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Leprosy Review

A journal contributing to the better understanding of leprosy and its control

British Leprosy Relief Association
LEPRA

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Leprosy Review is published by the British Leprosy Relief Association (LEPRA) with the main objective of contributing towards the better understanding of leprosy and its control. Original papers on all aspects of leprosy, including research, are welcomed. In addition, *Leprosy Review* seeks to publish information of educational value which is of direct benefit to the control of leprosy under field conditions, and hence to the individual patient. The Journal aims to interpret what is being done in other disciplines, particularly for field workers.

From time to time the Editorial Board invites special articles or editorials from experts in various parts of the world, and gives consideration to the production of a supplement or special number devoted to a particular subject or theme of major importance.

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Editorial

LEPROSY STIGMA

Stigma has been defined by Goffman[1] as an attribute that is deeply discrediting, and the stigmatized individual is one who is not accepted and not accorded the respect and regard of his peers; one who is disqualified from full social acceptances. Goffman uses the term 'discreditable individual' for the person who assumes his differentness is neither known about by those present nor immediately perceivable by them, and he goes on to describe three main groups of stigmatized individuals. Firstly, those with physical deformities, particularly of the face. Additional examples are scars on the wrists of those who have attempted suicide, and the injection marks on the arms of drug addicts. Secondly, those with blemishes of character, inferred by a history of mental disorder, epilepsy, imprisonment, drug addiction, alcoholism, homosexuality, unemployment, suicidal attempt, and radical political behaviour. Thirdly, those with tribal stigma of race, nation, social class, and religion.

Leprosy stigma

Applying Goffman's definitions to leprosy, we can see that all of his three groups of stigmatized individuals are encompassed by the one disease: in the group with physical deformities we have the face of the neglected lepromatous patient, the facial plaque of the nonlepromatous patient (especially if in reaction), facial palsy, claw hand deformity or footdrop (both of which may identify the leprosy sufferer in an endemic country), or the hypopigmented macules which are so conspicuous on a dark skin. In the group with blemished character we have segregation in a leprosarium, or a history of such segregation. For Christian and Jewish communities we can add the use of the word 'leprosy' in the Bible as a punishment for sin. In the group with tribal stigma we have the immigrant worker in, say, a country of Western Europe, who has been found to have leprosy; not only is he a foreigner but he is likely to have a pigmented skin and to belong to the working class, factors which render him 'inferior'. He may even not be a Christian. The 'tribal' factor in countries where leprosy is endemic is poverty, for society looks upon leprosy as a disease of poverty.

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The history of leprosy stigma

Leprosy stigma is as old as the disease, for when leprosy was recognized as a clinical entity in India and China about 600 BC it arose as an instinctive social reaction to a disfiguring, progressive, and incurable disease; not only has this reaction persisted up to modern times but the disease has been additionally stigmatized over the centuries. Skinsnes puts it in these words:[2]

'The pattern of social abhorrence and persistent reaction to leprosy is unique among diseases in its intensity, inventiveness and ubiquity. . . . The presence of this reaction and behaviour pattern is not an evidence of unique racial or national benightedness but is remarkably similar in major cultures of both the Orient and the Western World and reaches far back into antiquity.'

In Western Europe leprosy stigma reached its apotheosis in the Middle Ages when the leprosy sufferer was considered by society and the Church as 'unclean', was denied civil rights, and was expected to dwell in a lazar house or hospital situated 'outside the camp' (outside the city wall).[3,]
British Isles between 1000 and 1500 AD, I would draw attention to the on-going excavations which began in 1986 in the burial ground of the hospital of St James and St Mary Magdalene near Chichester, Sussex, half a mile north-east of the old city wall. A preliminary report in 1989,[5] states that of the 351 individuals exhumed, 83 skeletons (24%) have exhibited changes compatible with a diagnosis of leprosy. This lazar hospital was founded before 1118 and functioned for at least 300 years. This was a time when, according to Richards,[4] 'leprosy was regarded as moral or spiritual contagion rather than as a disease which could be transmitted from one person to another.' Leprosy reached its peak later in Denmark, for St Jorgen's Hospital in Naestved, the only one of 30 lazar hospitals so far excavated in that country, functioned between 1250 and 1550 AD.

An explanation has to be found for the fact that leprosy stigma in Britain, so prevalent in the Middle Ages, disappeared with the dying out* of the disease after the end of the 15th century, yet the taint of leprosy reappeared a few centuries later, and by the end of the 19th century stigma had caused Western nations to panic. Gussow[6] calls it the 'retainting' of leprosy and explains that it was due to a combination of events, chief of which was the discovery of hyperendemic leprosy in the colonial world. The imperialist countries of Western Europe were, during the second half of the 19th century, conquering large areas of Africa, Asia, and Polynesia, and were reporting that leprosy was hyperendemic among the 'inferior' people inhabiting their colonies, with the risk that the disease might contaminate the civilized world. The germ theory of disease, and Hansen's discovery of the leprosy bacillus in 1873, added fuel to the view that leprosy was highly contagious, a view which still has not been entirely dispelled. Furthermore, this was a period of religious revival in England. Intensive missionary activity prompted community interest in the 'leper' and established leprosaria in all the regions where they ministered. Support for Gussow's theory of the retainting of leprosy comes from a communication of mine, written jointly with Bridgett Jones,[7] describing cases of psoriasis diagnosed and recorded

* The term 'dying out', as applied to Western Europe, must not be taken literally, for an isolated focus of leprosy persisted in the Shetland Isles of Scotland up to 1798, and no doubt a similar situation held good in France and explained how the early French settlers took the disease to Canada.

as 'leprosy' in the Manchester Infirmary, England, between 1750 and 1770. There was no adverse reaction on the part of these patients to a diagnosis of leprosy. Fears that leprosy would spread from colonial territories to the countries of Western Europe proved unfounded, for the immigration of workers from endemic countries has not caused the anticipated epidemic; in fact, apart from one indigenous case reported from France,[8] and another from the Netherlands in a male engaged in the delivery of milk to householders in a Dutch city containing many immigrants, leprosy has been confined to immigrants and to the occasional national who has been infected during residence in the tropics. Abel & van Soest[9] have described their experience in treating immigrant workers and overseas students suffering from leprosy in the German Federal Republic. They explain that any illness poses a threat to their existing labile equilibrium, and if the disease is leprosy the disturbance of equilibrium is almost predictable: 'in nearly all cases we have observed that communication of the diagnosis caused a crisis'. They describe the initial despair of these patients, causing depression in some and aggression in others; all thought their situation 'catastrophic' or 'hopeless', and an Italian patient saw his illness as 'God's punishment'. A patient from Jordan was in real danger of suicide. Misconceptions about leprosy were not confined to these patients for they also were held by the general population, the two most common being that the disease was incurable and extremely infectious, and some Christian groups connected it with divine punishment. Their report ends with this plea: 'As much attention should be paid to the psychologic and social problem of these patients as to their somatic ones'. Reports of the postwar leprosy situation in France[10] and in the Netherlands[11] have been published.

Some encounters with leprosy stigma in England

STIGMA AMONG PATIENTS

Case 1. A 27-year-old male who had emigrated from India was given a kidney transplant in Addenbrooke's Hospital, Cambridge, for end-stage renal failure, but did not divulge that he had been treated for leprosy in his home country between the ages of 13 and 17, since when he had taken an occasional dapsone tablet. Two years later I was asked to see him, and I found him to have active lepromatous leprosy (LL) complicated by type 2 lepra reaction (with ENL and unilateral epididymo-orchitis). He responded well to treatment, but two and a half years later his renal function deteriorated, and after several months of haemodialysis he died of pulmonary infection and liver failure.[12] Had leprosy stigma not prevented him from giving a true medical history to his doctors in Cambridge, the outcome might have been very different.

Case 2. A 60-year-old male came to England with his family on his retirement from Indian Railways. A few years later he became a regular attender at his local hospital because of a chronic plantar ulcer, denying having had any illnesses in the past. The ulcer enlarged to such an extent that a below-knee amputation was carried out. The result was disastrous as his doctors had not noted the anaesthesia of his legs extending to his thighs, so whenever he attempted to wear his prosthesis he developed ulceration of his stump. Nodules appeared on his skin the following year, and when I saw him he admitted having been treated with dapsone for ten years in his home country.

Case 3. When a young male was told in India that he had leprosy, his aggressive reaction was to set out with his motorcycle on a world tour. Travelling through Iran, the

Soviet Union, across Europe from east to west, then taking ship to North America, he continued his road journey until he reached Calgary, in South West Canada, where he was hospitalized with a diagnosis of lepromatous leprosy (LL). The Canadian Government repatriated him, whence he promptly flew to London where he came under my care as a case of advanced LL with gross deformity of his fingers.

Case 4. An Englishman who had spent his working life in India came home to retire in the 1950s. He brought with him his two sons aged 17 and 15 respectively. The elder son was found, soon after arrival, to be suffering from borderline leprosy, but as he could not face up to the diagnosis he sought escape from his dilemma by joining the British Army. This he did (with his father's approval) and enlisted for seven years. During his service he attained the rank of sergeant, and it was only at final medical examination seven years later that his secret was revealed. He was admitted to the Jordan Hospital* with active LL and gross ulceration of both lower legs—see the illustration of ulcerated legs in the first four editions of *Textbook of Dermatology*.[13]

Case 5. A young Indian scientist working in London was greatly distressed on being told that the erythematous plaque on his face was due to tuberculoid leprosy (TT). Out-patient therapy with dapsone resulted in disappearance of the lesion after one year, and it was then that he admitted that he would have committed suicide had the diagnosis been made in his home country.

Case 6. On one occasion at the Jordan Hospital I received a telephone call at midnight from a provincial hospital requesting urgent admission of a Maltese male whose suicide attempt had just been foiled!

Case 7. Of three suicide attempts at the Jordan Hospital, only one was successful. The patient, a well-educated Indian male, was admitted with a diagnosis of leprosy and committed suicide that same night, leaving a note admitting that he could not face life with leprosy.

STIGMA AMONG PATIENTS' RELATIVES

An Italian engaged in the wool trade in Yorkshire went to his home country in 1960 and brought back a wife, but during her first pregnancy she was admitted to the Jordan Hospital with active LL. She and her husband were bewildered by the tragic turn of events, and it was only when she showed her family photograph to the senior nursing sister that the explanation was plain to see: in the centre of the group stood her father, and his face bore the stigmata of LL in the presulphone era. The patient recalled her father's visits to Genoa every six months, but had never been told the reason. A second example was that of a middle-aged, single English lady, born into a prominent family in the Caribbean, who was referred to the Hospital for Tropical Diseases in London. She was found to have LL and was transferred to the Jordan Hospital. So great was her family's fear of being stigmatized by leprosy that all contact with her ceased, apart from a regular remittance. When the time came for her to be discharged, sheltered accommodation was

* When the National Health Service was established in 1948 in Britain the then Minister of Health, worried by the influx of workers and students from the tropics, decided to make leprosy notifiable and to open a specialized hospital for leprosy patients requiring in-patient management, so the Jordan Hospital (named after the Biblical river of healing) was opened in 1950, with accommodation for 24 patients. It was situated in Earlswood, Surrey, a rural area 26 miles south of London, and it was closed in 1968 for reasons other than shortage of patients for it functioned to full capacity throughout its working life.

found for her in London, but so great had been her isolation, and so great the stigma, that she became a recluse and died prematurely.

PUBLIC MISCONCEPTIONS ABOUT LEPROSY

In 1950 when the Redhill–Reigate district of Surrey heard that their Victorian infectious diseases hospital in the village of Earlswood, no longer functioning, was being converted into a leprosy hospital, a protest group was formed. It took several public meetings, and the strong support of the then local Medical Officer of Health, Dr Bingham, to carry through the project. At the end of that year I moved into the doctor's house with my family, and although two of my children obtained places as day scholars at a local school, three years passed before any local children were allowed by their parents to visit the doctor's house. Later events affecting two of my patients can be recorded here. The first one involved a Maltese patient who had been treated at the Jordan Hospital and, on discharge, obtained a post in the office of an insurance company in Reigate, only to be summarily dismissed when the manager heard about his leprosy. The second event involved a female patient at the Jordan Hospital who was told by her husband that their two children had been expelled from their London school when the headmistress heard that their mother was being treated for leprosy. Both these unjust acts, prompted by misconceptions about leprosy, were resolved by diplomacy.

Leprosy and stigma in other European countries

SCANDINAVIA

In Denmark, where leprosy was an important endemic disease in the Middle Ages, involving the establishment of over 30 St Jorgen's (St George's) hospitals, only one of these has been systematically excavated, namely, St Jorgensgaard, near Naestved.[14] It functioned as a leprosy hospital between the years 1250 and 1550 AD, later than leprosy hospitals in England. In the countries further north it was an endemic disease of minor importance in the Middle Ages, but reached a peak by the middle of the 19th century with an overall prevalence in Norway of 1·67 per thousand,[15] and Gussow quotes figures reaching 70 per thousand in parts of the hyperendemic western districts.[6] The great increase in the number of lazar homes and hospitals in Norway during the 19th century (the St Jorgen's Hospital in Bergen having been established in the 15th century) had the objective of preventing procreation, for the Norwegian medical profession firmly held to the view that leprosy was a hereditary disease, even for a decade or two after Hansen's discovery of the leprosy bacillus in 1873. Therefore in-patients were free by day to sell their handwork in the market or to entertain visitors, so long as they conformed to segregation at night. Hence there was little evidence of stigma,[6] and Hansen was able to write: 'the Norwegian state has always handled its leprosy victims humanely'.[16] The motivation for many Norwegian families to emigrate to the Upper Mississippi Valley of the United States, beginning in the 1820s, was poverty rather than leprosy stigma, although it is likely that leprous adults may have had the additional motivation of avoiding sexual segregation. The reason for the disappearance of leprosy from Norway and neighbouring Scandinavian countries is still open to debate.[17–19]

SOUTHERN EUROPE

In contrast with Western Europe, leprosy did not die out after the end of the 15th century but has persisted as a minor endemic disease in all Southern Europe from Portugal in the west to Greece in the east. Leprosy stigma has persisted, with patients adding to the difficulties of eradication by keeping their disease secret. Spain has the highest prevalence and possesses the largest leprosarium in Europe—Fontilles in Alicante—where treatment is combined with teaching and research of international repute.

EASTERN EUROPE

In Imperial Russia, as in Scandinavia, leprosy reached a peak in the 19th century, and news of leprosy in Siberia was brought to Britain by an English nurse named Kate Marsden who, with Christian zeal and self-sacrifice, made a perilous journey to Siberia in 1891 to acquaint herself with the position of leprosy sufferers there and to arouse the public and official conscience in Russia to their terrible plight.[20] On her tour of the Yakutsk Province of Siberia she found small groups of these unfortunate people living as exiles scattered throughout the forests, having been expelled from their villages. Each group shared a single hut in which they existed, naked or in rags, the strongest members of the group going out to fetch whatever scraps of food their healthy relatives would leave for them at an appointed place in the forest. On her return to Moscow and St Petersburg Miss Marsden raised funds for building a leprosarium so that those driven into the forests could be brought into proper shelter where they could receive food, clothes, and nursing care.

A recent issue of *Leprosy Review*[21] carried a report about the Tichilesti Leprosy Colony in present-day Romania, a colony which was opened in 1877 with a capacity for one hundred inmates. At present it contains 54 patients, with equal numbers of men and women, mostly elderly. The most recent admission was four years ago. The medical superintendent anticipates a few more admissions now that medical information is freely available, but the reader is left wondering how many leprosy sufferers are avoiding incarceration by keeping their disease secret.

Leprosy misconceptions and stigma in countries outside Europe

INDIA

The earliest reliable evidence of leprosy in India can be found in the *Susruth Samhita* written about 600 BC, the most complete and accurate of the old descriptions, even mentioning chaulmoogra oil as treatment.[22] As for the present-day situation, Mutatkar[23] outlines the situation as follows:

1 The concept of heredity is deeply rooted in Indian culture since the social structure is based on the principle of hereditary inequality, making it difficult to change people's misconceptions about the hereditary nature of leprosy.
2 The Hindu view considers deformity as divine punishment, and people equate gross deformity with leprosy. This misconception is encouraged by the fact that patients who recover, and appear perfectly normal, keep their disease secret.

3 The Indian medical profession looks on leprosy as a disease apart and keeps away from it, tending to share public misconceptions.
4 Deformed beggars reinforce the association between leprosy and poverty.
5 Many misconceptions are held by the general public, some contributing to stigma, therefore educating the public and the medical profession on the true facts about the disease is the paramount necessity in order to overcome ignorance and prejudice. 'The problem with leprosy is not what the disease is, but what the people believe it to be'.

India's National Leprosy Eradication Programme (NLEP),[24] and its objective of getting the disease under control, is a welcome development.

CHINA

Earliest records of leprosy in China date back to about 500–300 BC[25] and up to relatively modern times the disease has met with social opprobrium because of its unique nature. Skinsnes[2] lists facial disfigurement, mutilation of limbs, chronicity and long incubation period causing mystery about its origins, inspiring horror, fear and disgust. Misconceptions added their quota to leprosy stigma, particularly the belief that it was transmitted by sexual relations with prostitutes and therefore was punishment for moral lapse. During the second half of the 19th century and the first half of the 20th, there was intense missionary activity in China, and care of leprosy sufferers had a prominent role. At the time of founding New China in 1949 there were 40 leprosaria in existence, 39 established by foreign missions, with accommodation for about 2400 patients.[26] Since the early 1950s the Chinese Government has taken over all leprosy work, and up to the time of his death in 1988 Dr Ma Haide (George Hatem) headed the campaign aimed at eradicating the disease by systematic diagnosis and treatment throughout the country, using standard drug regimens and BCG vaccination. He estimated that there were about 600,000 cases at the beginning of the campaign, and its thoroughness is shown by Yang Lihe's figure of less than 100,000 in 1983.[27] Another important statistic is that the proportion of new cases belonging to age groups less than 15 years has decreased from 16·0% (1955) to 0·16% (1984).[27] All Chinese commentators anticipate that basic eradication will be attained by the end of the century. With this decline, and the additional campaign of education and propaganda, leprosy stigma has likewise declined.

NORTH AMERICA

Canada Canada provides three interesting facets of leprosy history. Firstly, from 1639 onwards immigrants from France settled in the province of New Brunswick, and the first case of leprosy was diagnosed in 1815[28] or 1817[29] in a young married woman, Ursule Benoit. Other cases were occurring, and a medical commission in 1844 reported that the 'loathsome disease' was infectious and patients should be segregated. A lazaretto was established on an island in the river Miramichi, and in 1896 a modern hospital was built in Tracadie.[29] The leprosy epidemic ended in 1937 when the last two patients were admitted, 120 years after the disease was encountered. Secondly, turning our attention to the neighbouring province of Nova Scotia, many Scottish settlers arrived from the Hebrides and Shetland Isles after the British authorities expelled the French settlers (Acadians) in 1755. Leprosy was diagnosed in 1852 in a Mrs Betty MacArthy of Cape Breton,[30] and the

fact that she was English proves, to my mind, that there was at least one earlier undiagnosed case in that region, for there was no leprosy in England in the 19th century. In Scotland, on the other hand, leprosy was endemic in the northern islands until the end of the 18th century. We have Ashmead's[30] assurance that there was no leprosy among the Micmac Indians at that time. Thirdly, Canada provides an intriguing proposition: if Acadians had not been expelled from Nova Scotia in 1755 there would be no Carville today in the United States—see below.

The United States The origins of a leprosy problem in the United States dates back to the introduction of the disease by French settlers (Acadians) who emigrated to southern Louisiana when they were expelled from the Canadian province of Nova Scotia by the British authorities in 1755. Gussow[6] has fully documented the subsequent story, beginning with the Louisiana legislature establishing in 1884 a State Board of Leprosy Control which was directed to find a 'Leper Home'. The Board obtained a 5-year lease on 'Indian Camp', an abandoned plantation bordering the Mississippi river and about 85 miles north-west of New Orleans. They named it the Louisiana Home for Lepers, and the first patients were admitted at the end of that year. The Board intended to find a permanent site nearer the capital city, but met with such public opposition that they gave up the task and, in 1905, the state of Louisiana purchased Indian Camp. In 1917 the US Congress passed a bill to create a national leprosarium, and in 1921 the Louisiana Home for Lepers became under US federal jurisdiction as the US Marine Hospital, Carville,.a sanctuary and refuge for leprosy sufferers throughout the country, with admission on a voluntary basis. The patients had no doubt that leprosy stigma created Carville, and in subsequent years, under the leadership of Stanley Stein who founded the crusading journal *The Star*, they organized their energies and talents to combat stigma. In the 1940s, Carville came into prominence by discovering the first effective antileprosy drug, a sulphone named Promin, and since then has combined the housing and treatment of patients with an expanding programme of teaching and research. Since the early 1960s a number of diagnostic and treatment clinics for out-patients have been set up in those states favoured by foreign immigrant workers, and Gussow[6] reports a study in the mid-1960s which reported that strong public stigma could not be demonstrated. Today leprosy is a minor endemic disease in two American states, Louisiana and Texas, the latter state (and its endemic leprosy) having been annexed from Mexico in 1848.

