Modern trends in leprosy

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Summary

Leprosy is being regarded more and more as a general medical condition. The available data about its manifestations and treatment are becoming more widely known.

The problems of infectivity, animal inoculation and cultivation remain to a large extent unsolved. The recent successful inoculation of irradiated mice with fresh organisms is a major advance. It may well prove a means of testing new drugs and of confirming claims of successful cultivation, and more important still, of determining the viability of organisms obtained from both active and treated cases of leprosy.

Finally, it is in the field of delayed hypersensitivity (CMI) and autoimmune processes initiated by the mycobacterial infections that this slowly progressive, greatly variable and widely disseminated infection may become a most rewarding subject for study by the immunologist of the future.

Introduction

Leprosy remains to-day a disease surrounded with vague theories, and many unproven but generally accepted hypotheses. Now a few firmly-established experimental findings are emerging, and these together with the introduction of effective, if empirical, anti-leprosy drugs have revived a general scientific interest in the unsolved problems associated with leprosy in all its forms. This attitude towards leprosy has stimulated more general physicians, neurologists, dermatologists and orthopaedic surgeons to consider leprosy as a disease which they may see, diagnose and treat, rather than a condition which could only be dealt with by segregation, and found mainly amongst the under-privileged peoples of tropical countries.

Historically leprosy is claimed as a disease of great antiquity. Yet few of the early accounts give clear-cut clinical descriptions of the disease as we know leprosy today. The most convincing early description of leprosy comes from the work *The Complete Secret Remedies* by Hua T'o around A.D. 200 in China (Skinsnes, 1962). He describes changes in cutaneous sensitivity, in the appearance of the skin, in the sound of the voice, the deformity of the limbs and the changes in the bones of the face.

Araetus and Galen writing around A.D. 200 describe clinical conditions in Europe which are similar in appearance to cases of advanced leprosy as we know it.

The recent discovery by Møller-Christensen (1961) of changes in the bones of the skull, the anterior nasal spine and the central part of the alveolar process of the maxilla in those who have died from leprosy has allowed him to deduce the existence of leprosy in northern Europe around A.D. 500.

The question of the incidence of leprosy in England and France in the Middle Ages is difficult to resolve. Among the inmates of the 2300 lazaret houses of France and England in A.D. 1300 some cases of leprosy as we know it may well have existed. Between A.D. 1300 and A.D. 1800 the incidence of leprosy is generally accepted as having fallen over most of western Europe. This reduction in the incidence of leprosy is associated by many workers in this field with a rise in the incidence of tuberculosis during the same period.

MacCormac (1842) stated that in 1798 75% of the deaths in one London doctor's practice were due to tuberculosis. Yet tuberculosis was not unknown in Scandinavia and in 1855 3000 cases of leprosy were found to exist in Norway. To-day tuberculosis is a fairly prevalent disease in Portugal and the number of leprosy cases in that country is estimated as between 2000 and 3000.

The national effort in Norway during the middle of the Nineteenth Century led to the adoption of a policy of segregation and the setting up of the great settlement at Bergen. The Norwegian campaign to conquer leprosy, and to support a nation-wide programme of clinical and pathological study of the disease led to the first full detailed description of leprosy in western literature by Danielssen & Boeck (1848), and the detailed study of the pathological changes in the skin and peripheral nerves by Virchow (1864) 10 years before the publication of the discovery of the *Mycobacterium leprae* by Hansen (1874). Hansen, like Virchow, owed the opportunity of obtaining pathological material to Danielssen from the cases in the Bergen settlement; and for the next 50 years most of the established European pathologists, dermatologists and neurologists visited the Bergen settlement in order to study leprosy.

As time went on the number of new cases in Norway and in northern Europe gradually decreased (the present number of patients in Bergen is two), and world interest in leprosy, stimulated by the dramatic story of the life and death of Father Damien, moved to the Far East; and to India and Africa as a result of the activities of the various missionary societies.

Each mission set up its own segregation settlement for leprosy patients, and as time went on it was not to Bergen but to Africa or India that those interested in leprosy went to study the disease. Anyone who has seen the numbers of leprosy patients in these countries, and the need for treatment, cannot but understand how the emphasis has shifted from pathological and bacteriological investigations to the hard routine clinical examination and palliative treatment of an ever-increasing number of patients seeking help at mission stations day by day.

