RELATIONSHIP OF LEPROSY TO TUBERCULOSIS*

E. MUIR, M.D., F.R.C.S. (EDIN.)

In recent years two important conferences on tuberculosis have been held in London, in which the subject of leprosy was included in the programme. One of these was the Ciba Foundation symposium on *Experimental Tuberculosis, Bacillus and Host* in October, 1954, and the other was the *Fourth Commonwealth Health and Tuberculosis Conference* in June, 1955. Although in these conferences leprosy naturally occupied a very minor place, yet the fact that leprosy should receive this attention in a country where it is not an endemic disease is significant of the broader outlook on mycobacterial diseases.

There are many aspects from which we can view the relationship between leprosy and tuberculosis, so many in fact that it is possible in this paper only to review them discursively, drawing attention to the resemblances and divergencies of the two diseases, and the ways in which the study of the one has thrown light upon the study of the other.

In modern times leprosy has been looked upon as a tropical disease, but it is not so in any true sense. Till recently it was endemic in such cold climates as those of Iceland and Norway, and up to 3 or 4 centuries ago it was common in England and other countries of Western Europe. The sanitary, social and economic conditions which encourage the spread of leprosy have in recent years been ameliorated in Western Europe, but not to the same extent in many tropical and subtropical countries.

Sanitary, Social and Economic Advance

There are certain diseases which appear to belong to various stages in sanitary, social and economic development. Among these are notably yaws, leprosy, tuberculosis and possibly cancer, which, although they overlap each other, appear, reach their peak and again diminish in that order. Speaking generally, yaws is a disease of tribal life, common in primitive and more or less isolated communities. As communications improve, but sanitation lags behind, yaws diminishes and leprosy, a disease of villages, takes its place. As tuberculosis penetrates the community leprosy tends to die out; and again, as tuberculosis comes under control, cancer takes its place as the chief public health problem.

The replacement of yaws by leprosy is dependent (apart from the effects of modern treatment) chiefly on social and economic

* Paper presented at the conference on Tuberculosis and Leprosy, Dar-es-Salaam, Tanganyika Territory, January, 1957.

causes. The disappearance of leprosy as tuberculosis advances, though governed partly by social and economic causes and by improved sanitation, may also have immunological implications; but these will be discussed later. The apparent replacement of tuberculosis by cancer may depend on the rising age level of the community, and possibly on other factors such as the mechanisation connected with modern life.

Bacteriological Relationship

The causal organisms of both leprosy and tuberculosis belong to the genus of mycobacteria. Hansen in 1874 first described rod-like bodies in leprous nodules; but lacking suitable stains his descriptions were defective. Later, about 1879, the new staining methods of Weigert and Koch, with advice on their use by Koch, made it possible for Hansen (and about the same time Neisser) to confirm this discovery and describe *M. leprae* more in detail. *Myco. tuberculosis* was discovered by Koch some three years later, in 1882. Thus these two organisms were closely connected from their first appearance.

The whole range of mycobacteria has been likened by Hanks to a continuous spectrum, beginning at the lower end with saprophytes and ascending through commensals and intermediate forms to those which, like *Myco. tuberculosis*, are pathogenic and are yet cultivable *in vitro* and have a variety of animal hosts. Next in order comes Johne's organism which has certain particular *in vitro* growth requirements, and whose hosts are restricted to cattle and sheep. Then there is *Myco. lepraemurium* whose known hosts are restricted to rats mice and hamsters, and which is not yet cultivable *in vitro*. Lastly, at the top of the spectrum is *Myco. leprae*, also not cultivated *in vitro*, and confined to one host—man. In this series the increasing restrictions in living hosts and *in vitro* culture are connected with retirement from the open tissues of the host into intracellular life. Hanks points out that the tendency towards intracellular retirement is characterised by limited ability to gain energy from substrates *in vitro* and by susceptibility to tissue derivatives and serum. Survival in cells is associated with low oxygen requirements. Is there any connection between this and the freedom of the lungs from leprosy?

Hanks also points out that another difference between saprophytic and pathogenic mycobacteria lies in certain lipids contained by the latter, which act on the leucocytes to prevent their migration. Virulent strains of *M. tuberculosis* give off the " cord factor " (mycolanoic acid) which causes a type of local inflam-

mation, prevents phagocytosis and produces a medium where the mycobacteria can multiply.