THE CARIBBEAN

The island of Trinidad has provided an extreme example of leprosy arousing fear and prejudice in official circles, demonstrated in events which, inexplicably, were largely ignored by the medical press; the only report I have been able to locate was in *The Star* of February 1955.[31] The events occurred at Christmas 1954 extending to January 1955 when Dr Michael Corcos, the recently appointed Medical Superintendent at Chacachacare, an island leprosarium where compulsory segregation was the rule, allowed 130 patients to spend the festive season with their families. Some members of the Trinidad Legislative Council promptly called for his 'immediate removal or suspension'. The local press gave generous cover to 'the flood of patients let loose in the community' but was muted in its criticism of the Superintendent. On 7 January 1955 the Governor dismissed him and ordered him to leave Chacachacare with his family, and the patients responded with a protest 'sit-down' strike. Armed police were rushed to the island, and after five 'ring

leaders' had been taken into custody the strikers were persuaded to resume their normal routine. Although the immediate result of these events was the departure from Trinidad of Dr Corcos, a long-term result was the decision of the Government of Trinidad and Tobago in 1968 to close the leprosarium and to set up a Leprosy Control Programme. Diagnostic and treatment clinics were set up on the twin islands of Trinidad and Tobago in 1971, and by 1981 the numbers of known cases had fallen from 1638 (16/10,000) to 763 (7/10,000), together with a significant reduction in new cases in children.[32] The success of this Programme has led to an improved official and public attitude to leprosy. Turning to Guyana, a present-day urban community was asked a series of questions about diseases of the community, and on leprosy the great majority considered it to be incurable, disfiguring, shameful and fear-inspiring. The author[33] proposes that in the campaign to eradicate leprosy stigma the two essentials are:

1 the general public must be persuaded that it is curable: and
2 treatment must be on an out-patient basis.

Factors contributing to leprosy stigma

It is generally agreed that leprosy stigma handicaps the eradication of the disease, so let us consider the factors contributing to it:

1 The general public worldwide has many misconceptions about leprosy, some contribute to stigma, therefore health authorities in endemic countries, and in countries where leprosy is a disease of immigrants, should launch an information campaign stressing that the disease is curable and that patients on treatment are noninfectious. Religious leaders should explain to Christian and Jewish communities that 'leprosy' in the Old Testament, a divinely ordained punishment for sin (*Leviticus* 13 and 14), is not mycobacterial leprosy.[34–36]

2 The medical profession in many endemic countries looks upon leprosy as a disease apart, thus it is unable to contribute to the dispelling of public misconceptions. Leprosy must be given a more important place in the curriculum of medical students in endemic countries.[37–39] In nonendemic countries which have immigrant workers, dermatologists have a unique opportunity to diagnose early leprosy cases, therefore a sound knowledge of the disease should be a priority in their specialist training.

3 Leprosaria and leprosy colonies have, in the past, played a role in promoting and sustaining stigma, and additionally have done little to reduce leprosy incidence (the exception of 19th century Norway has already been discussed). Their closure over recent decades and replacement by suitably-sited out-patients clinics has been a welcome advance. A few 20th century leprosaria, like Carville in the United States and Fontilles in Spain, are exceptions in that there is no strict segregation and the institutions are centres of world renown in teaching and research.

4 Leprosy patients who have no signs detectable by the general public, and cured patients who look healthy, keep the diagnosis secret[40] and thereby contribute to leprosy stigma by allowing the public to gain an entirely wrong impression of the disease; they see it as incurable and inevitably disfiguring. This misconception is compounded when burnt-out cases beg for a living. Mutatkar[23] states that in 1962 the Gandhi Memorial Leprosy Foundation estimated that of the 5000 leprosy patients in Poona about 400 were beggars.

5 Laws discriminating against leprosy sufferers add their quota to stigma. For example,

India's Leprosy Act of 1898 was formulated to protect the public health by restricting their activities, and even though some states have repealed this Act it still exists in about ten (although for many years it has not been enforced). Another example is the Hindu Marriage Act of 1955 which permits divorce if a spouse is suffering from 'a virulent or incurable form of leprosy'; it is still in force, as are the Muslim Marriage Act, the Indian Christian Marriage Act, and the Special Marriage Act, all of which have similar provisions for divorce.[41]

6 Writers, journalists and politicians promote stigma when they use the words 'leprosy', 'leper' or 'leprous' to imply something evil, degrading or immoral, and many examples in English literature since the time of Chaucer have been supplied by Skinsnes and Elvove.[42] Contemporary journalists have been prone to follow suit, and the most glaring example of stigma-activating journalism has been supplied on the front page of a British daily newspaper, *The Sun*, on 28 September 1989, apropos of the projected visit of the Princess of Wales to a leprosarium in Indonesia. The main headline 'DI TO SHAKE HANDS WITH A LEPER' was followed by a subsidiary headline, 'Don't do it, says *SUN* doc'. A critical comment has appeared in the *British Medical Journal* (Figure 1).

7 Fund-raising agencies have, in the past, depicted the horrors of neglected leprosy in

Channel 4 *Hard News* 12 October

Sweeping away superstition?

The combination of royalty and a feared disease must have made an irresistible front page story on 28 September for the editor of the *Sun*. Another headline, "Don't do it, says *Sun* doc," suggested that leprosy is extremely infectious, with an appreciable risk of transmission occurring by hand to hand contact. A catalogue of selected facts and misinterpretations then followed, emphasising the nastier aspects of the disease: "Sores multiply on the skin, nose and mouth," the incubation period can be as long as 20 years, it can lead to blindness, and a vaccine is impossible "since leprosy is a tuberculosis germ, but it cannot grow outside the body."

With a curiously heightened but merely momentary sensitivity to the feelings of leprosy patients, the article then continued by advising Princess Diana not to make a visit to a leper colony in Indonesia as "the lepers would be offended if she refused to shake hands or did it wearing rubber gloves." Unfortunately that sensitivity had dissipated by the next day, when the paper carried a grotesque cartoon of Princess Diana wearing an extendable arm to shake hands with a leprosy patient.

Hard News, a Channel 4 programme commenting on presentation of news items in the national press, on 12 October produced a five minute piece in which a scientist, a nurse, a former leprosy patient, and a leprosy worker were interviewed. It succeeded in correcting most of the misleading facts and impressions in the article. Dr Jo Colston, who is on the WHO leprosy committee, emphasised that multiple drug treatment, which has been recommended by WHO since 1981, rapidly renders patients non-infectious. Additionally, as Indonesia actually has no leper colonies, it was speculated that the princess might perhaps be visiting a leprosy hospital, thereby contrasting the article's use of the stigmatising term leper colony, which has connotations of incurability and deformity, with the more positive emphasis on treatability implied by leprosy hospital.

Dr Vernon Coleman, the "*Sun* doctor," declined to appear on *Hard News* to defend his comments, as he was not prepared to travel for an appearance without a fee. In an interview with BBC Radio Essex, however, he admitted that his comments had been made under strict time constraints. He defended his estimate for the likelihood of contracting leprosy from shaking hands, "There's only a 1000 to one chance that she will catch it, but it's not worth the risk," as being merely "jargon for saying the risks are low." Had he watched the *Hard News* programme Dr Coleman would also have discovered, despite the "impossibility" of a vaccine, that at least four trials are currently in progress.

Hard News is to be congratulated on giving leprosy patients and their carers a much needed, valued, and appropriate right of reply to a peculiarly distasteful piece of tabloid journalism, but I suspect that only a minority of *Sun* readers will have seen the programme. Despite the corrections made by *Hard News*, there may be longer term effects of such newspaper articles. Their prominence on the front page, presumably because no

juicier news item is available; the size of the newspaper's readership; and the article's viewpoint, wrapped up in an overly sanctimonious and manifestly hollow concern for royalty, can only have reinforced the traditional prejudices and deeply felt fears derived from ignorance that have accompanied this disease since ancient times. More serious for the medical profession is the realisation that the article derived its power and respectability solely from the manner in which its conceptions of leprosy had been sanctioned by a single non-specialist practitioner, who apparently had had to rush to meet tight deadlines. Without that legitimisation the article would have carried little weight. In any event it can have done little to further Princess Diana's stated intention of "sweeping away superstition and prejudice."—DIANA LOCKWOOD, *Wellcome research fellow, London School of Hygiene and Tropical Medicine*

Figure 1. The above is reprinted, with kind permission, from the *British Medical Journal* (1989), **Volume 299,** No. 6706, p. 1036.

appeals in the press which have inadvertently encouraged stigma. A change of emphasis has been foreshadowed by an England-based leprosy Charity recently appealing for donations to aid treatment campaigns in the developing world: the headline ran 'LEPROSY CAN BE CURED'.

Conclusion

Just as medieval leprosy stigma disappeared from the countries of Western Europe with the dying out of the disease after the 15th century AD, so can present-day leprosy stigma disappear with the eradication of the disease by chemotherapy. A drive is necessary to get more endemic countries to use multidrug therapy MDT to the fullest extent because of its excellent results and the confidence inspired by a relatively short course of treatment. There is also a role for BCG vaccination at present and for a more effective vaccine in the future.

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Specificity of lymphocytotoxic autoantibodies (LCAbs) found in the serum of leprosy patients: Class I MHC antigens

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Summary Lymphocytotoxic autoantibodies (LCAbs) of the IgM class have been identified in patients with borderline tuberculoid (BT) and borderline lepromatous (BL) leprosy with Type I reactions (I) as well as lepromatous leprosy (LL) patients with erythema nodosum leprosum reactions (ENL). The observation that lymphocytotoxic activity (LCA) was reduced in the presence of platelets led us to determine whether LCAbs had specificities for Class I Major Histocompatibility Complex (MHC) determinants. Absorption of LCA positive sera with platelets, classically used to deplete Class I specific lymphocytotoxic antibodies, reduced LCA towards autologous as well as allogeneic target cells. This was true for LCA positive sera from all patient classifications (group BT in the autologous system, $p < 0{\cdot}01$; in all other patient groups, $p < 0{\cdot}001$). Introducing B-2m to cytotoxicity assays only marginally reduced LCA when added at high concentrations (5 mg/ml). An anti-Class I MHC antiserum which blocked the lytic activity of Class I tissue typing sera did not inhibit lymphocytotoxic activity. The data indicate that LCAbs while absorbed by platelets, are not specific for the Class I MHC antigens. The autoantigen recognized by these autoantibodies therefore remains to be identified.

Introduction

Leprosy has been termed an immunological disease because much of the pathology, particularly of leprosy reversal or Type I reactions (I) and erythema nodosum leprosum

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(ENL) reactions is associated with tissue and nerve autodestruction and not directly with the presence of *Mycobacterium leprae*.

Lymphocytotoxic activity (LCA) has been demonstrated in the sera of leprosy patients.[1–4] Complement dependent IgM autoantibodies have been found to be responsible for this activity. Elevated levels of these antibodies are present in the sera of leprosy patients undergoing either clinical hypersensitivity Type I or ENL reactions compared to leprosy patients without these reactions or control subjects.[4] These antibodies function in a temperature dependent manner. When tested at 37°C, 32% of sera derived from BT leprosy patients with a history of Type I reactions were positive for LCA ($n=24$). At 15°C the prevalence of LCA in the same sera increased to 88%. The difference in reactivity at these two temperatures is similar to and also significant in patient groups LL + ENL and BL + I. We assume that these antibodies have low affinity binding properties at 37°C and that the reduced temperature conditions of 15°C permit a closer physical association between these antibodies and their antigen/s. It is not yet known how these antibodies are stimulated, which target autoantigens they bind to and whether or not they are of immunoregulatory or pathological importance in these reactional states.

Numerous reports cite examples of immunoregulatory functions attributed to antibodies which bind to lymphocyte determinants. To illustrate, antibodies have been identified which induce the secretion of interleukin-2, stimulate T cell proliferation and cytotoxic T cell activation.[5] Keizer *et al.*[6] describe antibodies which bind to leucocyte function associated antigen-1 (LFA-1) which acts as a cell adhesion molecule mediating a variety of cell–cell interactions. The binding of one monoclonal antibody to LFA-1 alpha chain stimulates these interactions while others binding to the same molecule but possibly to different epitopes, inhibit cell aggregate formation.[6] To assess the potential role of LCAbs it is clearly important to define the antigen/s to which they bind.

LCA is also present in sera of patients with systemic lupus erythematosus (SLE) and correlates with the clinical course of the disorder.[7] LCA in SLE sera was reported to disappear upon absorption with platelets.[8] LCA in these patients was seen to be associated with anti B-2m antibodies which were evaluated to be IgG.[8,9]

The results of investigating the specificity of LCAbs in the sera of leprosy patients for B-2m and the Class I MHC complex itself are presented in this paper. We have selected LCA positive sera from patient groups previously determined to have significantly raised levels of this activity (LL + ENL, BL + I and BT + I). The specificity of LCAbs from these sera as well as LCA positive sera from other patient groups across the leprosy spectrum have been compared to endemic controls.

Materials and methods

Patients and controls

Sera were processed from patients diagnosed with leprosy and endemic controls at the Public Health Clinic Georgetown, Guyana; Liteta Hospital, Lusaka, Zambia; and the Marie Adelaide Leprosy Centre, The Aga Khan University, Karachi, Pakistan. All leprosy patients were classified using the clinical and bacteriological criteria specified by the Ridley and Jopling Scale.[10,11] Patients in hypersensitivity reactions either at the time of

bleeding or up to a year prior to bleeding were classified separately. Male and female patient and control subjects ranged from 10 to 65 years of age.

Microlymphocytotoxicity assay

The details of this method have been described elsewhere.[4] In brief, lymphocytes were isolated from 50 individuals selected to represent most known HLA-A, -B, and -C antigens. Test sera diluted 1:2 in complement fixation test media ((CFT) Oxoid Ltd, England) were dispensed into wells of a Terasaki microtitre plate and incubated with lymphocytes for 30 min at 15°C. Rabbit complement was added to each well, followed by a further incubation of $2\frac{1}{2}$ h at 15°C. The percentage of lymphocytotoxicity in each well was assessed using phase contrast microscopy. A pool of noncytotoxic AB sera was used as a negative control on each plate. Lymphocytotoxicity was scored using a 6 point scale from 0 to 8. A score of 1 corresponds to a killing of 10–20% of lymphocytes; a score of 2 = 20–40%; 4 = 40–60%; 6 = 60–80%; 8 = 80–100%. LCA positive sera which are characterized in this paper reacted to > 75% of the panel of donors tested.

Serum absorption with platelets

Platelets from 100 randomly selected individuals were pooled. These were washed thoroughly with phosphate buffered saline. Washed packed platelets were mixed with sera at a ratio of 1:2 for one hour on ice. Two separate absorptions, were performed on each serum sample with 2 aliquots of platelets. Sera were tested before and after absorption with platelets against allogeneic lymphocytes derived from 10 donors or in 5 replicates against autologous lymphocytes.

Introduction of B-2m to the microlymphocytotoxicity assay

A total of 35 test sera from leprosy patients with positive LCA and endemic controls with negative LCA, were used. The sera were diluted 1:2 in CFT containing varying concentrations (seven 10-fold dilutions from 5 mg/ml to 0·5 ng/ml) of B-2m (Sigma Chemical Co. Ltd, England). Sera and B-2m were preincubated for 2 h. Sera preincubated with CFT alone were used as a negative control. The sera were then tested without further dilution against lymphocytes derived from 10 allogeneic donors in the microlymphocytotoxicity assay.

Antiserum for B-2m/Class I MHC antigens

A commercially available chicken polyclonal antiserum against B-2m (Serotec, USA) when tested, was found not only to bind to B-2m but also to the Class I complex. In our hands, lymphocytes when preincubated with this antiserum, were found to no longer be lysed by Class I specific polymorphic tissue typing antisera. The polymorphic HLA-Class I reagents used were well characterized tissue typing reagents used in the Class I Tissue Typing Laboratory, The London Hospital Medical College. Lymphocytes from 4 different donors of known tissue type were tested pre and post incubation with either this anti-Class I or control noncytotoxic AB serum against the same set of 35 sera. As an additional control, five HLA Class I typing sera were tested blind against these

lymphocytes alongside leprosy LCA positive sera in the microlymphocytotoxicity assay. The results were read independently by the ABC Tissue Typing Laboratory at the London Hospital.

Results

Absorption of LCA positive sera with platelets

To test if Class I antigens were the target for LCA, platelets were used to adsorb possible anti-Class I antibodies from LCA positive sera. Absorption of LCA positive sera with platelets significantly reduced LCA in all patient groups (Figures 1(a) and (b)) irrespective of whether the target lymphocytes were allogeneic or autologous in origin. All groups demonstrated a significant reduction ($p < 0{\cdot}001$) in LCA towards allogeneic cells after sera were treated with platelets (Figure 1(a)). A significant reduction in LCA was also seen in patient group BT ($p < 0{\cdot}01$) and other groups ($p < 0{\cdot}001$) when tested in the autologous system (Fig 1b).

The effect of B-2m on LCA

B-2m is present on the membrane of all nucleated cells and platelets where it is bound non covalently to HLA Class I molecules. To test whether lymphocytotoxic antibodies were directed against B-2m, LCA positive sera were pre-incubated with the B-2m to absorb anti-B-2m antibodies. The results of using B-2m at 0·5 ng/ml and 5 mg/ml concentrations

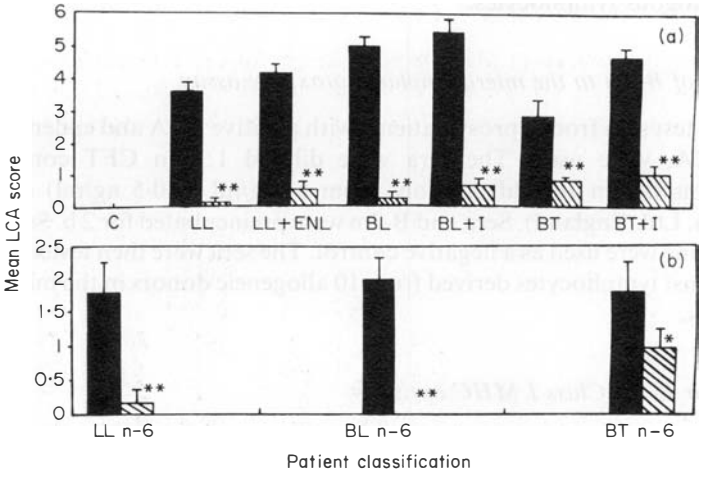

Figure 1. The effect of absorption of sera with platelets on LCA. (a) Allogeneic system: Five sera from each patient group were tested against lymphocytes from 10 different donors before (blackened bars) and after (hatched bars) absorption with platelets. (b) Autologous system: Six sera from each patient group were tested in 5 replicates against autologous lymphocytes before (blackened bars) and after (hatched bars) absorption with platelets. The mean LCA for each individual serum was calculated and the overall means of each patient group are presented. C, endemic control sera without LCA. Patient groups with LCA: LL, lepromatous leprosy; BL, borderline lepromatous leprosy; BT, borderline tuberculoid; I, Type I reaction; ENL, erythema nodosum leprosum. * = $p < 0{\cdot}001$, ** = $p < 0{\cdot}01$ (paired T test). The standard error of the mean are indicated for each group.

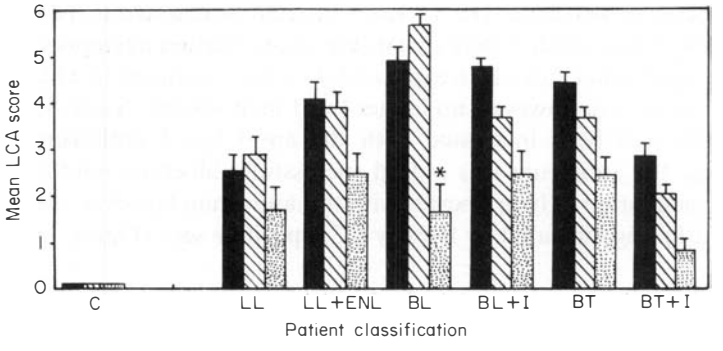

Figure 2. The effect of B-2m on LCA. Five sera from each patient group were tested against allogeneic lymphocytes from 10 different donors. LCA is compared between untreated sera (blackened bars) and sera pre-incubated with either 0·5 ng/ml B-2m (hatched bars) or 5 mg/ml B-2m (stippled bars). The mean LCA for each test serum was calculated and the overall means for each group are expressed with the standard error of the mean. C, endemic control sera negative for LCA, leprosy patient groups positive for LCA: LL, lepromatous leprosy; BL, borderline lepromatous; BT, borderline tuberculoid; I, Type I reaction; ENL, erythema nodosum leprosum. * = $p < 0{\cdot}01$ (paired T test).

are shown (Figure 2). Data for the intermediate dilutions tested are not shown since they were not different from pretreatment LCA. At a concentration of 5 mg/ml, B-2m marginally but not significantly reduced LCA in groups LL, LL+ENL, BL+I, BT, BT+I and reduced LCA significantly in BL patients ($p < 0{\cdot}01$).