Rogers' introduction (1916) of chaulmoogra oil in India, and later the enthusiastic claims of a leprosy cure, led many who did not understand the magnitude of the problem to undertake schemes to eradicate leprosy in various parts of the world. Unfortunately treatment with chaulmoogra is long and painful, and the results at best unpredictable. I have seen cases of leprosy treated by chaulmoogra oil injection and inunction in Nigeria now clinically normal and working in factories and shops in Kaduna in northern Nigeria. I have also seen old and chronic cases of leprosy in segregation settlements who have had years of chaulmoogra treatment without any lasting benefit. So in the main the 1920s and 1930s were years of disillusionment and despair. Leprosy continued unabated in most territories while the missionary societies and governments struggled to obtain effective segregation. It was not until the introduction of the new anti-leprosy drugs such as dapsone in the early 1950s that some hope returned and the future of the whole leprosy problem was altered.

Present-day distribution of leprosy

The incidence of leprosy in the world population was estimated by the World Health Organization (1960) as being between 10 and 12 millions. The majority of cases were to be found within the tropics. At this time there was no evidence that the incidence of the disease had altered in any way in spite of the wide-spread introduction of the new anti-leprosy drugs during the previous 10 years.

To-day in the United Kingdom no official figures are published, but it is usually stated that there are about 500 cases of leprosy at present under treatment. All have at some time or another been in territories where the disease is known to be endemic.

In northern Nigeria before the introduction of out-patient treatment centres in the villages, surveys revealed an incidence of leprosy ranging between 40 and 60 per 1000 of the population (Ross, 1956). In his study of the leprosy population in Australia, Humphry (1952) found an incidence of 61 per 1000 among the aborigines of so-called 'pure' descent.

In America both north and south, leprosy is still a problem. The disease is a serious matter in South America and is prevalent in the southern and western states of the U.S.A.

In the island of Nauru with a population of 1200 no leprosy existed in 1920. In 1924 two possible sources of infection were introduced into the island. In 1952 a survey of the population showed that 350 per 1000 of the islanders were suffering from leprosy (Wade & Ledowsky, 1952). A more recent survey in 1966 shows that the incidence has fallen to 213 per 1000 of the population. It is thought that few, if any, islanders migrate from Nauru and the population is considered a static one.

So the disease is prevalent in the tropics, and is variable in its distribution depending upon sources of infection and susceptibility of the populations. The findings in Norway show that the Aryan races are not immune to leprosy. The absence of any local contact cases in western Europe up to the present time suggests that the population as a whole is not as susceptible to this disease as once was thought. The incubation period can be so long (10 years) that the suggestion that no new cases will occur in this country because no new cases have been reported up to the present time cannot be supported by anything stronger than wishful thinking. Since we have so little knowledge as to the portal of entry of the *Mycobacterium* and of the method by which it spreads in the body, how can we declare what the future holds for this disease in western Europe when large numbers of immigrants, from tropical countries where leprosy is endemic, enter this part of the world every year? Yet the present trend is to treat the majority of leprosy patients in this country as out-patients and, in the absence of complications, allow these treated patients to lead as normal lives as possible.

Clinical forms and nomenclature

This is the aspect of any imperfectly-understood clinical or pathological condition which arouses the most resentment and the most passionate partisanship.

It is now realized that much of the controversy of the past stems from the clinical variations in leprosy that occur from country to country and from one racial group to another. The study of leprosy in all its forms is now accepted as best carried out in one territory where the disease is endemic rather than to

attempt to describe all the changes that can take place in leprosy patients throughout the whole world.

It is necessary for any clinician or medical scientist, however, to have some knowledge of the possible progress of this disease if he hopes to make any contribution to the many unsolved problems related to leprosy. Briefly, then, leprosy may begin as a single patch of skin of altered pigmentation in a child and progress, usually with remissions, to multiple patches of altered pigmentation with or without gross deformity of the hands and feet, and extensive peripheral nerve involvement. Finally the skin, peripheral nerves and the whole of the reticulo-endothelial system become invaded, and macrophages and Schwann cells around nerve fibres are loaded with large numbers of *Mycobacteria*.