In leprosy the relation of the infective organism to the phagocytic cell is somewhat different. When *M. leprae* are ingested by macrophages, one out of three things occurs, depending on the degree of resistance of the host: (a) if resistance is strong epithelioid cells are actively formed from the phagocytes and the bacilli are destroyed; (b) if resistance is weak the bacilli multiply in the cytoplasm, forming the large typical lepra cell, which later, as bacilli die and decompose, becomes the foamy cell often associated with the name of Virchow; (c) there seems to be evidence that between these two extremes, in both of which the phagocyte is immobilised, there may be a third possibility in which the cell after ingesting bacilli still remains mobile, at least temporarily, and may convey the bacilli through the tissues. It may be supposed that in the second of these occurrences (lepra cell type) there is some substance contained in and given off by the bacilli which paralyses the cell and makes it take up a passive role: whereas in the first occurrence (epithelioid cell type) either this substance is absent or is countered by the cell, which is thus able to destroy the bacillus.

Besides its intracellular breeding place, *M. leprae* has another place of refuge to which it invariably seeks to resort, namely the peripheral nervous system. In this respect it differs from all other known bacteria. It enters the fine cutaneous twigs and spreads upwards into larger branches and thence into the mixed nerves. Thus the cellular multiplication, which the presence of the bacilli calls forth, exerts pressure on both sensory and motor nerve fibres, resulting in their temporary blocking or permanent destruction.

There is evidence by the use of special methods of staining that *M. leprae* can enter the axons: whether or not it can travel up the nerves inside the axons there is no direct evidence, and it would seem more likely that upward progress is made through the lympth spaces along side of, but outside, the axons.

One of the contrasts between the tuberculosis group and the leprosy group of mycobacteria is found in the restrictions of experimental transmission in the latter group. Transference of rat leprosy infection is restricted to rats, mice and hamsters; with human leprosy animal inoculation has failed, and even the few recorded attempts at transmission to human volunteers have given negative or doubtful results. Unsuccessful attempts have been made in monkeys, rats, guineapigs, rabbits, hamsters and other animals. Expense and other difficulties have prevented attempts

in anthropoid apes. Recently Feldman has suggested that it may be possible to reproduce the disease by injecting the inoculum intradermally instead of subcutaneously, by lowering the resistance of the experimental host by suppressing its endocrines, or by injecting various substances which will enhance the virulence of *M. leprae*. It would appear, however, that the possible host must be fairly long-lived, as in man leprosy may take many years to develop.

Myco leprae also contrasts with *Myco tuberculosis* in our failure to cultivate the former *in vitro*. Repeated claims of successful cultures of *M. leprae* have been made in the last 50 years, but none of them has been substantiated. More recently, in place of the frontal attack on this problem, a flank assault has been launched by studying *Myco lepraemurium*, which has the advantage that any doubtful cultures can be tested in cheap and easily handled experimental animals. Hanks and others are studying the viability of these mycobacteria in various environments by means of respiration and hydrogen-transfer tests. The burning of hydrogen is a requirement of life, and therefore can be used as an indication of changes in metabolism.

Immunology

When we study the question of resistance in leprosy and tuberculosis the problems are no less difficult to solve. Yet this is the field in which possibly the two diseases impinge most closely. Calmette, who had lived in Belle-Isle in the west of Brittany, is reported as saying in 1905 that up to 50 years previous to that year leprosy had been common in Brittany. As long as leprosy remained, pulmonary tuberculosis was unknown: but after leprosy disappeared pulmonary tuberculosis ravaged the country, chiefly affecting the parts formerly occupied by leprosy. The registers of Belle-Isle bore out this assertion. Perhaps it would be better to say, not that with the passing of leprosy tuberculosis came, but that with the coming of tuberculosis leprosy departed.

There is much evidence to suggest that cross-immunity between tuberculosis and leprosy is, at least in part, responsible for the disappearance of leprosy as an endemic disease from England and other countries of Western Europe about 300 years ago, at a time when sanitation was still very bad. Also segregation laws at that time, though locally in existence, were not effectively applied and could not account for the more or less sudden vanishing. Leprosy lingered on longest in distant corners like Cornwall,

Shetland and Orkney in the British Isles, and the fiords of Norway, places where tuberculosis was slow in penetrating.

There is no test in leprosy, corresponding to the tuberculin test in tuberculosis, to give an indication of past contact with infection. The lepromin test (made by intradermal injection of a sterilised suspension of triturated leproma) gives positive results in the resistant forms of leprosy, but also in a considerable number of those who have had no contact with leprosy. The lepromin reaction is specific only when it is negative, which almost always occurs in the severe lepromatous type. Its chief use is in prognosis, which tends to be favourable when the reaction is positive, as it is almost invariably in the tuberculoid type. Further evidence of the relationship of leprosy with tuberculosis is shown by the fact that vaccination (whether oral or intradermal) with BCG converts a negative into a positive lepromin reaction in a large majority of cases. The important question at issue is whether a positive lepromin reaction induced in this way has the same significance as a positive reaction found ordinarily in the tuberculoid type of leprosy. We have no adequate proof yet that this is so, and proof that BCG vaccination raises resistance to leprosy can be arrived at only by long-term controlled trials, extending over a period of years. It is important that where BCG is being used for immunisation to tuberculosis in areas where leprosy also is endemic, arrangements should be made for combined controlled trials to ascertain the effect of BCG in raising resistance to leprosy.