The effect of blocking the Class I MHC on LCA

To determine whether Class I MHC was the target for LCA, target lymphocytes were pre incubated with an anti-Class I antisera before incubation with LCA positive sera. To ensure that this antiserum would indeed block Class I MHC expression, control sera of

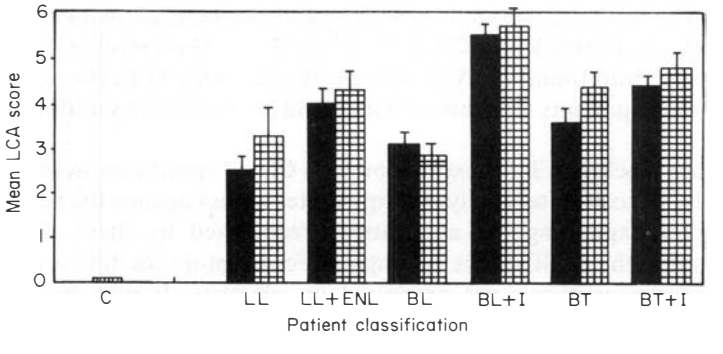

Figure 3. The effect of blocking class I MHC expression of lymphocytes on LCA. Five lymphocytotoxic sera from each patient group were tested against lymphocytes from 5 different individuals before (blackened bars) and after (blocked bars) incubation with anti-Class I antiserum. The individual means for each serum were calculated. The means and standard error of the mean of each patient group are presented. C, LCA negative endemic controls, Leprosy patient groups positive for LCA: LL, lepromatous leprosy; BL, borderline lepromatous; BT, borderline tuberculoid; I, Type I reaction; ENL, erythema nodosum leprosum.

known specificity for particular HLA Class I antigens were tested in the microlymphocytotoxicity assay. These tissue typing sera discriminated between lymphocytes in that they lysed only those lymphocytes which expressed the Class I antigens to which they had been raised. These same sera however, no longer lysed their specific lymphocyte targets once the target cells had been incubated with the anti-Class I antiserum. We therefore concluded that the antiserum was indeed successfully blocking binding to the Class I complex. Preincubation of lymphocytes with this antiserum however, made no difference to subsequent killing mediated by leprosy LCA positive sera (Figure 3).

Discussion

LCAbs in the sera of leprosy patients appear to recognize determinants common to both platelets and lymphocytes.[4] We have shown previously that serum LCA shows broad reactivity towards target lymphocytes derived from 50 individuals chosen for their expression of most known HLA antigens.[4] These data indicate that the antigen recognized is common to lymphocytes of most individuals. Very occasionally, target cells from some individuals are not lysed by these sera. It is possible that on the odd occasion when LCA is reduced or absent, that the antigen/s recognized by these antibodies are missing or masked. The observation that LCAbs are absorbed by platelets led us to speculate that the expression of the autoantigen may be linked or associated with the expression of the Class I complex. Changes in the alloantigenic domains may induce a conformational change of an associated and common antigen. Occasionally, such a change in conformation may prevent this common antigen from being recognized by LCAbs.

B-2m exists as both a free and bound molecule.[12,13] The introduction of free B-2m into the microcytotoxicity assay with LCA positive sera did not significantly reduce LCA in most patient groups. At the high concentration of 5 mg/ml, B-2m significantly reduced LCA in patients with BL. The variation in this assay as in all others involving sera with different levels of LCA and target cells which illicit different levels of response is high. The reduction of LCA in BL patients may well be a non-specific effect of high concentration of B-2m physically interfering with LCAbs from binding to their target antigens. In contrast, Revillhard *et al.*,[8] who found LCA in 50% of patients with SLE, showed that in half of these LCA positive patients that this activity could be inhibited by adding as little as 1 ng B-2m.

The fact that blocking Class I expression with Class I specific antisera had no effect on the ability of LCA positive sera to lyse lymphocytes argues against the possible role of the Class I complex expressing the autoantigen recognized by these antibodies. Many antigens including the MHC Class I complex, Fc receptors for IgG and IgE as well as common membrane antigens are expressed on platelets. It may be that a common membrane bound protein present on platelets as well as lymphocytes could be responsible for this activity. An alternative approach to concluding this investigation is to immunoblot sonicated platelet and lymphocyte antigens separated on polyacrylamide gels with LCA positive sera to identify at the molecular weight level the antigen bound. This method is currently being employed in our laboratories.

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La spécificité des auto-anticorps (LCAbs) trouvés dans les sérums des patients de lèpre

FAWZIA N RASHEED, MARY LOCNISKAR, D J MCCLOSKEY, RUMINA S HASAN, T J CHIANG, PATRICIA ROSE, R DE SOLDENHOFF, H FESTENSTEIN ET K P W J MCADAM

Sommaire - Auto-anticorps lymphocytoxiques (LCAbs) du type IgM ont été identifiés dans des patients avec des cas limites de lèpre tuberculeuse (BT) et de lèpre lépromateuse (BL) avec des réactions du Type I (I), et aussi dans des patients avec lèpre lépromateuse avec des réactions d'érythème lépreux noueux (ENL). La disminution observée dans l'activité lymphocytotoxique (LCA) en présence des plaquettes nous a mené à déterminer si les LCAbs avaient des spécificités pour des déterminants de la classe I du système majeur d'histocompatibilité. L'absorption des sérums LCA-positifs avec des plaquettes, méthode utilisée traditionellement pour épuiser les anticorps lymphocytotoxiques spécifiques à la classe I, a réduit la LCA vers des cellules-cible autologues et aussi allogéniques. Cela a été le cas avec tous les sérums LCA-positifs de tous les patients de différents groupes (dans le groupe BT du système autologue, $p < 0{,}01$; dans tous les autres groupes

de patients, p <0,001). L'introduction de B-2m dans les essais de cytotoxicité a seulement réduit légèrement la LCA en l'utilisant à hautes concentrations (5 mg/ml). Un antisérum anti-MHC classe I qui bloquait l'activité lytique des sérums classifiants des tissus de la classe I n'a pas réduit l'activité cytotoxique. Les données indiquent que, bien que les LCAbs sont absorbés par des plaquettes, ils ne montrent pas de spécificité vers les antigènes MHC classe I. Il reste donc à identifier l'auto-antigène reconnu par ces auto-anticorps.

La especifidad de los autoanticuerpos (LCAbs) linfocitotóxicos presentes en los sueros de pacientes con lepra

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Resumen - Se han descubierto autoanticuerpos linfocitotóxicos (LCABs) de tipo IgM en pacientes con reacciones del Tipo I (I) con casos inciertos de lepra tuberculoide (BTL) y casos inciertos de lepra lepromatosa (BLL), y también en pacientes con lepra lepromatosa (LL) con reacciones de eritema leproso nudoso (ENL). La disminución observada en la actividad linfocitotóxico en presencia de plaquetas nos llevó a intentar establecer si los LCAbs tenían actividades específicas hacia los determinantes de la clase I del sistema mayor de histocompatibilidad (MHC). La absorción de sueros LCA-positivos con plaquetas, método tradicionalmente utilizado para agotar los anticuerpos linfocitotóxicos específicos a la clase I, disminuyó la LCA hacia células-blanco autólogas y también alogéneas. Este fue el caso con todos los sueros LCA-positivos de los pacientes de cada grupo (en el grupo BT del sistema autólogo, p >0,01; en todos los demás grupos de pacientes, p <0,001). La introducción de B-2m en los ensayos de citotoxicidad sólo redujo ligeramente la LCA al ser utilizado en altas concentraciones (5mg/ml). Un antisuero anti-MHC clase I que impedía la actividad lítica de los sueros determinantes de tejidos de la clase I no inhibió la actividad linfocitotóxica. Estos datos sugieren que, mientras que si son absorbidos por las plaquetas, la actividad de los LCABs no es específica a los antígenos del MHC de la clase I. Por lo tanto, queda por identificar el autoantígeno que reconocen estos autoanticuerpos.

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Transmission of viable *Mycobacterium leprae* by *Aedes aegypti* from lepromatous leprosy patients to the skin of mice through interrupted feeding

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Summary Female *Aedes aegypti* which took partial blood meals from the skin lesions of untreated lepromatous leprosy (LL) patients were then allowed to continue feeding on 72–96-hr-old Swiss albino suckling mice (Rockefeller strain). The bitten portion of skin was removed, divided into two parts and processed for the extraction of bacilli by two different methods using chloroform and petroleum ether. The proboscis of some of the fed mosquitoes was dissected out and examined for viable bacilli (stained by fluorescein diacetate and ethidium bromide) and acid-fast bacilli (AFB). Out of 50 probosces dissected 45 were found positive for AFB, with bacillary counts ranging up to 246 (average 40·20 ± SD 41·80) per proboscis. The average percentage of viable bacilli (green solid) in the probosces immediately after feeding on LL patients was 43·90 and thereafter it decreased gradually to 3 on the seventh day. In the petroleum ether extract of mouse skin viable bacilli were observed in numbers up to 37 (average 15·25 ± SD 10.25) per smear. The number of fluorescing bacilli (green and red) correlated with the total number of AFB.

Introduction

Little is known about the mode of transmission of leprosy by blood sucking arthropods although leprosy bacilli (*Mycobacterium leprae*) are able to persist for several days in the gut and mouth parts and on the legs of mosquitoes, flies, bed bugs, etc.[1–2] Under experimental conditions the possibility of transfer of acid-fast bacilli (AFB) from lepromatous leprosy (LL) patients to mouse footpads by *Aedes aegypti* mosquitoes has been suggested by earlier workers.[3] Acid-fast bacilli were also demonstrated in the probosces of *Ae. aegypti* up to 156 hr after feeding on LL patients.[4] However, the viability of the transferred organisms and the survival period of viable bacilli within the mosquito proboscis have not been tested.

The present work quantifies viable *M. leprae* in the probosces of *Ae. aegypti* from 0–9

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days after blood feeding on LL patients and attempts to find out whether, through interrupted feeding, viable *M. leprae* can be transferred mechanically from dermal lesions of LL patients to the skin of mice.

Materials and methods

PATIENTS

All the 25 LL patients were volunteers attending the out-patient clinics of the Calcutta School of Tropical Medicine. Diagnosis was based on clinical examination and microscopic observation of skin smears for AFB. Patients were not given any anti-leprosy treatment before the experiments.

REARING AND FEEDING OF MOSQUITOES

Colonies of *Ae. aegypti* were established in the laboratory under sterile conditions according to the method described by Saha *et al.*[5] Laboratory reared 5- to 8-day-old *Ae. aegypti* adult females starved overnight were allowed to feed for 40 to 140 seconds on the skin lesions of LL patients (with a Bacillary Index of 3 to 4 on the Dharmendra scale)[6] using inverted glass tubes with mouths covered with cotton net cloth. Feeding was interrupted before a complete blood meal had been taken and the mosquitoes were placed in the dorsal skin of Swiss albino suckling mice (Rockefeller strain, Laboratory bred, 72- to 96-hr-old reared under sterile conditions) to complete their blood meals 1 hr after the initial feeding.

Twelve suckling mice were used for feeding experiments and each mouse was bitten by 6–10 infected mosquitoes. Similarly for the control experiment the mosquitoes fed on normal subjects were allowed to bite suckling mice.

EXTRACTION OF BACILLI

Two to four slit-skin smears from tissue fluid of dermal lesions of each LL patient were taken on a glass slide, air dried and fixed by single flaming. For extraction of bacilli from suckling mouse skin, the bitten portion of the skin was removed within 2 hr of feeding and divided into two parts. One part was minced, homogenized, and the bacilli were extracted by the chloroform extraction method[7] and stained for AFB on glass slides. For the other portion of the skin samples petroleum ether was used for extraction of bacilli. Tissue suspensions were prepared by homogenizing 1 part (gram) of tissue in 4 parts (millilitres) of ice cold 0·1 M potassium phosphate buffer, pH 7·2, in a 100 ml stainless steel Sorval Omni Mix tissue homogenizer cup at 15,000 rpm for 2 min on cracked ice. The tissue suspensions were transferred to sterile glass tubes and partitioned by adding 1·0 ml of petroleum ether to 0·1 ml of skin homogenate and mixing for 15–20 sec at room temperature. After 1–2 min to permit phase separation and large pieces of tissue to settle, bacterial smears were prepared from the petroleum ether layer (upper layer) by placing one or two drops of suspension on a microscope slide.

During each experiment the probosces of 4–8 mosquitoes fed on LL patients were individually dissected out under a dissecting microscope in a drop of normal saline on a glass slide within 2 hr of the infective bite. Further samples of mosquitoes were dissected every day for 9 days. Sterile conditions were maintained in all the above preparations throughout the study.

STAINING OF BACILLI

The slides were appropriately stained for AFB by the modified Ziehl–Neelson method and for fluorescing bacilli according to a procedure described by Kvach *et al.*[8,9] modified suitably as stated below. A mixture of fluorescein diacetate (FDA), 2 μg per ml and ethidium bromide (EB), 4 μg per ml, in 0·1 M potassium phosphate buffer, pH 7·2 was used for fluorescent staining. Two methods were employed for fluorescent staining of mouse skin extracts and human slit-skin smears. Petroleum ether partitioned cells made from infected suckling mouse skin were stained directly on the slides by placing 20–30 μl of FDA/EB working solution then covered with a cover glass and sealed with nail polish to prevent evaporation. The human slit-skin smears made from tissue fluid of dermal lesions of LL patient were stained in a coplin jar containing 45 ml of FDA/EB solutions for 15–20 min and subsequently gently rinsed by two successive washes of phosphate buffer. After air drying, the stained smears were mounted under a cover slip with Eukitt medium. All the slides were incubated at room temperature protected from light for 15–20 min to permit the *M. leprae* cells to stain. The probosces of infected mosquitoes were processed for AFB and fluorescing bacilli staining respectively using the same procedures. Appropriate control experiments were performed simultaneously by feeding the mosquitoes on normal healthy subjects.

AFB stained slides were examined under the oil immersion objective of a Zeiss Axioskop microscope equipped for differential interference contrast with magnification of 10x × 100x. The number of AFB was counted according to the methods described elsewhere in greater detail.[5,7,10,11,12] FDA/EB stained mycobacteria were observed under the oil immersion objective with incident, ultraviolet illumination equipped with a BP 390–420 exciter filter and red suppression filter. A total of 100–150 fields were examined on each slide. Green-fluorescing bacilli were considered to be viable and red-fluorescing bacilli considered to be dead. Beaded or bipolar green-fluorescing bacilli were considered as viable. Clumps of bacteria were excluded from counting. All the FDA/EB stained slides of probosces, mouse skin extracts or human slit-skin smears were subsequently stained by the modified Ziehl-Neelson method for determination of total AFB. The morphological indices (MI) were calculated for each slide.

Fifty and 35 probosces of infected *Ae. aegypti* were stained for AFB and fluorescing bacilli respectively. For the control experiment twenty and ten probosces of *Ae. aegypti* fed on normal human volunteers were stained for AFB and fluorescing bacilli. Twenty mice skin smears in each group (experimental and control) were examined for AFB and fluorescing bacilli.

Results and discussion

It was noted that both the fluorescent staining methods were satisfactory, green background fluorescence was minimal or absent, and the viable *M. leprae* cells stained rapidly with green fluorescence.

Table 1 shows the number of AFB and fluorescing bacilli in the probosces of *Ae. aegypti* after blood meals on LL patients. Out of 50 probosces dissected AFB were detected in 45 with bacillary counts ranging up to 246 per proboscis. Out of 35 probosces dissected, fluorescing bacilli were detected in 31 with bacillary counts ranging up to 121 per proboscis. Viable bacilli were detected within 2 hr of feeding in all 31 probosces with a

Table 1. Studies on the viability of *M. leprae* in the probosces of *Aedes aegypti* and skin extracts of suckling mice

Source of *M. leprae*	Total no. of AFB	Total no. of fluorescing (red & green) bacilli	Total no. of green-stained bacilli (viable)	Percentage of green-stained bacilli (viable)	Total no. of red-stained bacilli (non-viable)	Percentage of red-stained bacilli (non-viable)
Proboscis	40·20 ± 41·80 (0–246)	34·40 ± 29·34 (0–121)	17·17 ± 14·40 (0–53)	43·90 ± 20·60 (0–75)	17·20 ± 15·47 (0–68)	41·70 ± 19·90 (0–62)
Skin smear	25·00 ± 16·00 (0–59)	27·05 ± 14·86 (0–57)	15·25 ± 10·25 (0–37)	48·00 ± 20·40 (0–80)	11·80 ± 5·30 (0–21)	42·00 ± 18·80 (0–71)

* All values are given as mean ± SD and range (in parentheses) per proboscis or per skin smear.

bacillary count of green cells ranging up to 53 per proboscis. The average percentage of green solid bacilli immediately after feeding was 43·90, thereafter decreasing gradually to 6% and 3% on the sixth and seventh day after feeding respectively. No green bacilli could be detected in the proboscis on the eighth day. The percentage of red coloured solid bacteria increased steadily from the second day onwards. The survival of *M. leprae* for up to 4 days in the gut of mosquitoes has been reported earlier by Saha *et al.*[5]

Out of 20 smears made from 12 suckling mouse skin extracts and examined for AFB, 17 smears were found positive with a bacillary count of up to 59 per skin smear. In the 20 smears examined for fluorescing bacilli (viable and non-viable) 18 smears were found positive with bacillary count ranging up to 57 per skin smear. Petroleum ether extracts of suckling mouse skin showed up to 80% of green bacilli per skin smear. The remainder of the bacteria stained red (Table 1). The FDA/EB stained slit-skin smears of 20 LL patients showed 35–72% green stained *M. leprae*. The human skin smears from the same subject were simultaneously stained by the Ziehl–Neelson method, further confirmed the total number of bacilli as observed in FDA/EB stained smears.

The *in vitro* methods for the detection of AFB and for the identification and evaluation of *M. leprae* viability were simultaneously undertaken on 20 bacillary extracts obtained from mouse skin and 35 probosces of *Ae. aegypti*. The number of bacteria seen by the two methods showed significant correlation in skin smears ($r = 0{\cdot}95$, $df = 18$, $P < 0{\cdot}001$) as well as in probosces ($r = 0{\cdot}98$, $df = 33$, $P < 0{\cdot}001$). It is therefore concluded that the two staining methods provide a reasonable measure of the possibility of transfer of *M. leprae* to mouse skin through interrupted feeding by *Ae. aegypti*. Earlier studies have shown that FDA/EB method is a useful assay of bacillary viability with good correlation with the established mouse footpad model.[9,13,14] Furthermore, neither the proboscis of control unfed mosquitoes nor those of mosquitoes fed on normal human volunteers, nor mouse skin extracts bitten by control mosquitoes showed any AFB by either staining method.

The work of Narayanan *et al.*[3] suggested the possibility of mechanical transfer of AFB by arthropods. In their study, multiplication of the non-cultivable AFB, presumed to be *M. leprae* was demonstrated in four instances out of 208 mouse footpads examined after the footpads were bitten by *Ae. aegypti* previously fed on LL patients. Although the positive results obtained were too few to establish any clear conclusion about actual role of blood sucking arthropods in transmission of leprosy but their studies do show the occasional transfer of viable bacilli through interrupted feeding. The low rate of success could have resulted from the propensity of the *M. leprae* to provoke a chronic macrophage inflammation in the mouse footpad, susceptibility of inbred mice and growth kinetics, and immunological response of the mice resulting in failure of bacteria to

proliferate.[9,11,15,16] On the other hand minimal infective dose of *M. leprae* in mouse has been reported to be as low as 10 bacilli.[11] Hence, our results clearly indicate that the viable bacilli may be present in the probosces of *Ae. aegypti* in sufficient numbers after interrupted feeding on LL patients to initiate multiplication in mouse.

Mechanical transmission of viral disease, for example Rift valley fever, by way of interrupted feeding of mosquitoes has been reported by various investigators.[17] Similarly leprosy is likely to be mechanically transmitted to humans via interrupted feeding of mosquitoes. The transfer of viable AFB from LL patient to mouse skin by *Ae. aegypti* has been clearly demonstrated. Hence epidemiological significance of mechanical transfer of *M. leprae* through blood sucking arthropods should be kept in mind. However, the available findings do not permit us to make a statement on the infective dose for human based on mouse model data. More detailed studies on the actual role of mosquitoes in the transmission of leprosy are now warranted based on prolonged intervention trials of the effect of mosquito control on the leprosy transmission rate in order to prove that insects are a significant vector of leprosy.

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La transmission de Mycobacterium leprae par Aedes aegypti des patients de lèpre lépromateuse à la peau des souris à cause de d'une alimentation interrompue

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Sommaire - Des femelles de l'espèce Aedes aegypti qui ont pris des repas de sang partiels sur les lésions cutanées des patients de lèpre lépromateuse (LL) non traités, ont continué à s'alimenter sur des souris albinos en étape d'allaitement, de 72 à 96 heures d'age (race Rockefeller). La portion de peau piqué a été enlevé, coupé en deux parties, et traité pour l'extraction des bacilles par deux méthodes différentes: l'une à base de chloroforme et la deuxième à base d'éther de pétrole. Les trompes de quelques unes des moustiques alimentées ont été découpées et examinés pour la présence des bacilles viables (teintés avec diacétate de fluorésceine et bromure d'éthidium) et des bacilles acido-résistents (AFB). De 50 trompes éxaminées, 45 ont donné résultat positif pour AFB, avec comptes bacillaires jusqu'à 246 (compte moyenne de 40,20 ± écart type 41,80) par trompe. Le pourcentage moyen de bacilles viables (solide vert) sur les trompes juste après l'alimentation avec le sang de patients de LL était de 43,90 et à partir de ce point ce chiffre a baissé jusqu'à arriver à 3 au septième jour. Dans l'éxtrait de peau de souris à base d'éther de pétrole, un nombre maximum de 37 bacilles viables a été observé (compte moyenne de 15,25 ± écart type 10,25) par prélèvement. Le nombre de bacilles fluorescents (verts et rouges) correspondait avec le compte totale de AFB.