These three types of leprosy are found in Muslim countries and are described in the Hadith written at the time of the Prophet Mahommed. The Arabic term, Baras, is still used to-day for the single initial skin lesion seen in the child which would now be described as indeterminate leprosy if the skin lesion did not show any marked alteration in sensation, or tuberculoid leprosy if cutaneous sensation in the lesion is lost and the disease well localized. The Arabic term, Bahook, is used for the second stage when there are multiple skin lesions, and this is usually seen in older children and young adults and frequently involves the peripheral nervous system. This is described by western leprologists as borderline or dimorphous leprosy (Cochrane & Khanolkar, 1958). Finally the state of invasion of the skin of the whole body, involving in extreme forms the production of dermal nodules on the face and ears, is termed in Arabic Judzam, or by modern leprologists, lepromatous leprosy (Fig. 1).

In the Hadith the possible progression from Baras to Bahook and from Bahook to Judzam is clearly described as is the possibility of spontaneous remissions at the first two stages (Jamison, 1959).

Today the progression of the indeterminate case to a borderline state is the usual clinical finding, while the majority of lepromatous cases have not developed straight away into this extreme form of the disease, but have passed through a borderline phase. This over-simplified description of the clinical types of leprosy forms a starting point for the consideration of the recent work of Ridley & Jopling (1967). These workers have classified all the cases admitted to the leprosy hospital at Redhill between 1953 and 1967 upon the basis of their natural immunity, and have attempted to assess the level of this natural immunity by examination of the patient, of skin biopsies and skin smears for the presence of *Mycobacteria*, and the patient's response to the lepromin test. The variations in appearance of the initial

Fig. 1. Lepromatous leprosy.

indeterminate skin lesion and the associated changes in the peripheral nerves found in children where leprosy is endemic are not found in any large numbers in the immigrant leprosy population as seen in the last 10 years in the United Kingdom and so they are omitted from this study. More particularly, attention is paid to the evaluation of the significance of clinical and pathological findings in established cases in order to decide on the type of treatment and assess the eventual outcome of the disease.

Ridley & Jopling find that the greater the degree of delayed hypersensitivity as shown by the response to the lepromin test the more localized the disease clinically. Biopsy shows marked infiltration of the dermis of the skin with epithelioid cells, giant cells and lymphocytes, while the cutaneous nerve fibres are absent, as are also *Mycobacteria*, from this characteristic dermal infiltrate.

A similar absence of *Mycobacteria* and nerve fibres and the presence of epithelioid cells, giant cells and lymphocytes is found in the remnants of the cutaneous nerve bundle running from the tuberculoid lesion. Such leprosy cases usually respond well to small regular doses of dapsone, and the pathological

changes are confined to the affected skin and nerves. After 4 or 5 years, in my experience, the impairment of cutaneous sensation is greatly reduced and the alteration of pigmentation of the cutaneous lesion is to some extent restored to normal.

The differential diagnosis between tuberculoid leprosy and lupus vulgaris may, on clinical grounds, be difficult; and in the absence of silver-staining techniques sections of skin biopsies may also give no clear distinction between the two conditions. In both, biopsy sections show a similar cellular infiltration of the dermis and it is unusual to find *Mycobacteria* in either case; only by staining with silver can the presence of nerve fibres in the biopsy from a case of lupus, and their absence in that of a case of tuberculoid leprosy, be demonstrated. The sensory impairment sometimes reported in lupus vulgaris is a result of the thickening of the epidermis; while in tuberculoid leprosy the absence of cutaneous sensation is due to the absence of nerve fibres.

