virulence (Bloch, 1950). These starved coccal forms appear to have lost their cord factor.

A second important fraction of the tubercle bacillus, the tuberculoprotein, appears to be responsible for the hypersensitivity that plays such an important part in this disease. Seibert and Morley (1933) have shown that the tuberculoprotein of bacilli of low virulence has the same potency as that of bacilli of high virulence. On the other hand, the quantity of tuberculoprotein released by the coccal forms is less than that produced by the bacillary form, as one would expect from the reduction in the amount of cytoplasm. Injection of the coccal form into sensitized guinea-pigs does not produce the tuberculin reaction that the bacillary form will do (Lack and Tanner, 1953).

Infection by the tubercle bacillus is an unstable host-parasite relationship. Most other gram positive pathogens are predatory in that they produce extra-cellular enzymes which break down substrates in the host tissues and their pathogenicity depends very largely upon a successful attack on the tissues of the host. The tubercle bacillus, on the other hand, does not appear to produce any exotoxins and the damage which it may cause to the host is brought about indirectly. If it is non-pathogenic for a given host, it is either unable to multiply at all within the host cells though it may survive for a time or it may be a symbiont within the host monocytes. Virulent strains, on the other hand, appear to multiply so excessively within the monocytes that they burst them. This appears to be an important difference between strains that are and are not able to cause disease within the host. Monocytes that have ingested bacilli tend to cluster together. They also change to epithelioid cells and giant cells; such clusters are soon surrounded by a zone of lymphocytes and later this may be encircled by fibroblasts. This, of course, forms the histological tubercle.

Recent experiments by Favour (1951) have shown that lymphocytes from tuberculous hosts release an antibody which will bring about the cytolysis of cells that have bound tuberculoprotein, and that one difference between animals that do and do not develop hypersensitivity lies in the capacity of cells other than lymphocytes to bind tuberculoprotein and so be affected by this antibody. It may be that the caseation that frequently occurs within the centre of a tubercle is due to this mechanism.

Caseation may be regarded as a defence mechani-
ism as bacilli that are still viable are embedded in this area of coagulative necrosis. It is usual to find a progressive diminution in size of these bacilli as one moves from the periphery towards the centre of this cheesy material; much of the acid-fast material that is found is debris, but within the depths one may come across clusters of 'coccal' or diphtheroid forms that are very similar to those which may be produced by growing tubercle bacilli for long periods in inadequate media, and they may be revived by digesting the caseous material and inoculating the digest into guinea pigs. M. tuberculosis may remain viable for long periods in caseous material, though its calcification is probably their final burial. Before this occurs, however, the caseous material may liquefy and when this happens, bacilli dormant within the caseous may now proliferate and disseminate, greatly worsening the prognosis for the patient.

Relatively little research has been done on the factors responsible for the softening of caseous although this appears to be the central problem in adult tuberculosis. It seems likely that the softening is brought about through the activation of a host protease rather than through the activity of the contained bacilli. One enzyme that is capable of digesting solid caseous in vitro is plasmin. Some caseous material removed from a tuberculous spine was kept in nutrient broth at room temperature for one year. It had the consistency of processed cheese. Numerous smears showed that the organisms within it were very small and no bacillary forms could be found. This cheesy material was digested with plasmin and injected into a guinea-pig which developed tuberculosi within six weeks (Figs. 1, 2 and 3). Plasmin is present in body fluids as a pro-enzyme plasminogen which may be activated by tissue damage and by some types of infection. The ways in which plasminogen may be activated, and the part that may be played by this system in inflammation, has recently been discussed by Ungar (1952). Such a mechanism would explain a great deal about the activation of quiescent tuberculous foci by trauma and by secondary infection, though it must be emphasized that this is only a working hypothesis.

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