La transmisión de Mycobacterium leprae viables por Aedes aegypti de pacientes con lepra lepromatosa a la piel de ratones por alimentación interrumpida

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Resumen - Hembras de la especie Aedes aegypti que habían tomado parte de su alimento de la sangre de lesiones cutáneas de pacientes con lepra lepromatosa (LL) que no habían recibido tratamiento siguieron alimentándose sobre ratones albinos suizos lactantes (cepa Rockefeller) de 72 a 96 horas de edad. Se les quitó la porción de piel que había sido mordida, se dividió en dos partes y fue tratada para la extracción de bacilos utilizando dos métodos distintos: uno a base de cloroformo y otro a base de éter de petróleo. Se disecaron las probóscides de algunos de los mosquitos alimentados y se examinaron para la presencia de bacilos viables (teñidos con diacetato de fluoresceína y bromuro de etidio) y de bacilos acidoresistentes (AFB). De 50 probóscides desecadas 45 dieron resultado positivo para la presencia de AFB, con recuentos de bacilos llegando hasta los 246 (con media de 40,20 ± desviación estándar de 41,80) por probóscide. El porcentaje medio de bacilos viables (sólido verdoso) en las probóscides inmediatamente después de alimentarse sobre pacientes con LL era de 43,90 y a partir de ahí disminuyó gradualmente hasta llegar a 3 en el séptimo día. En el extracto de éter de petróleo de piel de ratón se detectaron bacilos viables hasta un máximo de 37 (con media de 15,25 ± desviación estándar de 10,25) por frote. El número de bacilos con fluorescentes (verdes y rojos) correspondía al número total de AFB.

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Treatment of leprous neuritis by neurolysis combined with perineural corticosteroid injection

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Summary A study on leprous neuritis, involving the ulnar nerve, was carried out on 39 patients. The evaluation of nerve function was done before and after treatment by a score chart. Patients were divided into two groups. Group A (21 patients) was subjected to neurolysis only, and group B (18 patients) were given the combined treatment of neurolysis and perineural corticosteroid injection at the same time as neurolysis and subsequently at the end of the second and third weeks. In group B, 83·3% of patients showed 10% or more increase in the post-treatment score in comparison with 57·1% in group A. Improvement was more marked in paucibacillary cases and when the duration of nerve involvement was less than 3 months. Patients with short segments of nerve involvement with minimal thickening had better recovery. This procedure was observed to be simple, easy and well accepted by the patients, with a marked beneficial effect.

Introduction

Neuritis in leprosy is a common complication. The pathological changes in the nerve are due to invasion of the nerve by *Mycobacterium leprae* leading to inflammatory changes with cellular infiltration. Inflammation leads to oedema inside the nerve, thus producing increased pressure, and the blood supply is compromised. The progress of inflammatory process and the resolution of oedema lead to increased fibrosis. In the initial stages these changes are reversible, provided relief is obtained, otherwise it will lead to permanent nerve damage. The bacillary load has of course to be diminished and the immunological tissue reaction is to be combated by suitable medication.[1,2] The other factor in neuritis is the compression of the nerve at the common anatomical sites, where the nerve distally passes through a rigid fibro-osseous tunnel, producing trauma by compression, friction and forced elongation leading to irreversible nerve damage.[1,3]

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The southern part of Orissa, India, where this study was carried out, is an endemic zone for leprosy. Leprosy patients in different stages of its complications are being reported although various reconstructive surgical procedures had been tried to correct the deformities in leprosy, its results were variable. In the present work prevention of complications in neuritis and resultant complications of the nerve affected were tried by surgical decompression (neurolysis) of the nerve combined with perineural corticosteroid injection.

Many conservative methods like perineural or intraneural injections of hydrocortisone, lignocaine and hyalase, application of heat in the form of hot compress, diathermy or waxbaths and ethylchloride spray had been tried in the past and its result were variable.[4–7] Surgical decompression (neurolysis) of the affected nerve had been advocated by many and the results were encouraging.[8–12] Neurolysis (external and internal) is believed to act by removing external factors and allowing release of oedema and compression. Corticosteroids are believed to act by absorption of oedematous fluid and by its anti-inflammatory properties.[13] Better results may be obtained by combining corticosteroids with neurolysis. Since nerve involvement is segmental, local corticosteroid injection (Triamcinolone acetonide) was preferred over oral corticosteroid therapy to avoid systemic complications of corticosteroids and to reduce fibrosis after neurolysis. By this method higher concentration is achieved at the site of injection, hence adequate effect is obtained. Simultaneous use of antileprosy drugs is essential to control the growth of the organism.

Methods

SELECTION OF PATIENTS

Patients on MDT as recommended by WHO (rifampicin, dapsone and clofazimine) and presenting with features of neuritis (pain, tenderness, sensory or motor deficit) were treated with prednisolone 30 mg per day in divided doses. It was gradually reduced and stopped over 3 weeks. Those patients who did not respond to prednisolone therapy, had inadequate response, or developed features of neuritis shortly after the cessation of prednisolone therapy were selected. Among them those with ulnar nerve involvement for less than 6 months and without atrophy of hand muscle were included in the study. All the patients were followed up for 1 year after treatment and were evaluated. Patients with multiple nerve involvement and children below 10 years of age were excluded from this study because evaluation is difficult.

MATERIALS

Patients were divided into two groups and were matched for age, sex, type and duration of leprosy. In group A 21 patients underwent neurolysis only and in group B 18 patients underwent neurolysis with perineural corticosteroid injections. The results of both groups were assessed and compared with their pre-treatment status.

PROTOCOL FOR EVALUATION OF NERVE DAMAGE

The protocol followed for this study was prepared as per the recommendation of the 'Workshop on neuritis' held at Scheiffelin Leprosy Research and Training Centre, Karigiri, India.[14]

Table 1. Protocol for evaluation of nerve damage

Sl no.	Test	Max score
1	Touch (nylon thread)	12
2	Static two-point discrimination	9
3	Moving two-point discrimination	9
4	Direction of movement	9
5	Tuning-fork test	3
6	Pin-prick test	9
7	Voluntary muscle power test	10
8	Nerve condition velocity	20
9	Nerve pain	3
10	Nerve tenderness	3
11	Stretch test	3
12	Compression test	3
Total score		93

OPERATIVE TECHNIQUE

Patients were operated on under local infiltration anaesthesia without the application of a tourniquet. The ulnar nerve was exposed up to 7 cm in the arm from the medial epicondyl and 3 cm in the forearm below the medial epiconyl. Epineurotomy was done by two longitudinal incisions on the epineurium. Damage to large blood vessels on the nerve were avoided. The wound was closed in a single layer. A compress was applied.

PERINEURAL CORTICOSTEROID INJECTION

Triamcinolone acetonide 20 mg with 1500 iu of hyaluronidase was injected around the thickened nerve after neurolysis and was repeated at the end of the second and third weeks.

FOLLOW UP

Patients were followed up at the end of 3 weeks, 3 months and 1 year following neurolysis for any complications of either operations or corticosteroid injections. Recovery from nerve damage was also evaluated.

OBSERVATIONS

Age, sex, type of leprosy, presenting features, duration of nerve involvement, pre-operative and post-operative scores were recorded in both the groups.

Results

Patients were evaluated at the end of 1 year of follow-up. Improvement after treatment in score by 10% or more was marked in 15 out of 18 patients (83·3%) in group B compared

Table 2. Patients treated with neurolysis only (group A)

Sl. no.	Age (years)	Sex	Type of leprosy	Duration of nerve involvement (months)	Clinical presentation			Score		Recovery score	Recovery (%)
					Thickened nerve	Tenderness	Pain	Pre-treatment	Post-treatment		
1	14	F	TT	less than 3	+	+	+	65	83	18	19·3
2	14	M	TT	less than 3	+	+	+	67	82	15	16·1
3	15	F	TT	less than 3	+	+	+	35	77	42	45·1
4	19	M	TT	less than 3	+	+	+	51	70	19	20·4
5	13	M	BT	less than 3	+	+	+	46	77	31	33·3
6	15	M	BT	less than 3	+	+	+	63	79	16	17·2
7	16	F	BT	less than 3	+	+	+	57	63	6	6·4
8	24	F	TT	3–6	+	+	+	17	29	12	12·9
9	18	M	TT	3–6	+	+	+	75	86	11	11·8
10	28	M	TT	3–6	+	+	+	30	65	35	37·6
11	19	M	BT	3–6	+	+	+	16	33	17	18·2
12	33	M	BT	3–6	+	+	+	71	86	15	16·1
13	21	M	BT	3–6	+	+	+	49	75	26	27·9
14	38	F	BT	3–6	+	+	−	26	32	6	6·4
15	22	M	BB	3–6	+	+	+	41	25	−16*	−17·2
16	50	M	BB	3–6	+	+	+	15	17	2	2·1
17	37	M	BL	3–6	+	+	−	14	15	1	1
18	19	M	BL	3–6	+	+	+	43	51	8	8·6
19	19	F	BL	3–6	+	−	−	63	71	8	8·6
20	35	M	BL	3–6	+	+	+	44	51	7	7·5
21	33	F	LL	3–6	+	−	−	44	50	6	6·4

* Deteriorated.
+, present; −, absent.

Table 3. Patients treated with neurolysis and perineural corticosteroid injection (group B)

Sl. no.	Age (years)	Sex	Type of leprosy	Duration of nerve involvement (months)	Clinical presentation			Score		Recovery score	Recovery (%)
					Thickened nerve	Tenderness	Pain	Pre-treatment	Post-treatment		
1	15	F	TT	less than 3	+	+	+	48	78	30	32·2
2	19	M	TT	less than 3	+	+	+	53	81	28	30·1
3	17	M	TT	less than 3	+	+	+	77	87	10	10·7
4	13	M	BT	less than 3	+	+	+	58	77	29	31·1
5	19	F	BT	less than 3	+	+	+	39	76	37	39·7
6	32	F	TT	3–6	+	+	+	60	81	21	22·5
7	14	F	TT	3–6	+	+	+	59	81	22	23·6
8	40	F	TT	3–6	+	+	+	64	79	15	16·1
9	22	F	TT	3–6	+	+	+	16	59	43	46·2
10	24	M	TT	3–6	+	+	+	48	81	33	35·4
11	22	M	BT	3–6	+	+	+	27	59	32	34·4
12	18	M	BT	3–6	+	−	−	50	76	26	27·9
13	19	M	BT	3–6	+	+	+	14	49	35	37·6
14	43	M	BB	3–6	+	+	−	34	16	−18*	−19·3
15	18	M	BL	3–6	+	−	−	46	57	11	11·8
16	21	M	BL	3–6	+	+	+	66	71	5	5·3
17	32	M	BL	3–6	+	−	−	43	50	7	7·5
18	20	M	LL	3–6	+	+	−	11	39	28	38·1

* Deteriorated.
+, present; −, absent.

with 12 out of 21 patients (57·1%) in group A. Improvement in score within 10% was observed in 8 out of 21 patients in group A compared with 2 out of 18 patients in group B. One patient in each group had decreased in score by more than 10% and had nerve involvement for 3–6 months with borderline leprosy (BB). When the nerve involvement was less than 3 months, better results were obtained in both groups, i.e. 6 out of 7 patients in group A and all 5 patients in group B had shown an improvement of score by 10% or more. In patients with nerve involvement for 3–6 months, 6 out of 14 patients (42·8%) in group A and 10 out of 13 patients (76·9%) in group B had shown improvement in score by 10% or more. In group A 7 out of 14 patients (50%) and in group B 2 out of 13 patients (15·3%) have shown improvement in score within 10% when the nerve involvement was for 3–6 months.

Discussion

Leprosy is primarily a disease of the peripheral nerves. Nerve involvement is complex. Inflammation with cellular infiltration and oedema lead to swelling of the nerve and compression of the nerve fibres. Neurolysis relieves the nerve from compression and gives the best result before irreversible nerve damage has occurred.[15] All the patients were clinically quiescent during the treatment and were on multidrug therapy. Seven patients had neuritis at the time of detection of disease. The remainder of the patients had the disease for 6 months to 2 years before they developed neuritis. The patients followed-up for 1 year were being reported because patients not showing an improvement within 1 year after surgery were not likely to respond.[16]

In group A improvement in score by 10% or more was observed in 57·1% of patients. Similar results have been observed by Vaidyanathan & Vaidyanathan[8] and Palande,[12] but the results were more gratifying in patients undergoing surgical decompression with perineural corticosteroid injection (group B), and improvement in score by 10% or more was marked in 83·3%. Better results in this group could be due to the additional benefit of corticosteroid, which acts by its anti-inflammatory properties, reducing oedema and fibrosis. This result could not be compared due to the lack of published data of similar type.

Relief from pain and tenderness were marked in all the patients of both groups but occurred earlier in group B. Recovery was better when the duration of nerve involvement was short, nerve function deficit was less, and in paucibacillary cases. Patients with a short segment of nerve involvement and minimal thickening had a better recovery. Patients with positive stretch test and compression test had severe nerve function deficit and showed poor recovery after treatment.

Only 2 patients who deteriorated had a lot of fibrous adhesions around the nerve and thickening of the nerves was more marked. Sharp dissection was required to free them from surrounding tissues excluding the nerve bed. Perineural corticosteroid injecctions were not repeated in these 2 patients showing no improvement to maintain a uniformity of therapy.

Though we strictly followed the protocol, more stress was given on touch sensation and nerve conduction velocity. These are reproducible.[17] Motor nerve conduction velocity is more accurate and gives a better picture of how the nerves are affected.

Under the coverage of specific treatment of the disease, progressive nerve damage

could be prevented by neurolysis. The beneficial effect of surgery is further accentuated by local corticosteroid injections at suitable intervals. We would recommend combined treatment of neurolysis with perineural corticosteroid injection, when the nerve involvement is of a short duration. More emphasis should be given to the early detection of neuritis and referral of these patients to suitable hospitals for treatment. Patients properly selected would benefit by this simple, inexpensive and easy procedure. However, our series is small and awaits more extensive study.

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Traitement de la névrite lépreuse par la neurolyse en combinaison avec des piqûres périneurales de corticoides

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Sommaire - Une étude a été menée, concernant le nerf cubital, sur la névrite lépreuse chez 39 patients. La fonction nerveuse a été évaluée avant et après le traitement par un tableau de marque. Les patients ont été séparés en deux groupes. Les 21 patients du groupe A ont été soumis à une neurolyse seulement, et les 18 patients du groupe B ont reçu un traitement combiné comprenant une neurolyse et des piqûres périneurales de corticoides au même temps que la neurolyse et aussi à la fin de la seconde et la troisième semaine. 83,3% des patients du groupe B ont montré une augmentation de 10% ou plus dans leur score après traitement contre 57,1% dans le groupe A. L'amélioration a été plus marquée chez des cas paucibacillaires, et dans les cas ou il y avait moins de trois mois que le nerf avait été attaqué. La récupération a été meilleure chez des patients avec segments courts de nerf attaqués avec une augmentation minimale de grosseur. Cette procédure s'est montrée simple, facile, et bien acceptée par les patients, ayant un éffet très favorable.

El tratamiento de la neuritis leprosa mediante un programa combinado de neurólisis e inyecciones perineurales de corticosteroides

M C DANDAPAT D H SAHU, L M MUKHERJEE, C PANDA Y A S BALIARSING

Resumen - Se llevó a cabo un estudio, basado en el nervio cubital, sobre la neuritis leprosa en 39 pacientes. Se evaluó la función nerviosa antes y despues del tratamiento mediante una tabla de puntuaciones. Los pacientes se dividieron en dos grupos. El grupo A, compuesto de 27 pacientes, fué sometido únicamente a una neurólisis y los 18 pacientes del grupo B recibieron un tratamiento combinado de neurólisis e inyección perineural de corticosteroides, repitiendose solo la inyección al fin de la segunda y la tercera semana. El 83,3% de los pacientes del grupo B mostraron un aumento de un 10% o más en su puntuación despues del tratamiento, comparado con un 57,1% en el grupo A. Fué más destacada la mejoría en casos paucibacilares, y cuando el periodo que llevaba afectado el nervio no excedía los tres meses. Aquellos pacientes con segmentos cortos de nervio afectados y con aumento mínimo de grosor se recuperaron mejor. Este procedimiento mostró ser simple, fácil y fué bien acogido por los pacientes, consiguiendo un efecto benéfico notable.

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Residual sight-threatening lesions in leprosy patients completing multidrug therapy and sulphone monotherapy

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Summary An analysis of data derived from standardized surveys of the ocular findings in cross-sections of the leprosy population in 23 areas is presented. It shows that 24·3% of the patients completing multidrug therapy and 32·9% of those completing sulphone monotherapy have on-going eye problems which have the potential to lead to blindness or severe visual impairment. Most of the ocular complications involve the lids, cornea and anterior uveal tract, but a significant proportion of patients had cataract threatening vision.

If left unsupervised, many of these patients will develop major visual problems which could have been avoided. It is important that completion of systemic leprosy therapy should not be regarded as a guarantee that the eyes are safe, and that regular ocular supervision should be continued long after the patient has been classified as 'cured'.

Introduction

Leprosy is an important disease in many developing countries and its ocular complications contribute significantly to world blindness statistics. In a recent multicentre study between 4 and 7% of leprosy patients were found to be blind and between 6 and 10% had severe visual impairment.[1]

Four main mechanisms may cause blindness or severe visual impairment:

1 Lagophthalmos leading to exposure keratopathy.
2 Reduced or absent corneal sensation leading to corneal ulceration.
3 Acute or chronic iridocyclitis.
4 Cataract.

Lagophthalmos and corneal hypoesthesia may develop in all types of leprosy, whereas iris involvement occurs primarily in multibacillary disease. Cataract may be secondary to anterior segment damage, particularly iridocyclitis, but in most regions where leprosy is endemic, cataract is the commonest cause of blindness in the general community and its association with leprosy is often coincidental.

In many countries leprosy patients now receive multidrug therapy (MDT) according to recommendations by the WHO in its report on chemotherapy of leprosy for control

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programmes.[2] The dosage of drug combinations and the duration of treatment have been established, and the WHO has set down guidelines for the registering of patients and also for their discharge from care after completion of MDT. It should be recognized however that ocular complications of leprosy may occur long after a so-called 'cure' has been achieved, some may be undetectable except by sophisticated ophthalmic examinations, and damage sustained to the eyes during the early stages of the disease can progress and may not be reversible.

The purpose of this paper is to draw attention to the fact that a significant proportion of patients who have completed their therapy and are therefore eligible for discharge have ongoing eye problems which have the potential to lead to blindness. Much of this blindness is preventable provided that there is continued ophthalmic supervision and appropriate therapy.

Present study

Since 1983 LEPRA has organized a world-wide survey on the ocular complications of leprosy in randomly selected cross-sections of the leprosy population. The protocol includes the recording of details of the disease, its duration, status and therapy as well as a simple objective examination of the lids and anterior parts of the eye—the structures affected by leprosy.[2] Over 3500 patients have been recruited into the study and examined under standardized conditions in 33 centres scattered throughout the world.

Following the institution of MDT in 1982 patients began to be released from control in the mid-1980s and their numbers continue to increase as more centres follow the WHO guidelines.

Since 1986 a total of 2321 patients have been examined in 23 centres (Table 1); 524 had completed their course of therapy and had negative skin smears. Of these 354 (15·2%) had completed MDT and 170 (7·3%) had completed monotherapy with sulphones. These two groups of patients were examined in order to determine the prevalence of blindness, severe visual impairment and potentially sight-threatening lesions (PST).

Eye problems were regarded as significant if they were thought likely to lead to blindness or severe visual impairment. The concept of PST lesions, originally introduced by Lamba *et al.*[4] has been modified slightly. They are a particularly important feature of the disease, since they are often amenable to relatively simple preventive therapy. Routine supervision of continued ocular therapy or measures to prevent blindness may not

Table 1. Centres studied in LEPRA surveys since 1986

South America	Brazil, Bolivia (2)
Africa	Tanzania, Ethiopia, Kenya (2), Nigeria, Malawi
South-East Asia	Thailand (2), Hong Kong
South Pacific	Tonga, Fiji, Solomon Islands, Australia
Indian sub-continent	
North*	Simla, Bihar, Nepal, Bangladesh
South*	Ahmedabad, Maldive Islands, Trivandrum

* For the purposes of this study the Indian sub-continent was divided into north and south by the Tropic of Cancer.

however be available in many areas of the world, and it is important therefore for leprologists to be able to anticipate ocular problems by identifying those patients at risk.

Ocular complications of leprosy have a variety of manifestations and many are easily detected by a simple and systematic eye examination and can be treated effectively by nonophthalmologists.[5] The following components of the routine standardized eye examination in the 524 patients completing MDT and monotherapy have been recorded and analysed:

1 *Blindness and severe visual impairment*

Using a standard Snellen's E Chart at 6 m, patients with corrected visual acuity of less than 3/60 in the better eye were recorded as *blind*. Those with acuity less than 6/60 in the better eye were recorded as having *severe visual impairment*. All causes of blindness were included in these two groups.

2 *Lid involvement*

Significant lid involvement was recorded when there was lagophthalmos with incomplete corneal cover on forced lid closure. Under these circumstances the cornea is at risk from trauma and infection, especially if corneal sensation is reduced or absent.

3 *Corneal involvement*

Significant corneal involvement was defined as absent corneal sensation or corneal opacities reducing vision to below the level of 6/36. Corneal opacities are not reversible and are more likely to progress with age. In addition a hypaesthetic and already compromised corneal epithelium renders the eye more susceptible to recurrent damage, which in an insensitive eye, may not be noticed by the patient at a time when it could be treated.

4 *Iris involvement*

Significant iris involvement was recorded in those patients with either a non-reacting pupil less than 2 mm in diameter or an irregular or eccentric pupil with detectable synechiae. In lepromatous leprosy, chronic iris changes with progressive miosis and unreacting pupils is a common cause of visual disability and tends to be overlooked since it is often symptomless and requires sophisticated instrumentation, such as a slit-lamp, for diagnosis. An irregular pupil with synechiae indicates a previous episode of acute iritis, carrying the risk of further attacks, secondary glaucoma or cataract. An eccentric pupil may also be a feature of ciliary body involvement.