Borderline leprosy is so called because clinically it is a borderline lepromatous condition, also called dimorphous, a term introduced by Cochrane, who claimed that the majority of skin biopsies from the lesions showed both tuberculoid and lepromatous characteristics. The condition is capable of a great variety of clinical and pathological manifestations. Ridley and Jopling have divided this type of leprosy into three groups which they term borderline tuberculoid, true borderline and borderline lepromatous leprosy, depending upon the patient's immunity. Borderline tuberculoid leprosy has a weakly positive response to lepromin, scanty, if any, *Mycobacteria* in the infiltrate, scanty nerve fibres running through the infiltrate and, as a rule, a small number of skin lesions. These cases are claimed to respond to treatment satisfactorily but, in my experience, the greatest care should be taken in giving a prognosis. The skin lesions will not necessarily all give a similar pattern of cellular infiltration, nor will they give the same distribution pattern of nerve fibres and *Mycobacteria*, and even the weakly positive lepromin response may vary from time to time and from place to place. Regular treatment is, therefore, essential in all of these borderline cases. In this type of leprosy seen in northern Nigeria nerve enlargement is particularly common, affecting the ulnar nerve above the elbow and the lateral popliteal below the knee. The patches of infiltrated skin show variable degrees of anaesthesia; nerve biopsies from the dorsal cutaneous branch of the radial nerve at the wrist can show *Mycobacteria* in the cells of Schwann even though there is no apparent sensory impairment and the skin supplied is unaffected. Variation in cutaneous sensitivity, as with peripheral nerve enlargement, are signs of leprosy which most established leprologists look for, but few feel confident to assess unless

the sensitivity is grossly impaired or the nerves are grossly enlarged. In Oxford we have devised a method of testing one aspect of cutaneous sensation using nylon threads in holders as stimulators. Six nylon threads of graded thickness are used and each is applied in a random fashion to a shaved area of skin; the patient, who is blind-folded, is asked to indicate with one finger where he has been touched. In cases of borderline leprosy this test has been applied to the skin of the lesion, to the skin of normal appearance beyond the lesion and to a comparable area of normal skin on the opposite side of the body. The results of all three tests are compared with the sensitivity response pattern to stimulation of normal skin derived in a similar way from normal volunteers from the same racial and economic background. In our experience the sensitivity pattern of apparently normal skin in those cases of borderline leprosy where the lepromin response is positive lies within normal limits. In true borderline and lepromatous borderline cases the sensitivity of normal skin outside the lesions on both sides of the body shows a greater degree of responsiveness than is obtained from the normal control series. This increase in responsiveness to sensory testing is associated with an increase in the number of fine nerve fibres in the skin.

Increasing evidence is accumulating that all forms of leprosy, other than the well-localized tuberculoid type, affect the nerves of the skin and secondarily produce skin lesions depending upon the extent and intensity of the initial infection with *Mycobacterium leprae* and also the patient's immunity. In the borderline group reduction of natural immunity is indicated by the number of skin lesions and by their sensitivity. The presence of *Mycobacteria*, a negative response to lepromin, and a progressive reduction of epithelioid cells and of lymphocytes in the infiltrated dermis in biopsies of the lesion and their replacement by foamy macrophages is an indication of deterioration and of the development of lepromatous leprosy. When the change from borderline to lepromatous leprosy has taken place the sensitivity of all normal skin and of the skin of the lesions shows a responsiveness to nylon thread stimuli in excess of those found in the control series. Lepromatous leprosy is, then, a further stage in the loss of the cell-mediated immunity of the patient and a characteristic infiltrate composed of foamy macrophages with nerve fibres running through it is seen throughout the skin of the whole body. The peripheral nerves reveal the Schwann cells loaded with *Mycobacteria* and the only object of treatment in these cases is to reduce the mycobacterial infection, while there is little hope of restoring a natural immunity which over the years has gradually been lost. Even after years of treatment it has been possible to demonstrate the

presence of *Mycobacteria* in the Schwann cells deep in nerves such as the ulnar at the elbow.

Experimental pathology of leprosy

In recent years the experimental pathologist has considered leprosy in conjunction with other Mycobacterial infections, especially tuberculosis, when investigating the underlying immune process and in the search for successful forms of treatment.

However, leprosy presents a series of particular problems which are being studied in laboratories and hospitals in various parts of the world today. These problems may most easily be summarized in the form of questions which can later be discussed.