The question has been raised as to whether infection with leprosy causes cross-sensitivity to tuberculosis. Edwards and Palmer suggest that in certain countries (India, Egypt, etc.) there is a non-specific factor which causes a low-grade sensitivity to tuberculin. Lowe and Mcfadzean found similar evidence in Nigeria. The Chronicle of WHO also, during a campaign of BCG vaccination in East and in West Pakistan, found a striking divergence of tuberculin results in these two areas. In West Pakistan there were doubtful reactions in only 4 per cent of the total: while in East Pakistan they were much more frequent (about 40 per cent). In fact in the latter area the presence of non-specific sensitivity would seem to limit considerably the use of the tuberculin test. As leprosy is much more frequent in East than West Pakistan the question might be raised as to whether this non-specific agent may not be leprosy, at least in part, though another possibility might be the presence of non-pathogenic mycobacteria in the body.

Clinical and Pathological Contrasts

One of the most striking contrasts between tuberculosis and leprosy lies in the difference between the organs and tissues which each attacks. The lung, which is the most important organ affected by tuberculosis, is entirely exempt in leprosy, even though the latter attacks the whole of the rest of the respiratory tract as far down as the large bronchi. Conversely, tuberculosis leaves the upper respiratory passage alone except for infection of the larynx caused by constant coughing up of bacillus-laden sputum. Unlike tuberculosis, leprosy does not affect directly the gastro-intestinal system and the kidneys, though these are indirectly affected by waxy degeneration as a result of prolonged and massive infection and septic complications. The testis is the only internal organ to be attacked and destroyed, and this is possibly connected with gynecomastia, a not uncommon complication in leprosy. The liver may be the site of a gross infection, but this seldom causes any proportional, or indeed any serious, interference with function, except when there is secondary amyloid degeneration.

The skin is the organ in which tuberculosis and leprosy have most in common. While with few exceptions all forms of leprosy affect the skin, it is the tuberculoid type which most closely resembles cutaneous tuberculosis, both clinically and histologically. In both of these, and also in Boeck's sarcoid, there is the tubercle formation of epithelioid cells often accompanied by giant cells. In all of these three conditions the process may go on to caseation, though in tuberculosis this is commoner in the lymph nodes, and in leprosy it is commoner in the larger affected nerves.

A remarkable feature of leprosy in the skin is the absence of scar formation after healing takes place. There is seldom the loss of tissue and deep scarring so often occurring in tuberculosis. In spite of the whole thickness of the skin having been affected, there remains in a healed lepromatous lesion only the wrinkled " crushed tissue-paper " appearance without any tightness. This is due to the kind of tissue which replaces the granuloma, and its nature is worthy of careful study.

Clinically and histologically the chief feature which distinguishes tuberculoid leprosy and tuberculosis of the skin is that in the former the cutaneous nerves are affected, as may be seen in biopsy sections and, clinically, by testing the tactile and other forms of sensation. Some forms of tuberculous cutaneous lesion (as also sarcoid) resemble lepromatous leprosy in which loss of sensation may be slight or nil; but these can easily be distinguished from leprosy by the absence of acid-fast bacilli.

The eyes are affected in both lepromatous leprosy and tuberculosis. In both there is interstitial keratitis; but while tuberculous keratitis causes loss of tissue and ulceration, lepromatous leprosy, spreading from the sclera over the upper limbus, causes a diffuse corneal opacity or nodulation. Ulceration of the cornea occurs chiefly in tuberculoid leprosy due to want of protection following lagophthalmia and paresis of the muscles of the eyelids. In both diseases there is irido-cyclitis, but invasion of the choroid, commoner in tuberculosis, seldom occurs in leprosy.

Invasion of the bones, especially the cancellous tissue, is common to both diseases. In lepromatous cases during lepra reaction this results in extreme pain in the ends of the larger long bones, but it is as a rule only in the smaller bones of the fingers and toes that destruction takes place, and that is generally secondary to neural destruction rather than to invasion of the bones themselves.