5 *Cataract*

Cataract was considered to be significant if the visual acuity was less than 6/36 and there were visible lens opacities or an absent red reflex. This is the commonest cause of blindness in areas where leprosy is endemic. It may be difficult to diagnose in the presence of a small pupil, but since damage to the post-equatorial segment of the eye rarely occurs in leprosy,

diminished vision with an absent red reflex is more than likely to be due to cataract and therefore represents a developing problem that can only be resolved by surgery.

A patient with one of the above conditions was considered to have a potentially sight-threatening lesion irrespective of whether one or both eyes were involved. Many patients had multiple problems of the lids and eye and when there was more than one complication, the one with the most affect on vision was recorded. Patients who had cataract without any other signs of ocular leprosy were recorded separately.

Results

Cross-sections of 23 leprosy populations were studied and the groups divided into six geographic regions shown on Table 1. In Bolivia, Kenya and Thailand more than one survey has been undertaken, but the areas chosen have always been geographically distant from each other so that no overlap of patients has occurred.

AFFECTED PATIENTS

Tables 2 and 3 show the analysis of patients who had completed MDT and sulphone

Table 2. Analysis of patients who had completed multidrug therapy

Region	Total examined	Completed therapy	Affected patients	Visual acuity	
				< 3/60	< 6/60
South America	223	1	0 (0%)	0	0
Africa	509	45	9 (20·0%)	3	4
South-East Asia	266	66	18 (27·3%)	2	2
South Pacific	285	13	4 (30·7%)	0	0
North India	610	32	3 (9·4%)	0	0
South India	428	197	52 (26·4%)	19	25
Total	2321	354 15·2%	86 24·3%	24 6·8%	31 8·8%

Table 3. Analysis of patients who had completed sulphones

Region	Total examined	Completed therapy	Affected patients	Visual acuity	
				< 3/60	< 6/60
South America	223	15	1 (6·7%)	0	0
Africa	509	52	25 (48·1%)	0	0
South-East Asia	266	29	9 (31·0%)	1	2
South Pacific	285	36	13 (36·1%)	3	3
North India	610	13	4 (30·8%)	0	1
South India	428	25	4 (16·0%)	4	4
Total	2321	170 7·3%	56 32·9%	8 4·7%	10 5·9%

monotherapy and demonstrate that there was a considerable variation in the different regions studied. The percentage of those off MDT who were found to have significant ocular involvement also varied from 30·7% in the South Pacific area to 9·4% in North India with an average of 24·3% overall. In patients completing sulphones the overall average of those with sight-threatening conditions was 32·9% with a variation of from 6·7% in South America to 48·1% in Africa.

BLINDNESS AND SEVERE VISUAL IMPAIRMENT

Several patients in this series were already blind or had severe visual impairment—6·8% blind and 8·8% with severe visual impairment in the group off MDT, and 4·7% blind and 5·9% with severe visual impairment in the group completing sulphone monotherapy. (In this analysis the blind patients are included in the numbers of those with severe visual impairment.)

SIGHT-THREATENING LESIONS

The patients in this study were divided into two main groups according to the WHO modification of the Ridley—Jopling classification:[6]

1 Paucibacillary (PB)—where skin smears were negative at all sites. This included patients considered indeterminate, tuberculoid (TT) and borderline tuberculoid (BT) under the Ridley–Jopling classification.
2 Multibacillary (MB)—where skin-smears were positive. These included mid-borderline (BB), borderline lepromatous (BL) and lepromatous (LL) patients.

Eighty-six patients completing MDT were considered to have sight-threatening lesions: 37·2% were found to have significant lid problems, 39·5% had evidence of corneal disease threatening sight, and 23·3% had complications relate to iridocyclitis (Table 4). Not surprisingly over 60% of these patients had multibacillary leprosy which is known to be associated with a higher prevalence of eye complications than other forms.[7]

In 56 patients who had completed sulphone therapy and had significant ocular involvement, 41·1% had problems related to lid function, 42·8% had evidence of corneal disease and 16·1% had iris involvement (Table 5). In this group the percentage of affected patients with multibacillary and paucibacillary disease were comparable.

Table 4. Total affected off MDT = 86

	Total	Lids	Cornea	Iris
MB	52 (60·5%)	17	20	15
PB	30 (34·9%)	15	14	1
Unknown	4 (4·6%)	0	0	4
Total	86	32	34	20
		37·2%	39·5%	23·3%

Table 5. Total affected off sulphones = 56

	Total	Lids	Cornea	Iris
MB	25 (44·6%)	7	11	7
PB	22 (39·3%)	11	10	1
Unknown	9 (16·1%)	5	3	1
Total	56	23 41·1%	24 42·8%	9 16·1%

CATARACT

A separate analysis of the prevalence of cataract without any ocular signs of leprosy showed that, out of the 354 patients who had completed MDT, 66 (18·6%) had lens opacities reducing the visual acuity to below the level of 6/36. Multibacillary patients formed 75·7% of this group and paucibacillary 24·3%. Out of the 170 patients who had completed sulphone monotherapy a total of 28 (16·4%) had a similarly reduced level of visual acuity due to cataract. Multibacillary patients formed 42·9% of the group, paucibacillary 46·4% and in 10·7% the type of leprosy was unknown.

Discussion

In 1982 the WHO Study Group published its recommendations for chemotherapy in leprosy control programmes. This report was stimulated by the recognition of poor drug compliance in many patient populations and the increasing emergence of primary and secondary dapsone resistance in all forms of the disease.

The recommended therapeutic regime for PB patients was dapsone 100 mg daily, unsupervised, plus rifampicin 600 mg once monthly, supervised for 6 months. All therapy was discontinued after this course. The regime for MB patients was dapsone 100 mg daily plus clofazimine 50 mg daily, unsupervised, plus rifampin 600 mg and clofazimine 300 mg once monthly, supervised. This regime should be continued for at least 2 years and preferably until the patient became smear-negative, when anti-leprosy treatment could be stopped.

The geographic variations in numbers of patients completing treatment in this study reflect local policies on the timing of the commencement of MDT, and it is to be expected that over the next few years many more patients will fall into this category in all areas.

No specific guidelines for ophthalmic supervision after completion of MDT were set up, although it was recommended that MB patients remain within control for a further five years and PB patients for two years. However in practice many patients may be taken off the leprosy register and discharged completely from further care. With the recognition that completion of therapy holds no guarantee of total cure or safeguard against further relapses, and that a considerable number of patients will have residual disability problems, several centres are evolving 'care after cure' policies. But in many others, where staffing levels among trained leprosy workers may be inadequate, de-registration and release from control is the accepted policy after completion of MDT or monotherapy.

The prevalence of blindness and severe visual impairment in both these groups of patients completing therapy conform with the more general prevalence studies for cross-sections of leprosy populations previously reported.[8] There is a higher prevalence of

blindness (6·8%) and severe visual impairment (8·8%) in the group off MDT than in the group off sulphone therapy, where blindness was found in 4·7% and severe visual impairment in 5·9%. The difference between these two sets of figures reflect the fact that the majority of patients in the MDT group had the multibacillary form of the disease and were therefore more likely to have serious eye problems. In addition many of the old relapsed dapsone-resistant patients may have been switched to MDT because of repeated reactions which also carry an increased risk to vision. In the sulphone group by contrast there was a more even distribution between MB and PB patients, the latter being less susceptible to ocular damage.

From the ophthalmic point of view there are a number of conditions which, if present in the eye and not monitored or treated carefully, may well lead to blindness. Impairment of lid closure, especially if associated with poor corneal sensation, can lead to corneal ulceration, opacification and even perforation. This can be prevented by adequate attention to lid care and corneal protection. In this study lid and corneal damage were each seen in over a third of the patients completing MDT and sulphone monotherapy and there was no statistical difference between MB and PB cases. An examination of lid function and corneal sensation would therefore seem to be essential in all patients about to be discharged from control.

The presence of active or residual iris disease may render an eye more susceptible to acute and chronic glaucoma and secondary cataract, and an asymptomatic chronic low-grade iridocyclitis may persist in patients with lepromatous leprosy long after they have been classified as cured. The latter will eventually produce a miotic pupil, resistant to conventional dilatation, and often associated with a profound ocular hypotension which may eventually lead to a phthisical eye. Damage to the iris and ciliary body occurs almost exclusively in MB cases and was seen in about a fifth of patients completing therapy. Many of the clinical signs are difficult to detect without sophisticated instruments and experience and the condition is therefore likely to be underdiagnosed, especially as vision may not be significantly affected until late in the disease. Leprosy workers should therefore be alert to this risk and should pay special attention in MB cases to pupil changes such as alterations in its size, shape and reactions.

Cataract itself is a common condition in all of the areas studied and is the major cause of blindness. It occurred in the absence of any ocular signs of leprosy in 18·6% of patients completing MDT of whom 75% had multibacillary disease. In those patients completing sulphone monotherapy significant cataract was found in 16·4%, but the ratio between multibacillary and paucibacillary patients was almost even. In the absence of any other eye signs these cataracts must be regarded as coincidental, but the high prevalence of the condition in MB cases completing MDT is an interesting observation which if confirmed in future studies reopens the question as to whether 'leprosy' cataracts can occur and merits further investigation.[9] Sadly, because of the stigma attached to the disease, in many regions the leprosy patient with cataract may not receive the surgical services offered to other members of the population.

The results of these combined surveys show that 24·3% of patients completing MDT, who might well be released from control and therefore from supervision, have on-going eye problems that are potentially sight-threatening. In addition 32·9% of patients completing monotherapy have similar evidence of long-term ocular damage. Many patients also have cataract causing significant visual impairment and these will inevitably add to the increasing reservoir of blind leprosy patients whose only chance of restoration of vision is surgery.

Although patients with major ophthalmic problems are likely to remain under care and supervision, those with potentially sight-threatening lesions who have few visual symptoms but who form an equally important group, may well be discharged.

Leprosy patients, who may already have severe sensory and motor disabilities, require special attention if they have additional problems with vision, regardless of whether they are caused by the disease or not. It is of great importance for the welfare of these patients that these problems should be rectified by surgery if possible or at least modified by optical aids. The leprosy patient with impaired sight is ill-equipped to care for the eyes and limbs and is often entirely dependent on outside help, and may be at greater risk of further general complications. The completion of therapy and possible consequent discharge from ophthalmic supervision may lull the patient into a false sense of security, particularly since many early ocular problems can go undetected and symptoms may be minimal.

These results emphasize the importance of continued ophthalmic care for patients who have completed MDT or dapsone monotherapy. Failure to re-examine the eyes at regular intervals is likely to lead to an unacceptably high level of eventual visual impairment, much of which could be avoided or treated if detected early enough and referred for appropriate therapy. A bacteriological 'cure', as defined by the existing WHO recommendations and as practised in many centres, gives no guarantee that future ocular problems have been avoided. Indeed if these figures are representative of cases being released from control, they highlight an important logistic problem for leprosy workers, suggesting that in certain areas as many as one in five leprosy patients released from control may harbour sight-threatening lesions that can eventually lead to blindness.

Acknowledgment

None of these studies could have taken place without the conscientious contributions made by the 39 final-year medical students who carried out these surveys, often under conditions of difficulty and hardship, and who should rightly be listed as co-authors.

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Lésions restantes qui menacent la vue chez des patients ayant completé les cours thérapeutiques à drogues multiples et de monothérapie de sulphone

T J FFYTCHE

Sommaire - Une analyse est présentée ici des données provenant des sondages normalisés des résultats oculaires obtenus à partir des échantillons de la population de lèpre en 23 zones. Les résultats de cette analyse montrent qu'un 24,3% des patients qui ont complété la thérapie à drogues multiples et un 32,9% de ceux qui ont complété la monothérapie de sulphone ont des problèmes des yeux persistants qui peuvent potentiellement arriver à produire la cécité ou un grave affaiblissement visuel. La plupart de ces complications oculaires impliquent les paupières, la cornée et le tractus uveal antérieur, mais chez une proportion considerable des patients la vue était menacée par des cataractes.

Sans supervision, beaucoup de ces patients commenceront à avoir des problèmes majeurs de vue qui auraient pu être évités. Il est important de ne pas regarder le fait de compléter la thérapie systématique de lèpre comme assurance que les yeux du patient soient hors de danger, et de continuer la supervision oculaire régulière bien aprés avoir classifié le patient comme "complètement gueri".

Lesiones post-recuperativas que amenazan la vista de pacientes tras cumplir la terapia multimedicinal o la monoterapia de sulfona

T J FFYTCHE

Resumen - Se presenta un análisis de datos obtenidos a partir de estudios normalizados de los resultados oculares en una sección representativa de la población de enfermos de lepra en 23 zonas. Muestra que el 24,3% de los pacientes que han completado el tratamiento de drogas múltiples y el 32,9% de aquellos que han completado la monoterapia de sulfona tienen problemas de ojos que persisten y pueden potencialmente llegar a producir la ceguera o graves impedimentos visuales. La gran parte de estos problemas están relacionados con los párpados, la córnea y el tracto uveal anterior, sin embargo, una proporción importante de pacientes estaba en peligro de perder la vista por cataratas.

Sin supervisión, muchos de estos pacientes desarrollarán graves problemas de vista que podrían haberse evitado. Es importante el no suponer que el completar una terapia sistemática de lepra sea garantía de que los ojos del paciente queden a salvo, y que la supervisión regular de los ojos del paciente debe de continuar mucho tiempo después de clasificarlo médicamente como "completamente curado".

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Reduction in caseload after multidrug therapy in an urban leprosy control programme— a retrospective study in Bombay

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Summary A fall in the active registered case prevalence rate together with a fall in the active caseload per worker after the introduction of multidrug therapy (MDT) is becoming a managerial issue in leprosy control. A retrospective analysis was undertaken to assess the caseload per paramedical worker with reference to active cases for treatment (3341), cases for surveillance (2227) and cases for care after cure (165) at the end of December 1989. All these cases were under the care of 24 paramedical workers.

The analysis showed that the caseload per worker was 239 (active cases 139, plus surveillance cases 93, plus care after cure cases 7), though active registered case prevalence rate declined from 1·82/1000 (before starting MDT) to 0·79/1000 by the end of December 1989. The case detection rate was 0·49/1000 by the end of 1989. So, although the active registered case prevalence rate declines, the worker will have enough to do because of the need for surveillance and the detection of relapses, early neuritis, early disabilities and care after cure. Simultaneously, new case detection and treatment must be continued.

All these aspects need to be considered when programme managers are reviewing leprosy control strategy.

Introduction

The introduction of multidrug therapy (MDT) in leprosy control programmes has resulted in some drastic reductions in active case prevalence rates. This has induced anxiety as well as euphoria among programme managers and funding agencies, especially among voluntary organizations. The fall in the active prevalence rate has resulted in a significant reduction in the active caseload per paramedical worker (PMW). This has become an important managerial issue as programme managers and the funding agencies of vertical programmes prepare their future strategies for leprosy control. The Government of India has proposed that the leprosy services should be integrated into primary health care once the active prevalence rate has fallen below 2 per 1000.[1] However, it has been observed that the incidence rate falls very slowly.[2] Askew[3] has suggested that where there is a declining active caseload, the PMWs could be responsible for deformity

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care and physiotherapy, etc. Noordeen[4] pointed out that because of the low endemicity resulting from MDT, other problems remain—such as the possible occurrence of relapses and difficulties involved in contacting chronic defaulters and more distant patients and the breakdown of old subclinical infections.

So, while assessing PMWs workload and preparing to integrate with primary health care, leprosy programme managers must keep all these additional factors in mind. A retrospective study was undertaken by the Bombay Leprosy Project to look into these crucial managerial issues.

Materials and methods

The Bombay Leprosy Project operates a leprosy control programme in H and G municipal wards covering a population of 1·8 million (1989 estimate). In addition, the Project also treats patients living outside the control area. Between 1977 and 1989, 13,487 patients were registered, both from within and outside the project area and MDT was introduced in 1982 following the recommendations of WHO.[5] All these patients were under the care of 24 trained paramedical workers. A retrospective analysis was undertaken to discover the caseload per worker with reference to active cases, patients under surveillance and patients requiring disability care at the end of December 1989.

Observations and discussion

All active patients were brought under MDT between 1982 and 1989. The rest were assessed as cured with monotherapy and discharged.

From outside the project area 4,552 (34%) (Table 1) patients were registered. In a city like Bombay, many patients prefer to take treatment far from their homes. This creates case-holding problems for leprosy workers who need more time for patient education and follow-up.

Out of 5733 cases in different categories 1323 (23%) had disabilities. In a total of 1323 disabled patients, 536 (16%) were under treatment and 622 (28%) were under surveillance (Tables 2 and 3). A total of 165 patients had completed surveillance and were released from control and moved to the care-after-cure register. Although patients with Grade I disability are not usually accounted for when presenting disability figures these patients

Table 1. MDT coverage

MDT coverage	Project area (No. of cases, MB+PB)	Outside project area (No. of cases, MB+PB)	Total
Cases registered (1977–89)	8935 (66%)	4552 (34%)	13,487*
Cases on MDT (1982–89)	4268 (58%)	3046 (42%)	7,314

* A total of 6173 cases were on monotherapy before 1982 and were considered inactive and unfit for MDT.

Table 2. Distribution of leprosy patients (at the end of 1989)

Distribution of patients	Project area (No. of cases)	Outside project area (No. of cases)	Total
Active cases under MDT	1423 (43%)	1918 (57%)	3341 (100%)
Cases under surveillance (Post RFT)*	1437 (65%)	790 (35%)	2227 (100%)
Cases for care after cure	132 (80%)	33 (20%)	165 (100%)
Total	2992 (52%)	2741 (48%)	5733 (100%)

*RFT, Release from treatment.

Table 3. Distribution of disability cases

	Total no. of cases	No. of cases with disability*		Total no. of cases with disability	No. of cases without disability
		Grade I	Grade II		
Active cases	3341	233 (7%)	303 (9%)	536 (16%)	2805 (84%)
Cases for surveillance	2227	332 (15%)	290 (13%)	622 (28%)	1605 (72%)
Cases for care after cure	165	86 (52%)	79 (48%)	165 (100%)	—
Total	5733	651 (11%)	672 (12%)	1323 (23%)	4410 (77%)

*Classification of disability grading was done according to revised grading recommended by WHO (1988)[6].

nevertheless require considerable attention, in addition to the exhibition of MDT, in order to prevent their decline into a Grade II disability. This is an aspect of the PMWs work that tends to be overlooked but is nevertheless both important and time-consuming. In due course, disabled patients under MDT (536 cases) and disabled patients under surveillance (622 cases) would be transferred to the care-after-cure register.

Programme managers tend to consider a fall in the active registered case prevalence rate and a fall in the active caseload as indicating a need to change the strategy for leprosy control. However, as well as treating active cases, the same worker has to follow-up surveillance patients for detecting relapses, late reversal reactions and silent neuritis. As a result, the caseload per worker goes up to 232 (active cases 139, plus cases for surveillance 93). It is questionable whether early silent neuritis, reversal reactions and early disabilities could be detected unless the surveillance examination is done more frequently (especially in the borderline group) than the current recommendation to undertake surveillance once a year.[7]

As one or two physiotherapy technicians cannot take care of 1323 disabled patients satisfactorily, PMWs have to assist the physiotherapy technicians to take care of disabled cases. The disabled caseload after cure was 7 per PMW. The rest of the 1158 disabled cases who are under treatment as well as under surveillance will join the care-after-cure programme gradually.

Unfortunately, little attention is paid to disability care during cure in MDT

Table 4. Caseload per paramedical worker (at the end of December 1989)

No. of PMWs	Active cases	Cases for surveillance	Cases for care after cure	Total
24	3341	2227	165	5733
1	139	93	7	239*

*A caseload of 239 per PMW includes 55 (23%) patients with disability.

programmes. If care during cure is to be practised, 1158 disabled patients, who have not yet entered the care-after-cure register, will need more attention and will add further to the PMWs workload.

The new case detection rate (NCDR) ranged between 0·33 and 0·65/1000 after introducing MDT in 1982. In 1989, it was 0·49/1000 (Table 4). It must be remembered that case detection has to be continued in addition to the above caseload.

From this retrospective analysis, it can be seen that when assessing the PMW workload and designing the future leprosy control strategy in an endemic situation, in addition to an active caseload and a reduction in the active registered case prevalence rate, activities like new case detection, surveillance and disability care are also to be considered. However, as the urban profile may not be representative of the rural profile, a separate study in endemic MDT districts is essential before advocating any parameters.

Acknowledgments

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Réduction dans le nombre des cas par employé comme résultat de la thérapie à drogues multiples dans un programme urbain de contrôle de la lèpre - une étude rétrospectif à Bombay

C R REVANKAR, P L PAWAR, L S BELURKAR, R R PAI ET R GANAPATI

Sommaire - Une chute dans le taux de fréquence des cas actifs liée à une chute dans le nombre de cas actifs sous le contrôle de chaque employé depuis l'introduction de la thérapie à drogues multiples (MDT) est en train de devenir un problème administratif dans le contrôle de la lèpre. Une analyse rétrospective a été menée pour évaluer le nombre de cas traités par chaque auxiliaire médical par rapport aux cas actifs pour traitement (3341), cas pour surveillance (2227) et cas pour soin après récupération, à la fin décembre 1989. Tous ces cas étaient sous la responsabilité de 24 auxiliaires médicaux.