- (1) How does the *Mycobacterium* penetrate the human body?
- (2) Once in the body where does the *Mycobacterium* survive?
- (3) What factors govern: (a) the survival, (b) the multiplication, and (c) the destruction of this organism?
- (4) *Mycobacterium leprae* has not been successfully cultivated on any artificial media. In lepromatous leprosy, however, more *Mycobacteria* are found in the body than in any other known mycobacterial infection. Why does an organism multiply so easily in the human body and nowhere else?
- (5) Treated cases of leprosy show an increase in proportion of granular *Mycobacteria* in skin biopsies. Such changes are assumed to indicate the death, or impeding death, of the organisms. Is this a justifiable assumption?
- (6) The inoculation of mouse footpads with a suspension of fresh *Mycobacterium leprae* resulted in the multiplication of the organism to a limited extent in the footpad, provided a particular concentration (10^4 – 10^6) is used and a particular time (8 months) is taken before the concentration in the foot is studied. Why should these times and concentrations be so important? Why should the organism remain localized in the mouse foot for so long?
- (7) The effect has recently been studied of inoculation of fresh *Mycobacterium leprae* into the footpads of mice that have previously been thymectomized and irradiated. In these mice without effective immunological mechanisms multiplication of the *Mycobacteria* has been extensive. It has been found that lesions similar to those found in human lepromatous leprosy are produced not only in the inoculated foot but in all the feet and also in the skin of the nose. How does the organism reach these tissues and what makes them particularly susceptible to leprosy?
- (8) What part does autoimmunity play in the production of the peripheral nerve lesions of tuberculoid and borderline leprosy?

These are but a few of the questions which are being asked about leprosy today and obviously, since research into these problems is still continuing, no clear-cut answer is available. It may be of interest to give some indication of the way these questions are being studied.

The *Mycobacterium leprae* has for generations been assumed to enter the body through the skin. Recently various other routes have been proposed (Weddell *et al.*, 1963) such as the intestinal and respiratory tracts; and in babies, breast milk from infected mothers has been suggested as a possible source of infection. It is difficult to accept that the skin is the only portal of entry; it is equally difficult, in the absence of any significant data, to support alternative methods of entry. The incubation period is so long that it is not surprising that leprosy patients cannot remember in detail what happened to them 3 or 4 years ago.

Khanolkar (1955) and other Indian workers claimed that the organism could be found in all cases of contact with the disease. In such cases no skin lesions were to be seen, but the macrophages of the dermis contained *Mycobacteria* or remnants of *Mycobacteria*. These *Mycobacteria* could be seen in sections of skin biopsies and also demonstrated by a concentration method. Unfortunately we have not been able to confirm these findings in Nigeria; we investigated five house-contacts of an untreated lepromatous case and by serial sections of biopsies and by concentration of homogenized pieces of skin, we were unable to show the presence of any convincing *Mycobacteria* (Weddell *et al.*, 1963). The demonstration of *Mycobacteria*, or more particularly the remnants of *Mycobacteria*, in sections of skin biopsies stained with carbol fuchsin is made difficult by the staining of mast cells with carbol fuchsin and the almost impossible task of differentiating the remnants of *Mycobacteria* from the acid-fast mast-cell granules. The only convincing *Mycobacteria* were seen in relation to Schwann cells in the skin biopsies of early indeterminate leprosy lesions. What factors govern their survival, multiplication and destruction are not known. Survival without multiplication or some delayed hypersensitivity manifestation may pass unnoticed; initiation of multiplication is sometimes associated with the termination of pregnancy, family disasters, famine, sickness such as smallpox, and all the various disturbing factors that might in a western community give rise to the reactivation of tuberculosis. It is the destruction of the organism and the simultaneous destruction of the peripheral nerves in cases with well-developed delayed hypersensitivity mechanisms

that is the most intriguing of the recent problems to be studied. Allergic experimental peripheral neuritis can be produced in an experimental animal stimulated by the inoculation of foreign nerve tissue, in combination with Freund's complete adjuvant, and it is possible that dead nerve together with myelin and a few *Mycobacteria* from a degenerating Schwann cell could have a similar effect. Such speculation without evidence is of no value, but the challenging situation in early cases of leprosy in endemic areas must have an explanation. In a child with an area of skin showing some reduction in pigmentation and perhaps some alteration in cutaneous sensation characteristic of the early indeterminate leprosy lesion, attention is focused on the peripheral nerves, the ulnar above the elbow and the lateral popliteal below the knee; if these nerves are thick or tender, then unfailingly the diagnosis of leprosy is made. The changes in these peripheral nerves are not associated with the presence of *Mycobacteria* and are not near the indeterminate leprosy lesion of the skin. How can such distant changes be explained? In tuberculoid leprosy again the infiltration of the dermis and of the nerve running to it together with the marked anaesthesia and the strongly positive response to the lepromin test suggest a very well marked delayed hypersensitivity response. Is there perhaps an autoimmune component in destruction of nerves, which is initiated by *Mycobacterium leprae* in certain subjects? This type of delayed hypersensitive condition has at any rate an obvious fascination for the immunologist (Lumsden, 1963).