Nowhere is the contrast between leprosy and tuberculosis more striking than in the nervous system. As in the respiratory system, the two diseases seem to have divided the territory between them, allotting the central portion of the nervous system to tuberculosis, and the peripheral to leprosy. Apart from its resistance to culture outside the human body, the most characteristic feature of *Myco. leprae* is its affinity for the peripheral nerves, and it is possibly this neurophilic faculty which preserves it from extinction. This is illustrated in the typical ring-shaped tuberculoid lesion in the skin. The infection seeks to invade the surrounding skin, spreading from the initial focus radially through the neuro-vascular plexus. It is, however, resisted by macrophages (epithelioid cell formation) which its presence has called into action. The site of this resistance is indicated clinically by the raised, expanding, ring-shaped margin; and the success or otherwise of the resistance is determined by whether or not this expanding margin is halted or continues to widen. But the infection has a second line of advance, by entering the cutaneous nerves and spreading up them to the larger branches and mixed nerves. Similar resistance takes place in the nerves to that in the skin, which is shown clinically by the thickening and tenderness of the affected nerves. Both in skin and nerve the epithelioid tubercle formation is the same, but the process more frequently goes on to caseation and abscess formation in the nerve than in the skin. The analogous lesion in tuberculosis is the chronic brain abscess.

In the lepromatous form of leprosy also the nerves are

invaded, and to a much more massive extent than in the tuberculoid, as there is infinitely less resistance and tissue reaction. Consequently thickening and tenderness of nerves are absent or much less. If tubercular meningitis be taken as the counterpart of lepromatous nerve invasion, the mildness of *Myco. leprae* compared to *Myco. tuberculosis* is well brought out. It is only during lepra reaction that a similar acute condition is found.

To sum up, there are two outstanding differences between the natures of leprosy and tuberculosis. In tuberculosis the type of disease depends partly on the strain of bacillus, and partly on the resistance of the host. In leprosy there is no indication of differing strains, and the two main types depend entirely on the resistance of the patient. The other main difference between the two diseases lies in the nature of the reaction of the bacillus to the phagocytic cell. In tuberculosis the typical virulent bacillus makes a frontal attack, paralysing the cell and forming an extracellular medium in which the bacillus can multiply. In leprosy, in its typical lepromatous form, the bacillus lets itself be ingested by the cell and then from inside, like the malarial plasmodium in the erythrocyte, settles down and multiplies. Thus the acute tubercular lesion is typified by tissue destruction, the severe leprosy lesion by granuloma, either diffuse or nodular.

Therapeutics

It was experimental work on tuberculosis that first pointed the way to the trial of sulphones in leprosy. The result of these trials has transformed the prognosis of leprosy, and in addition to the benefit to the individual patient there is reason to believe that the wise use of sulphones may do much towards bringing leprosy under final control. Still the sulphones, though a great advance on previous treatment, have certain drawbacks in the form of toxicity, causation of lepra reaction (erythema nodosum) and particularly the long period required to remove infection. In seeking for still better therapeutic agencies, it is to clinical and experimental tuberculosis, as well as to experimental work on other mycobacteria such as *Myco lepramurium*, that leprosy workers turn for further pointers. More than pointers there cannot be, as is seen from such variances as the following: sulphones are useful in experimental tuberculosis and leprosy, but not in clinical tuberculosis or rat leprosy; INH is valuable in clinical tuberculosis and rat leprosy, but of little or no value in human leprosy.

of drug resistance.

Efforts are in hand to discover a less toxic drug, with more rapid action, especially in clearing up infection and rendering the patient noninfective.

Epidemiology and Control

If, as has been suggested by some writers, the tuberculization of a community, either by natural spread of infection or by the use of BCG or similar forms of vaccination, raises resistance to leprosy sufficiently, then it might be possible to tip the balance of the struggle between *M. leprae* and the community so that a continuous process of diminishing infection is set up.

At many centres, especially throughout the tropics and subtropics, investigations are on foot to estimate the effect of BCG vaccination on resistance to leprosy, and to study evidence of cross sensitisation between *M. leprae* and *M. tuberculosis*. There is urgent need to collect, correlate and study reports of what has already been done along these lines, and to plan on a wide international basis the steps that should be taken in further investigations.

Meanwhile, efforts at control of leprosy by providing widespread facilities for treatment should be pressed forward, due arrangements being made for training of personnel, and providing for adequate supervision. Formerly, chief stress was laid on isolation of the patient with leprosy much more rigorously than the patient with tuberculosis. Now with clearer knowledge and better tools, while not neglecting to isolate the patient as much as practicable, the chief stress should be laid on early diagnosis and on early and adequate treatment.