L'analyse a montré que le nombre de cas par employé était de 239 (139 cas actifs + 93 cas pour surveillance + 7 cas de soin après récupération), bien que le taux de fréquence des cas actifs avait baissé de 1,82/1000 (avant de mettre la MDT en pratique) jusqu'a 0,79/1000 à fin décembre 1989. Le taux de détection des cas nouveaux était de 0,49/1000 à la fin de 1989. Alors, bien que le taux de fréquence des cas actifs est en baisse, les employés auront suffisament à faire à cause des besoins de surveillance et détection de rechutes, des névrites précoces, des incapacités précoces et des soins après récupération. En même temps, la détection des nouveaux cas et le traitement doivent continuer. Tous ces aspects doivent être tenus en considération par les administrateurs du programme au moment de réviser la stratégie pour le contrôle de la lèpre.

Reducción en el número de casos bajo el control de cada empleado como resultado de la terapia multimedicinal en un programa urbano de control de la lepra - estudio retrospectivo en Bombay

C R REVANKAR, P L PAWAR, L S BELURKAR, R R PAI Y R GANAPATI

Resumen - Una disminución en el índice registrado de frecuencia de casos activos junto con una disminución en el número de casos activos bajo el control de cada empleado desde la introducción de la terapia de drogas múltiples (MDT) se está convirtiendo en un problema administrativo en el control de la lepra. Se ha llevado a cabo un análisis retrospectivo con el objeto de averiguar el número de casos tratados por cada empleado paramédico con referencia al número de casos activos para tratamiento (3341), casos para observación (2227) y casos para vigilancia post-recuperación completa (165) para fines de diciembre de 1989. Estos casos estaban repartidos entre 24 empleados paramédicos.

El estudio mostró que el número total de casos por empleado era 239 (139 casos activos + 93 casos para observación + 7 casos de vigilancia post-recuperación), aunque el índice registrado de frecuencia de casos activos bajó de 1,82/1000 (antes de la introducción de la MDT) a 0,79/1000 a fines de diciembre de 1989. El índice de detección de casos a finales de 1989 era 0,49/1000. O sea que aunque el índice registrado de frecuencia de casos activos esté en descenso, los empleados se mantendrán ocupados con la vigilancia y la detección de recaidas, neuritis temprana, invalidez temprana y la vigilancia post-recuperación completa. Al mismo tiempo, la detección de nuevos casos y el tratamiento deben continuar.

A la hora de revisar el programa de control de la lepra, los encargados deberán de tomar en cuenta todos estos factores.

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Keratosis spinulosa developing in borderline–tuberculoid lesions during type I lepra reaction: two case reports

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Summary Two cases of borderline–tuberculoid leprosy which developed keratosis spinulosa over the anaesthetic areas alone during type I lepra reactions are described. Both patients only developed spiny papules during the period of reaction and subsided with control of the reaction. The probable mechanism of this peculiar phenomenon might be due to the generation of epidermal growth factors by local T cell activation during the type I lepra reaction.

Case 1

A 25-year-old male Indian manual labourer reported to the Dermatology OPD of our hospital with two hypopigmented lesions on the forearm and weakness of his right hand; these had been present for $1\frac{1}{2}$ years and had not received treatment. On examination he had two well defined, hypopigmented, anaesthetic, hairless patches on the medial aspect of his right forearm, together with partial ulnar clawing and slight wasting of hypothenar muscles. The right ulnar nerve was thickened and tender. Skin smears from the lesions were negative, and biopsy showed well formed epitheloid granulomas surrounding dermal appendages with a free, narrow zone immediately beneath the epidermis. A diagnosis of borderline–tuberculoid (BT) leprosy was made, and treatment was instituted with rifampicin 600 mg monthly and dapsone 100 mg daily.

Ten days after the second dose of rifampicin the patient reported with severe pain over the ulnar nerve and increased weakness of the hand, together with development of spiny lesions over the two patches. The patches were erythematous, tender and mildly oedematous, and their surfaces were covered with minute spiny keratotic papules. Skin smear was negative for AFB, but we could not carry out a lepromin test. Biopsy showed marked hyperkeratosis with follicular plugging, oedema in upper and middermis, and tuberculoid granulomas concentrated mainly around hair follicles; these eroded the basal layer of epidermis. These findings confirmed a diagnosis of Type I lepra reaction (reversal) and prednisolone 80 mg and clofazimine 300 mg were added to rifampicin and dapsone. Pain and erythema subsided, and the papules disappeared by the end of three months. Prednisolone dosage was decreased, and stopped within a period of three months. Clofazimine was also decreased and reduced to 50 mg within a period of 6 months and continued along with rifampicin and dapsone to complete one year. The patches remained quiescent, though anaesthetic, throughout the 16 months of follow-up.

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Case 2

A 35-year-old-Indian manual labourer presented with Type I lepra reaction, having received dapsone monotherapy from the local hospital for the previous six months. On examination he had a large patch over the left shoulder extending to the upper arm. It was well defined, erythematous and tender, and its surface was covered with spiny papules (Figure 1). A small macule on the left forearm had similar changes, and the left superficial peroneal nerve was thickened and tender; skin smear was negative. He was treated with prednisolone 40 mg, clofazimine 300 mg and dapsone 100 mg daily with rifampicin 600 mg once a month. The lesions improved dramatically and prednisolone was decreased and withdrawn over a period of three months, by which time the spiny papules and erythema has disappeared. Clofazimine was also reduced to 50 mg and continued to complete six months and no recurrence of activity appeared over the next one year follow-up period.

No evidence of associated systemic disease was found in either of these two patients.

Discussion

Apart from the well known changes occurring in reactions we know of very few reports of complications specifically affecting leprosy skin lesions. There has been a report of vitiligo developing in the margins of two tuberculoid (TT) lesions,[1] and another of comedones in

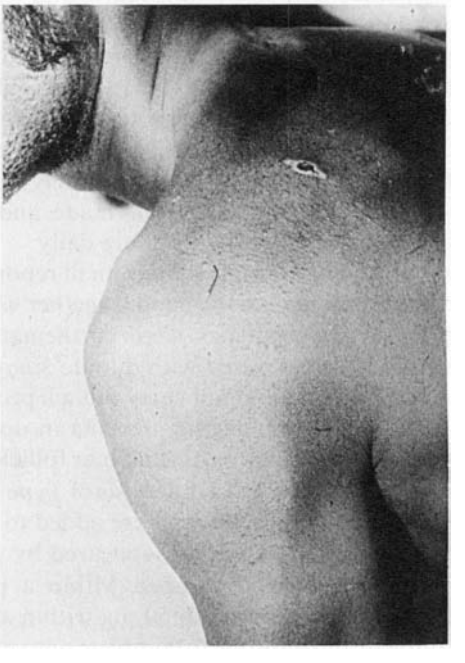

Figure 1

BT lesions which had been massaged with coconut oil.[2] Keratosis spinulosa developing in skin lesions of leprosy patients, whether in reactions or not, has not previously been reported. This dermatosis consists of minute follicular papules, each with a horny spine in the centre, grouped in plaques and developing on various sites. This skin reaction has been reported in lichen scrofulosorum, in cutaneous mycoses, in miliary papular syphilis and occasionally in drug reactions, subsiding spontaneously after a few months.[3] The fact that in our patients it was confined to the patches of BT leprosy during Type I reaction suggests that it was a clinical manifestation of an immune reaction in the skin. Type I reaction (reversal) is an example of delayed type hypersensitivity (DTH),[4] and Kaplan *et al.*[5] have investigated epidermal changes in other examples of DTH such as the tuberculin reaction and the reaction when antigen is injected intradermally into skin lesions of tuberculoid (BT and TT) leprosy patients. They found marked thickening of epidermis associated with both the size and the number of keratinocytes increasing, together with changes in keratinocyte Ia-antigen expression in the epidermis. These authors suggest that one or more epidermal growth factors may be generated in the course of a delayed immune reaction in the dermis. Thangaraj *et al.*[6] have demonstrated significant epidermal changes in lesions of leprosy patients undergoing Type I (reversal) reactions in the form of increase in epidermal cell layers, the consistent presence of Ia in all keratinocytes, an increase in Langerhan's cell numbers, and scattered T cells within the epidermis. Their studies indicate that local T cell activation can lead to the production of lymphokine, such as gamma-interferon (interferon) with subsequent induction of Ia on epidermal cells, constituting an important event in reactional leprosy patients. In the light of these observations it is hardly surprising that a clinical epidermal change, such as keratosis spinulosa, should occur as a manifestation in Type I lepra reaction, and we wonder why it has not been reported before now.

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Développement de kératose épineuse dans des lésions des cas limites tuberculoides dans des réactions de lepre du type I: rapport de deux cas

T P THANKAPPAN ET G SULOCHANA

Sommaire - On décrit deux cas limites de lèpre tuberculoïde avec développement de kératose épineuse limité aux zones anesthésiques dans des réactions de lèpre du type I. Les deux patients ont développé des papules épineuses seulement pendant la période de réaction et qui ont disparues avec la mise sous contrôle de la réaction. Le méchanisme probable de ce phénomène étrange peut être dû à la production des facteurs de croissance épidermiques par l'activation des lymphocytes-T pendant la réaction de lèpre du type I.

Desarrollo de queratosis espinosa en lesiones tuberculoides inciertas en reacciones de lepra del tipo I: informe de dos casos

T P THANKAPPAN Y G SULOCHANA

Resumen - Se describen dos casos inciertos de lepra tuberculoide con desarrollo de queratosis espinosa limitado a las zonas anestésicas en reacciones de lepra del tipo I. En los dos pacientes se desarrollaron pápulas espinosas sólo durante el periodo de reacción, que desaparecieron al controlarse la reacción. El mecanismo probable de este extraño fenómeno puede ser debido a la producción de factores de crecimiento epidérmicos por activación de linfocitos-T durante la reacción de lepra del tipo I.

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Self-administered dapsone compliance of leprosy patients in Eastern Nepal

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Summary Self-administered dapsone intake by leprosy patients in Eastern Nepal was monitored with a urine spot test. Of 341 outpatients 55 (16·1%) were found to be noncompliant. A significant relationship was found between noncompliance and age and between noncompliance and caste. Sex, disease classification, type of treatment, duration of treatment, history of leprosy reactions and travel time to the clinic did not influence the compliance.

In remote areas the urine spot test can be useful in leprosy control programmes.

Introduction

The regular intake of antimycobacterial drugs by leprosy patients is considered to be important in preventing the development of drug resistance. In the dapsone monotherapy era secondary dapsone resistance was faced;[1] with the introduction and implementation of multidrug therapy (MDT) in 1982[2] it is feared that resistance to rifampicin or clofazimine might develop due to irregular treatment. Since a good correlation between the intake of dapsone and clofazimine has been reported,[3] dapsone compliance has been considered to be a valid indicator for compliance of patients on MDT.

In the past, several tests have been developed to measure dapsone levels in urine. The importance of a simple field test has been emphasized.[1] Especially in remote areas, like large parts of Nepal, where sophisticated laboratory facilities are not available, only simple tests are feasible. A urine spot test, as described by Huikeshoven in 1986,[4] proved to be simple, cheap and reliable. Although in some studies this test has been found insensitive,[5] other studies resulted in a more favourable conclusion.[6–8] Recently this test was compared with results of D/C ratios for dapsone in urine and found to have a very high sensitivity.[9]

This study was done to obtain information about the compliance-rate of leprosy patients in Eastern Nepal, in the flat terai as well as in the hills, and to determine whether any patient characteristic influences this compliance rate.

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Patients and methods

From April to June 1989, urine was collected from 341 leprosy outpatients on their monthly visit to the leprosy clinic, and tested immediately. A total of 278 urines (81·5%) were collected in the terai (lowland) at the busy Biratnagar clinic, while the other 63 urines (18·5%) were collected in the hills at five different leprosy clinics.

Patients receiving MDT totalled 279 (81·8%) and 62 were on monotherapy (18·2%), because they were known to be grossly irregular clinic attenders (8 patients) or because of the current policy of the Biratnagar clinic (54 patients). According to this policy new patients were started on monotherapy and only changed to MDT after having attended the clinic regularly for a few months. The main justification of this policy, which is at the moment under review, is the large number of Indian patients who come across the border to the Biratnagar clinic and who have proved to be more irregular than the Nepali patients. This may pose a potential resistance problem. Patient data were collected from the files and from interviews.

The urine spot test described by Huikeshoven[4] was used. Filter paper impregnated with a modified Ehrlich's reagent was prepared by the laboratory of Anandaban Leprosy Hospital. It was taken to Biratnagar and the other clinics while kept in an airtight container with silica gel and used within six weeks of preparation. Negative and positive control solutions were prepared on the spot at the different leprosy clinics;[10] the negative control solution was made of 1 N HCl and urine from a person not taking dapsone; for the positive control a dilution of crushed dapsone tablets in 1 N HCl was added to the negative control solution.

With a drop of the positive control solution as well as with a drop of urine of a patient taking dapsone, a peripheral yellow ring (urea) and an orange central spot (dapsone) appears on the impregnated paper. A drop of 1 N HCl was added to each spot to reduce false negative and false positive results. Tests were considered positive when the orange central spot was equal in colour or darker than the positive control. A negative test result means that dapsone was not taken according to the schedule of 100 mg per day, and possibly that the level of dapsone in blood has fallen below the minimum inhibitory concentration for *Mycobacterium leprae*.

Results

The overall compliance of the patients tested was 83·9% (Table 1).

A significant relationship was found between age and noncompliance (Table 2). Patients younger than 15 years were significantly less compliant than older patients and

Table 1. Dapsone compliance.

	Compliant	Noncompliant	Total
Number	286	55	341
%	83·9	16·1	100

Table 2. Dapsone noncompliance and patient characteristics

	Total	Compliant	Noncompliant	(%) Noncompliance
Age				
<15	27	18	9	33·3
15–45	219	181	38	17·4
>45	95	87	8	8.4
Caste				
High	82	80	2	2·4
Middle	156	128	28	17·9
Low	103	78	25	24·3
Region				
Terai	278	229	49	17·6
Hills	63	57	6	9·5
Duration of treatment				
<6 months	107	89	18	16·8
>6–24 months	135	114	21	15·6
>24 months	99	83	16	16·2

patients above the age of 45 were more compliant than younger patients ($P < 0{\cdot}025$ in Chi-square test).

Members of a higher caste were more compliant than members of middle or lower castes ($P < 0{\cdot}001$). No significant difference in compliance was found for sex, disease classification, type of treatment (MDT or mono), duration of treatment, history of leprosy reactions and time needed to travel to the clinic. In this study patients in the hills appeared to be more compliant than those in the terai, but this was not significant.

Discussion

The compliance-rate in Eastern Nepal as obtained in this study proves to be encouraging and comparable to other figures from Nepal.[9] As reported from other studies[11,12] there seems to be a significant relationship between noncompliance and age. This was also found in Eastern Nepal, though to our knowledge a higher compliance of patients above the age of 45 years has not been reported before. Except for the caste to which patients belonged, other significant relationships between patient characteristics and noncompliance were not found. That members of a high caste proved to be more compliant, might be explained by their usually higher socioeconomic status and level of education. A significant difference in compliance for duration of treatment as reported in other studies,[11,13] was not found.

In remote areas like the hills of Eastern Nepal, the use of the urine spot test proved to be feasible. Local field staff was very motivated and enthusiastic and had no difficulties in performing the test. As the test is easy, cheap and reliable, its use in leprosy control programmes on a larger scale is strongly recommended.

Acknowledgments

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La complaisance des patients de lèpre qui se sont auto-administrés de dapsone

Y D M VAN TRIER ET R DE SOLDENHOFF

Sommaire - La prise de dapsone auto-administrée par des patients au Népal Oriental a été surveillée par moyen d'un essai superficiel d'urine. Les résultats ont montré que de 341 patients, 56 (16,1%) n'ont pas suivi le traitement. Une corrélation importante a été observée entre cette non-conformité et l'âge et entre la non-conformité et la caste. Le sexe, la classification de la maladie, le type de traitement, la durée du traitement, le passé médical de réactions de lèpre et le temps de voyage à la clinique n'ont pas influencé la conformité.
Dans des zones écartées, l'essai superficiel d'urine peut être utile dans les programmes de contrôle de la lèpre.

La conformidad de autoadministración de dapsona en pacientes de lepra en el Nepal Oriental

VAN TRIER Y DE SOLDENHOFF

Resumen - Se investigó la toma de dapsona autoadministrada por pacientes de lepra en el Nepal Oriental por medio de una prueba superficial de orina. Según los resultados, de 341 pacientes externos, 55 (el 16,1%) no habían seguido el tratamiento. Se observó una correlación importante entre esta no conformidad y la edad y la no conformidad y la casta de los pacientes. El sexo, la clasificación de la enfermedad, el tipo de tratamiento, la duración del tratamiento, los antecedentes de reacciones de lepra y la duración del viaje hasta la clínica no afectaron la conformidad.
En zonas remotas la prueba superficial de orina puede ser útil en los programas de control de la lepra.

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Transmission of health information on leprosy from children to their families: another approach to health education

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Summary A controlled study was carried out in the North Arcot District of Tamil Nadu, South India to determine whether health information given to schoolchildren would influence the knowledge and attitudes of their families concerning leprosy. A total of 41 children and almost all of their household members participated in the study.

The study, conducted by questionnaire, involved a pre-test of knowledge and attitude about leprosy of seventh standard students and their families. After one group of children received health education about leprosy and the other received information about tuberculosis, an identical post-test questionnaire was administered to all participants.

Although significant improvement in knowledge about leprosy was detected in the leprosy educated group of children compared with controls, no transmission of information on leprosy was detected in the family members of either group. The attitudes of the children who had been educated about leprosy may have been adversely affected by the health education session.

The reasons for our failure to detect significant transfer of information about leprosy in this setting are discussed, as well as the need for additional research in this area.

Introduction

In recent years, health education about leprosy has come to play an increasingly important role in leprosy control programmes.[1–4] Several studies have shown that health education in the community improves self-reporting of cases, reduces the likelihood of deformity at presentation and decreases the stigma of leprosy.[5–14] Most studies on the effectiveness of health education have focused on the improvement of knowledge of those who were direct recipients of the information. One approach to health education about

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leprosy which has not yet been explored is the education of schoolchildren as a means to educate their families and other members of the community. The present study was designed to determine whether health information given to schoolchildren would influence the knowledge and attitude of their families concerning leprosy.

Patients and methods

During the months of March and April in 1984 a health education study was carried out in a primary school in a rural community in the North Arcot District of Tamil Nadu. The children attending the school were drawn from three villages: Model Colony (population 620), Anvarthikanpet (population 777) and Ranapuram (population 453). The main occupation in the area was farming—20% of the villagers owned their own land while 40% were farm labourers; 30% of the villagers were dhal merchants. The average income for the head of household was 600 rupees (£20) per year.

There were 359 children in the school which had classes up to the eighth standard. A seventh standard class (ages 11–13) was chosen for the investigation. Males made up 74% of the class. Approximately 80% of the children came from Hindu families with the remainder made up of Muslims and Christians.

During the first part of the study, the knowledge and attitude of the children and their family members concerning leprosy was tested by means of a standardized questionnaire which was administered in their own language by a health educator. The 32 questions required either a yes/no response or were the open-ended type for which the educator filled in the response. This pre-test questionnaire did not focus specifically on leprosy but contained a number of questions about tuberculosis. It tested attitude and several areas of knowledge about leprosy. The questions covered the following topics:

1 What diseased is feared the most?
2 Curability of leprosy.
3 Cause of leprosy.
4 Who in the community is responsible for spreading the disease?
5 Contagiousness of the infection.
6 Recognition of the disease.

In addition to knowledge acquisition as a means to determine transfer of information from children to their household members, we questioned household members about their familiarity with leprosy and where that knowledge was acquired.

The participants were not informed about the purpose of the study or what might be expected of them in the future. One month later, the seventh standard class was divided in random fashion into two groups of approximately equal size. One-half of the class received a comprehensive educational session about leprosy from a health educator who had considerable experience in leprosy control. On the same day, the other half of the class (controls) received an educational session about tuberculosis from the same individual. To make the flow of information as natural as posible, the children were deliberately not prompted in any way to discuss the health information talks with their families; neither were they discouraged from doing so.

Two weeks after the educational sessions, the children and their family members were re-tested with the identical questionnaire (post-test) and in the same fashion as at the start of the study.

Table 1. Demographic characteristics of the household members of leprosy education and control groups of children

Characteristics	Leprosy education ($n=57$)	Controls ($n=59$)
Mean age (years)	34·9 ± 22·6	34·6 ± 26·4
Sex		
M	27 (47.4)*	28 (47·5)
F	30 (52·6)	31 (52·5)
Marital status		
Unmarried	5 (8·8)	14 (23·7)
Married	46 (80·7)	42 (71·2)
Widowed	6 (10·5)	3 (5·1)
Level of education		
Illiterate	24 (42·1)	22 (34·9)
Non-matriculated	24 (42·1)	28 (48·7)
Matriculated	8 (14·0)	9 (16·4)
Graduate or diploma	1 (1·8)	—
Occupation		
Housewife	18 (31·6)	16 (27·1)
Student	1 (1·8)	2 (3·4)
Farmer	16 (28·1)	15 (25·5)
Labourer	7 (12·3)	13 (22·0)
Other	15 (26·2)	13 (22·0)

*( ) percentage.

As noted in Table 1 there were no significant differences between the leprosy education and control families with respect to age, sex, marital status, education level and occupation. The mean age of the 21 schoolchildren in the leprosy education group was 11·8 ± 1·3 years compared with 12·3 ± 1·3 years in the 20 controls. The sex ratio and religious composition was similar for both groups.

Statistical analysis was carried out by paired Student's *t*-tests and chi-squared analysis using the Yates correction for small sample sizes.