The difficulty of cultivation of the organism has been a challenge to bacteriologists for nearly a century. Year by year claims are made of successful cultivation on newly constituted media; year by year failure to confirm the original findings leads to disappointment and disillusion. The new techniques of animal inoculation after thymectomy and irradiation should prove a reliable testing ground for supposedly successful cultures on artificial media and prevent later disappointments (Rees *et al.*, 1967).

The morphological changes found in *Mycobacteria* in treated cases of leprosy have to some extent been supported by their appearance under the electron microscope. It is claimed that this appearance can give an indication of viability. All this may be true, but it is not known what powers of regeneration such altered organisms may have, should they be placed in surroundings capable of stimulating regeneration.

The work on the footpad of the mouse and the extension to the irradiated thymectomized mouse footpad has been the most important advance in leprosy research for the past decade. It opens a great number of possible research projects and shows at last that the problem of cultivation is not in-

soluble. One word of warning for those who might think that such work is easy to undertake. There are a number of *Mycobacteria* which can infect laboratory animals, particularly rodents in a debilitated condition, especially if suffering from ulceration of the skin. These *Mycobacteria*, like *Mycobacterium leprae*, may not grow on artificial media.

The question of spread of the *Mycobacteria leprae* in the thymectomized mice from foot to foot and to the skin of the nose could be answered by assuming that the nasal mucosa is first infected via the blood stream. Alternatively, the lungs could first be affected and form a focus from which dissemination takes place.

The view that *Mycobacterium leprae* grows best in those tissues that are well innervated but cooler than the rest of the body is widely held. In this connection it should be remembered that the cells of Schwann have a high metabolic rate and there is no evidence to suggest that an increase in body temperature as a whole or a warming of the affected part has any beneficial effect on the progress of leprosy in man.

Treatment

The most widely-used anti-leprosy drug at the present time is 4,4-di-amino-di-phenylsulphone, dapsone or DDS (Davey, 1964). This drug, taken in small doses once a week, has altered the outlook of thousands of leprosy patients throughout the world. It was the introduction of this drug that enabled Ross to set up the outpatient treatment centres throughout northern Nigeria between 1955 and 1960, centres which were run on market days in the villages and administered by Nigerian leprosy inspectors. The results obtained in the outpatient treatment centres were on the whole satisfactory. However, in many segregation settlements the results of dapsone administration have not been so successful; this has been blamed on the higher dose given and upon the nature of the cases treated. It is certainly true that side-effects to dapsone occur most readily in advanced lepromatous cases; it is important that the initiation of treatment should take place gradually.

Over recent years the advised dosage level for dapsone has varied enormously, and similar changes of policy will no doubt continue to occur in the future. The lack of information about the drug's method of action makes the formulation of rigid rules for treatment impossible. Obviously dosage levels which produce toxic side effects and induce states of permanent sensitization must be avoided, particularly in territories where dapsone is the only available anti-leprosy drug.

Many other anti-leprosy drugs are in use and have been introduced initially as a general rule because of

their effect upon tuberculosis in experimental animals. Various claims have been made for their success, and the problem of the best treatment for the advanced lepromatous case is almost as controversial as the problem of the best method of classification of the disease itself. The claims made for one particular anti-leprosy preparation in one part of the world are frequently not confirmed in others (Davey, 1964).

Segregation is a perpetual problem associated with the treatment of leprosy and depends largely upon the attitude of the local population to the disease. It will be effective if there is a general fear of leprosy in the community as in eastern Nigeria and in Malaya. Attempted segregation in Muslim communities such as northern Nigeria, where no such fear exists, is always liable to failure, and to encourage a state of affairs where the majority of leprosy patients refuse treatment rather than risk the possibility of segregation in an alien settlement.

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