Results

All 41 members of the seventh standard class and 116 of the 120 family members currently living in their households completed the study. Four family members completed the initial questionnaire but were not available for the post-test. Fifteen household members were temporarily absent from their homes throughout the duration of the study. No one refused to take part in the study. Thus, the compliance rate for those who were available to enter the study was 97%.

In the analysis of the results of the pre-test questionnaire no significant differences were found in knowledge level or attitude concerning leprosy between the study groups of children or their families (Table 2).

In the evaluation of the post-test questionnaire responses, children in the leprosy education group showed improvement in knowledge in five of six areas tested. In three of these areas the pre- and post-test responses were statistically different. In contrast, the

Table 2. Attitude and knowledge of schoolchildren and their families about leprosy

Questions	Test	Percent response			
		Children		Families	
		Leprosy education	Control	Leprosy education	Control
1 Which disease do you fear the most? (leprosy)	Pre	19·0	22·7	26·3	11·9
	Post	40·0	40·9	39·1†	17·0
2 Can leprosy be cured? (Yes)	Pre	4·8	35·0	35·7	31·5
	Post	55·0*	36·4	43·1	31·1
3 Cause of leprosy? (Germs)	Pre	14·3	4·5	10·5	8·5
	Post	50·0*†	13·6	4·3	2·1
4 Who is responsible for spreading leprosy? (Infectious persons only)	Pre	0	4·8	1·8	3·6
	Post	18·2*	21·1	25·5	16·7
5 How can one detect a person with leprosy? (Correct response)	Pre	57·1	36·4	66·7	57·6
	Post	75·0†	36·4	72·3	64·6
6 How contagious is leprosy? (Not very)	Pre	4·8	4·5	21·1	13·6
	Post	20	27·3	12·8	16·7

* Difference between pre- and post-test: $P < 0{\cdot}05$ by chi-squared analysis.
† Difference between leprosy education group and controls: $P < 0{\cdot}05$ by chi-squared analysis.
( )Response to the question.

control group of children showed a modest improvement in knowledge of leprosy, but none of these changes was statistically different. Compared with control children, the post-test knowledge level of those who had been educated about leprosy was statistically significantly improved in two areas. The only area in which both groups of children appeared to be adversely affected by the health education session was in their attitude towards leprosy. In comparison with their pre-test responses, almost twice as many children in both groups indicated in the post-test that leprosy was the disease which they feared most.

Analysis of the responses of the household members of both groups showed that in only two areas were there any improvement in knowledge between the pre- and post-tests. None of these changes was statistically significant. It is interesting to note that the only significant difference between the responses of the two groups was in the post-test questionnaire in which the leprosy education group expressed a greater fear of leprosy (Table 2).

At the beginning of the study, 60% of household members who could remember stated that they had not received specific information in writing or verbally about the disease. Most of those who had learned something about leprosy in the past could not recall their source of information. In the follow-up questionnaire, only 8 (8·5%) of the household members recalled specifically that they had received information about leprosy from their child during the study period.

Discussion

In order to ascertain whether health information would be spontaneously transferred

from schoolchildren to their families, we had to assess whether or not the children had gained in knowledge as a result of the health education session. We did detect significant improvement in knowledge of leprosy among the children educated about leprosy and a modest improvement in the controls. The change in the control group may have occurred by chance or by contamination; the latter resulting from a sharing of knowledge by two groups of children.

It was disconcerting to find that in comparison with the pre-test almost twice as many children in the post-test indicated 'leprosy' as the disease which they feared the most. We considered several possibilities for this finding. First, we believe that it is more likely that the children's recent exposure to the subject may have acted as a cue to influence their response in the post-test: a response which may not have been a reflection of their true attitude to the disease. Second, it is possible that change in knowledge does not itself guarantee a change in attitude. This emphasizes the need for 'booster doses' in health education programmes. A similar phenomenon may have accounted for the significant difference between the leprosy educated and control families' response to the same post-test question, assuming that some children discussed the health education session on leprosy with their family members. However, it is noteworthy that in the pre-test twice as many household members in the leprosy education group compared with controls chose leprosy as the disease which they feared most, indicating a possible (statistically insignificant) pre-test bias between the groups. Finally, it is possible, though unlikely, that our health educator's session inadvertently enhanced his pupils' fear of leprosy.

It is clear from our results that there was minimal transfer of health information on leprosy from children to their families. This was further confirmed by the small proportion of household members who could recall having received information on leprosy from their children during the study period.

Our inability to detect significant transfer of information from schoolchildren to their families may have occurred because the sample size was too small. Alternatively, this finding may have been due to cultural factors. In the usual family hierarchy in India the direction of knowledge flow is from elders to their offspring and not visa versa. As the mean age of the sample population was in the early adolescent period, perhaps the behavioural pattern at this stage of development involves more sharing with peers than with family members. This fact might have been a negative influence on the transfer of information within the household. Since we wanted to determine whether there would be a transfer of knowledge spontaneously, we did not encourage the children to discuss the subject of leprosy with their families and thus did not facilitate the reversal of the usual flow of information. Also, the subject of leprosy itself has a cultural taboo and stigma which may have further hindered intrafamilial discussions. In spite of the disappointing results of our study, we feel that there may be a potential for positive knowledge transfer about leprosy from schoolchildren to their families in South India. In a follow-up study we plan to increase the size of the study population and by means of a homework assignment to encourage the children to discuss with their families health information acquired in the classroom.

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La transmission d'information sur la santé auprès de la lèpre des enfants à leur familles: un autre chemin de l'éducation hygiénique

R PREM KUMAR, J S KEYSTONE, M CHRISTIAN ET K JESUDASAN

Sommaire - Une étude limitée a été menée dans la région de Tamil Nadu en Arcot du Nord au sud de l'Inde avec l'objet d'estimer si l'information sur la santé donnée aux écoliers pouvait influencer les attitudes et la connaisance de leurs familles sur la lèpre. Quarante-et-un enfants et la plupart des membres de ses familles ont participé à l'étude.

L'étude, menée par questionnaire, comprenait un examen initial des connaisances et attitudes sur la lèpre des étudiants du septième niveau et de leurs familles. Après qu'un groupe d'etudiants aurait reçu une éducation hygiénique en rélation avec la lèpre et l'autre groupe une information sur la tuberculose, tous les participants ont reçu un deuxième questionnaire, identique au premier.

Bien que, rélatif au groupe témoin, les enfants qui ont reçu de l'information sur la lèpre ont montré une amélioration considerable en leur connaisance sur cette maladie, la transmission de cette information sur la lèpre vers les familles d'aucun des deux groupes ne semble pas avoir eu lieu. Les attitudes des enfants instruits sur la lèpre peuvent avoir été influencées de façon négative par la session d'hygiène.

On discute les raisons pour lesquels on n'a pas detecté un transfert considerable d'information sur la lèpre dans ces circomstances, aussi que le besoin de faire des études supplémentaires dans ce domaine.

La transmisión de información sanitaria acerca de la lepra de niños en edad escolar a sus familias: otra ruta para la instrucción sanitaria

R PREM KUMAR, J S KEYSTONE, M CHRISTIAN Y K JESUDASAN

Resumen - Se ha llevado a cabo un estudio limitado en el distrito de Tamil Nadu en Arcot del norte, al sur de la India con el objeto de averiguar si la información sobre la salud transmitida a los niños escolares puede llegar a influenciar el conocimiento sobre y las actitudes hacia la lepra de sus familias. Participaron en el sondeo cuarenta y un niños y casi todos los miembros de sus familias. El estudio, llevado a cabo por medio de un cuestionario, consistía en una prueba inicial sobre el conocimiento y las actitudes hacia la lepra de estudiantes de séptimo nivel y sus familias. Después de haber recibido un grupo de niños instrucción sanitaria concerniente a la lepra y otro grupo información sobre la tuberculosis, se repartió un segundo cuestionario, idéntico al primero, a todos los participantes.

Aunque, relativo a los controles, se detectó en el grupo de niños que recibieron información sobre la lepra un aumento considerable en sus conocimientos sobre la enfermedad, no se detectó la transmisión de esta información hacia los miembros de la familia en ninguno de los dos grupos. Las sesiones de educación sobre la salud pueden haber tenido efectos adversos sobre las actitudes de los niños.

Se discuten las razones por las cuales no detectamos una transmisión importante de información sobre la lepra en estas circumstancias, y tambien la necesidad de llevar a cabo estudios suplementarios en este campo.

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An evaluation of a microcomputer information system for leprosy control two years post-implementation

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Summary As part of a national programme to improve the management of health services in Papua New Guinea, a microcomputerized information system was designed and implemented in seven provinces. Four other provinces later adopted this system. One component of this information system was a program to assist disease control officers to monitor the treatment received by leprosy and tuberculosis patients.

In contrast to other components of the information system, the leprosy and TB computer program was not maintained nor used after two years. This article describes the computer program developed and discusses possible reasons for its nonuse.

Introduction

The worsening financial situation in many developing countries has resulted in a decrease of funds available for health care services. This has caused an increased emphasis on managerial efficiency in order to make constrained financial resources go farther. Improved management of health care programmes depend upon better utilization of available sources of data to point out problem areas and indicate where resources can best be applied.

Microcomputers have been advocated and applied in many development programmes as a means of improving the quality, quantity, timeliness and usefulness of data available to health care managers.[1] Microcomputers have been applied as an information management tool to analyse rapidly population surveys,[2,3] to monitor immunization coverage,[4,5] to inventory drug supplies,[6] and to assist in management of decentralized provincial health departments.[7] Revanker, Gugal & Sorensen have described a microcomputer system to assist in the management of leprosy programmes.[8]

Most publications describing the use of microcomputers in developing countries have been written shortly after the development and implementation of information management projects. There has been relatively little written about the long-term durability and maintenance of these information systems.

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This article will describe the results of a two-year follow-up evaluation of a microcomputerized information system developed for the management of leprosy and tuberculosis programmes in provincial divisions of health in Papua New Guinea.

Description of the information systems

During 1986 and 1987, a project funded by the Asian Development Bank (ADB) was aimed at improving the management of health programmes in seven provinces in Papua New Guinea. This project was a component of a national programme to improve the management of health services under a decentralized system where the provincial departments of health were given administrative responsibility for most health programmes.[9]

Microcomputerized information systems were designed and implemented in the seven provinces which were included in the ADB project. The details of the information system and the types of reports available as well as the various stages of implementation, training and on-going management support to increase the use of the information produced, have been described elsewhere.[7]

The hardware in each province consisted of two IBM XT compatible microcomputers with 8088 processors, 640 K RAM, 20-mbyte hard disks and single 5·25-inch disk drives. The two computers shared a dot matrix printer. The main power supply was linked to a voltage regulator and stand-by power supply. The initial hardware cost, per province, was approximately US $5000 and came from the ADB project budget. On-going maintenance and supplies was estimated to cost $2000–3000 per year which was a provincial health department responsibility.

The software programs were developed using D-base III and D-base III +. While the usefulness of the various programs is limited for other countries, since they were developed to suit the specific circumstances of Papua New Guinea, they are available from the author. The author was involved with designing the reports, graphs and tables, testing and refining the software programs and providing management support and training to the provinces.

One component of the provincial information system was a program to assist disease control officers to monitor the treatments received by leprosy and tuberculosis patients. This system was very similar to the one developed in India and described by Revanker *et al.*[8] It allowed for individual patient monitoring and feedback to treatment centres. The information entered on each patient included name, age, treatment centre, date treatment started, reason treatment started (new patient, relapse, relocated) type of disease (multibacillary, paucibacillary), date treatment stopped and reason for stopping. Estimated ages, rather than date of birth, was used because people in PNG commonly do not know the latter.

A series of reports could be produced from this information and are described in Table 1. By using the microcomputer, each individual leprosy patient could be tracked through completion of treatment. A reminder system was built in to indicate when it was past time to end therapy. Reports were available to allow provincial disease control officers to compare the patients registered with the treatment cards at each treatment centre. End-of-the-year analyses reports, tables and graphs offered the opportunity to study disease trends throughout the province.

Table 1. Reports available for the leprosy control computer programs

Reports	Information available
1. Monthly and year-to-date summary. This could be produced monthly and provide a running total for the year. The December report could be used as a final annual summary.	Treatment centre, district and provincial totals of patients starting treatment, ending treatment and overall totals by type of disease.
2. Patient list	A list of all patients on treatment for each treatment centre including all information collected on each patient.
3. Reminder list	A list of all patients whose treatment should have been completed by the date of the report.
4. Lost and transferred patients	A list of all patients reported to be lost or transferred out to other treatment centres, and transferred in.
5. End-of-year analysis	Incidence and prevalence rates for each treatment centre, district and the entire province. Individual age and sex breakdown with bar graphs to illustrate.

Details of the different levels of the health care system in Papua New Guinea have been published previously.[10] The population of the provinces involved in the ADB project ranged from 60,000 to 300,000. The reported leprosy prevalence rate ranged from a high of 5·8 per 1000 to a low of 1·8 per 1000.[11] The number of new cases of leprosy reported ranged from 10 to 85 and the number of existing cases ranged from 186 to 687. The reports received from treatment centres were monthly summaries of totals with no individual patient information. Supervisory visits were made periodically by disease control officers to treatment centres to review treatment cards but financial constraints had made this an increasingly rare occurrence.

In most provinces, disease control officers were health extension officers who had worked their way up into a supervisory position after having served in health care centres. Health extension officers receive 3 years of training and one year of supervised practice following completion of grade 10 or 12. Disease control officers were responsible for both the provincial TB and leprosy programmes. In addition to the disease control officers, provincial health departments had supervisors of other programmes such as maternal-childhealth, environmental health, water supply and nutrition. All reported to the provincial assistant secretary of health who was a medical officer or health extension officer.

Multidrug therapy was being tried in two of the seven provinces. The initial response of the disease control officers to the microcomputer programs was enthusiastic. New information collection forms were developed in the provinces to collect information on all patients starting and ending treatment. During a three week, on-site training programme, the local provincial health department personnel were shown how to enter data and produce reports. Follow-up visits by the management support team were made to assist in the interpretation of reports, tables and graphs. By the end of the project, the entire microcomputer information system had been installed and was functioning in all seven provinces.

Follow-up

In May of 1988, a follow-up evaluation was conducted. The microcomputer system had been in place from one to two years in all seven provinces. In the ensuing time period, four more provinces had adopted the system, making 11 out of 20 provinces with computerized information systems. Multidrug therapy had been expanded to all provinces and management support activities out of the national office, including periodic provincial visits, had continued.

A standardized evaluation tool was developed to determine if: 1, the information in the system was being kept up to date; 2, the reports were being produced and disseminated to programme managers; 3, the information was being used for management decisions.

Evaluation information included: a structured questionnaire for provincial programme supervisors; the actual reports themselves to check for their availability, frequency of production and use; and annual reports, budget documents or other reports submitted to provincial governments.

The extent of use of the information system was categorized into three levels: considerable; some; none. If the supervisor stated that they used the programme, could give examples of its use and there was evidence of its use (provincial or divisional reports with data, objectives set and progress toward objectives known, computer reports in files with marks indicating analysis, etc.) then the extent of use was classified as considerable. If the supervisor stated they used the information and there was minimal evidence of its use, the extent of use was classified as some. If the supervisor stated they did not use the information or if there was no evidence of its use, the extent of use was classified as none.

Results

Table 2 describes the results of the evaluation on the use of the information system for four categories of supervisors in the provinces. The disease control officers were using the system far less often than the others. In only two of eleven provinces was the TB/leprosy information system usage judged to be considerable. In none of the provinces was the TB/leprosy data up-to-date. In most provinces little data had been entered since the initial training sessions.

Table 2. Extent of utilization of the information system

Supervisor of:	No. evaluated	Extent of use		
		Considerable	Some	None
Maternal and child health	10	8	1	1
Nutrition	8	5	1	2
Water supply	8	5	0	3
TB/leprosy	11	2	2	7

Discussion

In contrast to most of the provincial information system, where the maintenance and use of the system over two years was found to be fairly good, the computer program developed for TB/leprosy control had largely fallen into disuse. There were four hypotheses developed to explain this:

1 Multiple drug therapy (MDT) was being introduced into the provinces at the same time as the computerized information system. While the system was developed to assist the disease control officer to manage MDT patients better, the increased work load of implementing MDT might have detracted from the efforts needed to maintain the information system.

2 The TB/leprosy computer program was part of an overall provincial health information system. It was one component which required entry of individualized patient information; most other components required the entry of monthly totals only. Access to the computer for data entry might have been a problem. In most provinces, the information system was operated by an information officer who received data from each of the individual programs. The information officers might have given preference to programs which required less data entry. However, no evidence was found that the TB/leprosy programmes were generating data which were not being entered into the computer; little to no data were being collected.

3 The component of the information system developed for the TB/leprosy programmes was developed based on data which were not routinely collected. There were two components of the entire provincial health information system which the follow-up evaluation showed to be underused; both depended on sources of information which were not being routinely collected by the provincial divisions of health at the time the computer system was developed. One of these was the TB/leprosy programme which depended upon new, individualized, patient data where only treatment centre summaries had been collected before; the other was a divisional personnel system with no method of systematically updating individual files. Both these components of the information system would have been a valuable addition to the management tools of the divisions of health; their potential value was not questioned. They were, however, impractical because the flow of information needed to maintain them was not a well established pattern.

4 The computer did not make the job of the disease control officers easier. They continued to collect and hand tally monthly treatment centre summaries in order to meet national reporting requirements (even though this could have been done automatically on their computer had the data been kept up-to-date). The computer system required new information to be collected and data entry to occur. While the individualized patient information would have helped the disease control officer better track the care provided at treatment centres (especially in the light of infrequent supervisory visits) there was added work necessary to obtain the information.

Microcomputers can be a useful addition to the management tools used in developing countries. They can make collection, storage, analysis and usage of information for management more efficient. It does, however, require considerable effort and moderate cost to start-up such systems and to train national staff to operate them. Start-up costs

often come from external funding sources although in PNG several provinces purchased their own hardware and several more were considering this option. To create a favourable cost-benefit ratio, it is important to create computer programs which are useful and practical and which can be sustained. From the PNG experience, these recommendations can be made for those developing computer-based information systems in developing countries: 1, Do not try to use the computers to create new information systems; use them to make existing systems more efficient and informative; 2, allow any newly desired information to be collected manually for a specified time period to see if it is practical and useful and if the information can be collected dependably; 3, Do not introduce too many programme components at one time (i.e., MDT, new information collection, computer systems).

At the end of the evaluation, a recommendation was made to the national Department of Health to design a TB/leprosy component for the provincial information system based on the long-established monthly treatment centre summaries and to retain the system designed for individual patient data on the computer to be used by those interested.

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Une évaluation d'un système d'information de micro-ordinateur pour le controle de la lèpre deux ans après sa mise en pratique

D CAMPOS-OUTCALT

Sommaire - Comme partie d'un programme national pour améliorer l'administration des services sanitaires en Papouasie-Nouvelle-Guinée, un système micro-informatique d'information a été conçu et mis en pratique en sept provinces. Le système a été adopté postérieurement par d'autres quatre provinces. L'un des élements de ce système d'information c'était un programme pour aider aux agents de contrôle des maladies à contrôler les traitements reçus par des patients de lèpre et de tuberculose.

Par contraste avec les autres élements du système d'information, le programme informatique pour le contrôle de la lèpre et la tuberculose n'a pas été maintenu ni utilisé après deux ans. Cet article décrit le programme développé et discute des possibles raisons pour lesquels il n'a pas été utilisé.

Una evaluation de un sistema de informacion de microordenador para el control de la lepra dos años despues de su ejecucion

D CAMPOS-OUTCALT

Resumen - Como parte de un programa nacional para mejorar la administración de los servicios de sanidad en Nueva Guinea Papúa, se diseñó un sistema de información a base de microordenadores que fué puesto en práctica en siete provincias. Posteriormente adoptaron el sistema cuatro provincias más. Uno de los componentes de este sistema de información era un programa diseñado para asistir a los agentes de control de enfermedades a controlar los tratamientos que recibían los pacientes de lepra y de tuberculosis.

En contraste con los otros componentes del sistema de información, el programa para el control de la lepra y de la tuberculosis no se mantuvo ni seguía en uso al cabo de dos años. Se describe en este artículo el programa de ordenador desarrollado y se discuten posibles razones por las cuales no se utilizó.

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SPECIAL ARTICLE

A look at world leprosy*

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Introduction

In many ways, leprosy is a unique disease. The fear, abhorence and social stigma that was associated with it in the ancient past, and which lingers even to this day, was understandably a reaction to the extremely crippling mutilations it caused for which neither a remedy nor a preventive could be found. Leprosy was the ultimate disease and the leprosy patient the ultimate pariah in practically every civilization, to the extent that in several languages leprosy came to be referred to as the 'big disease'. Leprosy was dreaded not because it killed but because it left one alive. There was simply no hope for the afflicted.

Looking at leprosy today one can see a vastly changed situation. Leprosy is no more the 'Cinderella' of diseases. The average patient does not suffer from the extreme mutilations widely seen in the earlier days. Most patients live in their own communities and, where facilities exist, can be diagnosed, often early, can receive effective treatment and can be cured with no residual disabilities. There is increasing evidence, at least in some parts of the world, that the intensity of the social stigma is decreasing.

In terms of scientific developments, leprosy has made more progress in the last 20 to 30 years than throughout the whole of the preceding human history. Today, it is in the forefront of modern developments in such fields as immunology and molecular biology. However, the most important progress in recent years has been in the field of chemotherapy of leprosy leading to leprosy control through multidrug therapy (MDT).

The problem of leprosy

Because leprosy is a disease with a chronic course there is a general assumption that the leprosy situation everywhere is rather static. This is not true and leprosy is as capable as any other communicable disease of dynamic changes over periods of time, except that the time scale is different. In terms of magnitude of the problem it is difficult to estimate the current number of cases of leprosy in the world. Case diagnosis and definition are not

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always clear or consistent, and the enumeration of cases in many regions of the world is incomplete or irregular. Despite these difficulties, estimates are extrapolated from available data from time to time. The WHO estimates for 1966 and 1976 were 10·8 and 10·6 million cases respectively; prevalence in the early 1980s was estimated to be 10–12 million cases. Although no estimate has been made recently, it is likely that the current global figures are much lower than they were in the early 1980s.

There are several problems with regard to estimating the prevalence of leprosy.[1] Often it is based on information available from limited areas and on registered cases on which estimates of prevalence are made after applying certain arbitrary correction factors.

Most estimates are made on very inadequate information and seem to remain unchanged for years, if not decades. The assumption was that patients who were eliminated, either because of death or because they were cured etc., were replaced in equal numbers by new patients. In many countries the assumption was never verified and neither were the estimated figures adjusted for natural growth of population. In countries where sample surveys or other modified procedures had been employed, invariably the estimates have turned out to be much higher than the original ones. This was partly because of (a) identification of very early cases who are known to have a high tendency for self-healing, and (b) a good number of inactive cases being included which arose from the difficulty in discriminating them from active cases in cross-sectional surveys. In countries where effective leprosy control programmes have been in operation, with reliable periodic surveys, the difficulties in estimating the magnitude of the problem have been less severe.

The second major problem in relation to measurement of the magnitude of leprosy is the definition of a case of leprosy. There is a considerable amount of confusion in the minds of leprosy workers as to what is a case of leprosy and what is the cure or end point of disease. The introduction of fixed duration of MDT has now offered opportunities to make things easier. In relation to leprosy control, we can consider the following four categories of individuals.[2]

1 Those needing chemotherapy or who are under chemotherapy.
2 Those who have completed treatment and require surveillance.
3 Those who have completed surveillance but need care because of disabilities.
4 Those who have completed surveillance and do not need any further attention.

For epidemiological and operational purposes, including computing of prevalence rates, only those who need or who are under chemotherapy should be considered as cases of leprosy. Thus, for purely operational purposes the state of 'cure' is reached once chemotherapy is completed. While individuals under surveillance following chemotherapy would require some kind of active or passive follow-up, they would not be considered as cases. After completing surveillance a proportion of patients may still require care because of their deformities, and again for operational purposes these should not be considered as cases.

Population at risk

Approximately 1320 million people live in 28 countries where leprosy is a serious problem, i.e. the registered prevalence is over 1 case per 1000 persons, and thus may be

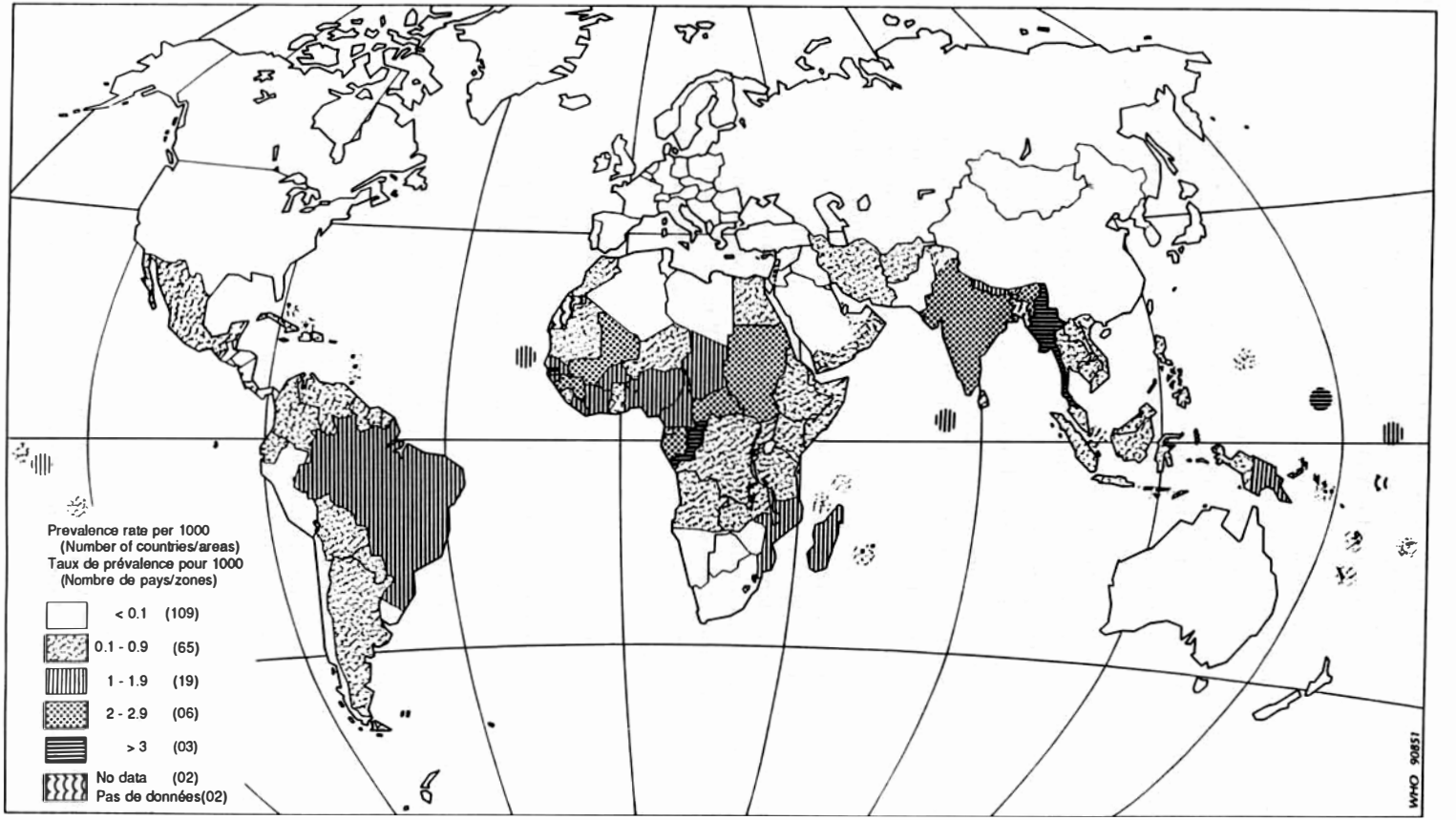

Figure 1. Prevalence of registered leprosy cases in the world, 30 September 1990.

considered as at significant risk of contracting the disease. If one reduces the limit of registered prevalence to 0·1 case per 1000 persons then the number of countries affected would increase to 93 covering a total population of about 2460 million.

Registered cases

Information on leprosy cases registered for treatment is much more reliable than information on estimated cases, as it is based on actual records. There had been a very steady increase in the number of registered cases between 1966 and 1985: 2,831,775 in 1966, 3,599,949 in 1976 and 5,368,202 in 1985. The latter figure represented an increase of 49·1% over 1976, and 89·6% over 1966. The prevalence of registered cases had correspondingly increased from 0·84 cases per 1000 population in 1966 to 0·88 in 1976, and 1·2 in 1985; the geographical distribution of leprosy in 1990 is shown in Figure 1. However, since 1985 there has been a steady decline so that in 1990 the total number of registered cases is 3·7 million, representing a reduction of 30%.

Although information on registered cases appears to be more reliable as it is based on actual records, there are several problems in evaluating this information for the purpose of leprosy control. Firstly, all registered cases are not necessarily under regular treatment whatever the drug regimen. The regularity of treatment varies widely from programme to programme, and often in the region of 50% or so, particularly among patients under dapsone monotherapy. Even among patients who collect their drugs from the clinics, there is a certain proportion who do not consume the drugs as expected. This has been brought out in more than one study on urine checks for dapsone. The next problem in evaluating information on registered cases is that often it is not updated. Inactive cases continue to remain in the registers either because a patient is lost for follow-up or because of the inability to periodically assess the patient's clinical and bacteriological condition. In addition, there are also the problems of duplicate registration of patients in more than one clinic. However, the situation appears to have improved in recent years, partly as a result of the introduction of MDT. This has made it necessary for workers responsible for leprosy control to review their records and to classify patients according to their bacteriological state. In spite of the problems discussed above, the information on registered cases is very valuable for planning, monitoring and evaluating leprosy control activities.

New case detection

Availability of reliable information on detection of new cases in the programmes varies from country to country. From information available to us, the number of new cases detected in 1989 was about 580,000, indicating a case detection rate of about 1 per 10,000 population. A large majority of the new cases were detected in the South-East Asia Region of WHO (85%). When analysed at different levels, the relationship between the number of registered cases and the annual number of new cases detected provides some indication on the effectiveness of case detection activities and the extent of inclusion of inactive cured individuals among registered cases.

The distribution of registered cases, the prevalence rates and the proportion of cases

Table 1. Distribution of registered leprosy cases by WHO regions, 1990*

WHO region	Population—latest official estimate ('000†)	Registered cases	
		No.	Prevalence rate per 1000
Africa	522,475	482,669	0·92
Americas	724,002	301,704	0·42
Eastern Mediterranean	391,460	99,913	0·26
Europe	845,948	7,246	0·01
South-East Asia	1,310,847	2,693,104	2·05
Western Pacific	1,497,539	152,739	0·10
Total	5,292,270	3,737,375	0·71

* Or for the most recent year for which data are available.
† Population data from *World Health Statistics Annual 1988.*

Table 2. Reported registered leprosy cases by WHO region for the years 1966, 1976, 1985 and 1990

WHO region	No. of registered cases			
	1966	1976	1985	1990
Africa	1,685,526	1,398,220	987,607	482,669
Americas	177,813	241,248	305,999	301,704
Eastern Mediterranean	40,963	63,236	74,892	99,913
Europe	19,589	20,452	16,794	7,246
South-East Asia	790,851	1,748,468	3,737,157	2,693,104
Western Pacific	117,003	128,325	245,753	152,739
Total	2,831,745	3,599,949	5,368,202	3,737,375

by WHO Region as of 1990 (or for the most recent year for which information is available) are shown in Tables 1 and 2. Although only a proportion of estimated cases are ever registered for treatment, the information on registered cases reflects, to a large extent, the leprosy situation in any given region and its relative importance *vis-à-vis* other regions.

The number of registered cases by regions has varied over the years, as shown in Table 2 for the years 1966, 1976, 1985 and 1990. However, the information is not strictly comparable over the four years as the number of countries for which information was available has also varied over this period.

The South-East Asia Region, which contributes to the largest share of registered cases in the world, had shown a dramatic increase between 1966 and 1985 with a steep decline in 1990. A large proportion of the cases and changes are in India.

The African Region shows a steady decline in the number of registered cases over the

past two and a half decades. Whether this is due to reduced case-finding activities, to a true reduction, or to both, is not clear.

With regard to the Western Pacific Region, Table 2 indicates a marked increase for 1985, followed by a decrease in 1990. The increase for 1985 is due mainly to the inclusion of information from the People's Republic of China which was not available earlier.

The American Region shows a steady increase in the number of registered cases. A large proportion of this increase is contributed by Brazil.

With regard to the Eastern Mediterranean Region, Table 2 indicates a steady increase over the years. This appears to be largely due to increased case detection.

In the European Region there is a steady decline, the problem itself being quite limited.

Multidrug therapy (MDT)

The last decade has seen several important developments in leprosy and leprosy control. The most important ones were the recognition of the alarming increase in the resistance of *Mycobacterium leprae* to dapsone (both secondary and primary) and the threat this posed to the limited gains made in leprosy control until then, to the availability of more potent

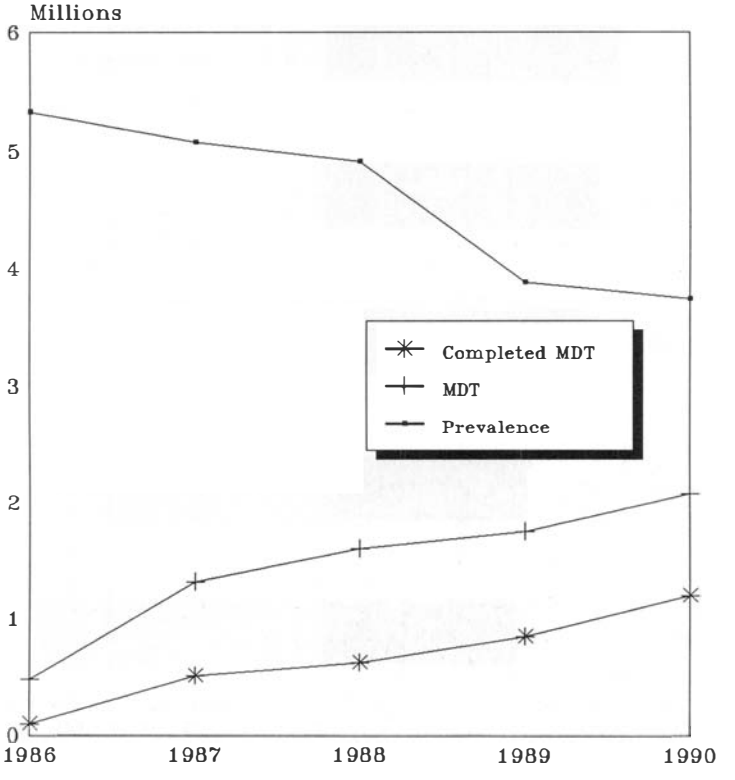

Figure 2. Leprosy prevalence and MDT coverage in the world, 1986–90.

antileprosy drugs and, last but not least, to the recommendations in 1981 of a WHO Study Group on Chemotherapy of Leprosy for Control Programmes to combat drug resistance and to make leprosy treatment more effective and acceptable. The WHO recommendation on MDT is recognized today as a major technological improvement in leprosy control. Indeed, it represents a landmark in the history of leprosy.

With the problem of dapsone resistance increasing in its dimensions, and with the availability of better bactericidal drugs against *M. leprae* such as rifampicin in the 1960s, the application of leprosy treatment through combinations of drugs became a clear possibility. It was realized that with leprosy patients harbouring very large bacillary populations similar to those of tuberculosis patients, successful chemotherapy should be one which was capable of preventing the selection of drug-resistant mutants as well as killing all, or nearly all, of the drug-sensitive organisms. With the selection of drug-resistant mutants being prevented and the killing of nearly all drug-sensitive organisms, it was expected that relapse after stopping chemotherapy could virtually be prevented.

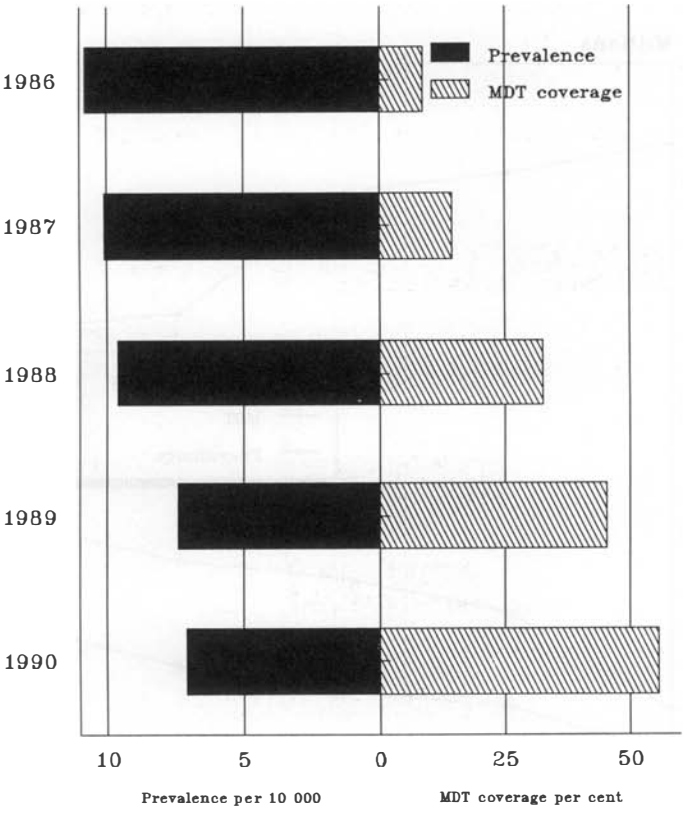

Figure 3. Global leprosy prevalence and MDT coverage, 1986–90.

Recommendations of the WHO Study Group

The standard MDT regimens for paucibacillary and multibacillary leprosy recommended by the WHO Study Group are by now familiar to many health workers.

The recommended standard regimen for paucibacillary leprosy is rifampicin 600 mg once a month for six months, plus dapsone 100 mg daily for six months. The administration of rifampicin should invariably be fully supervised, but dapsone may be given unsupervised.

The recommended standard regimen for multibacillary leprosy is: rifampicin: 600 mg once a month, unsupervised; dapsone: 100 mg daily self-administered; clofazimine: 300 mg once a month, supervised, and 50 mg daily self-administered.

Treatment should be continued for at least two years and, wherever possible, up to smear negativity. In many programmes, dapsone-treated multibacillary patients continue to receive dapsone monotherapy, often for life, even after becoming smear negative. Where resources permit, it is recommended that such patients should be given MDT for two years and chemotherapy should then be stopped. The recommendations were made under very special circumstances which included the urgency of the situation as a result of widespread dapsone resistance, and the need to apply all available knowledge and technology in a practical way. The recommendations were directed primarily towards leprosy control and less towards the individual treatment of patients. Maximum advantage was taken of all available information and operational and cost factors were given due consideration. The Study Group fully realized the limitations of the then available information and recommended more research in relevant areas, and the collection of information on experiences with regard to relapse following completion of MDT.

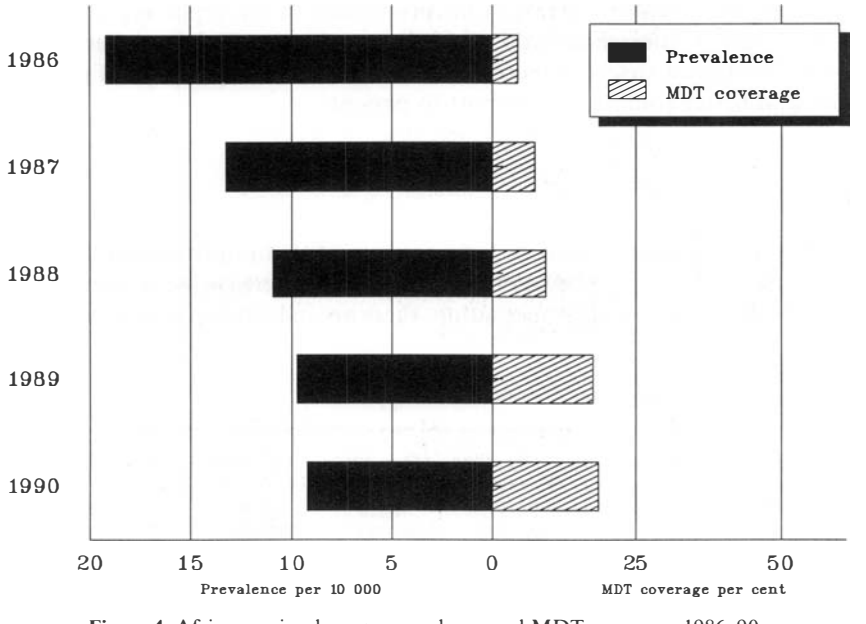

Figure 4. African region leprosy prevalence and MDT coverage, 1986–90.

Acceptance of the recommendations on MDT

The recommendations received enthusiastic support from most of the leprosy-endemic countries, WHO Regional Committees, international and national nongovernmental organizations (NGOs), donor agencies and professional bodies. However, there were problems of acceptance in some countries and projects. These were ultimately resolved largely as a result of positive experiences in areas which had introduced MDT fairly early and through a better understanding of MDT as a public health tool in achieving disease control. Some countries had introduced modifications to the WHO recommended regimens, but these were generally minor and within the essential requirements for MDT. In several countries MDT provided the opportunity to increase the priority for leprosy control and strengthen their political commitments. This was also true for NGOs and donor agencies.

Progress with implementation of MDT

The coverage of leprosy patients with MDT has rapidly increased over the past few years and in September 1990 reached 55·7% of the total registered cases. The increasing acceptability of MDT among national health services and leprosy patients themselves is due to: (a) the fixed, and relatively short duration of MDT treatment; (b) the low-level of toxicity and treatment-related side-effects; (c) the very low relapse rates following completion of treatment (0·12% per year for PB and 0·22% per year for MB based on information from 18,980 PB cases and 9292 MB cases); (d) the high level of acceptance of clofazimine discolouration (0·4% refusal in 31,923 patients); and (e) significant reduction in frequency and severity of ENL reactions. One more advantage of the WHO/MDT regimens is the considerable increase in the proportion of self-reporting cases at an early stage of the disease. Consequently, this has led to a reduction in the number and degree of deformities among new cases; an increased acceptance and compliance of patients to the treatment; and better community support to patients.

MDT coverage

Table 3 and Figures 2 to 8 show the global progress of MDT implementation from 1985 to 1990. For the first time, and in spite of the considerable increase in the number of newly-detected cases during MDT implementation, there are indications of a decline in the total

Table 3. Progress with implementation of multidrug therapy (MDT)

Year	Oct. 1985	Oct. 1986	Oct. 1987	Oct. 1988	Oct. 1989	Sept. 1990
Registered cases (000's)	5,368	5,341	4,813	4,908	3,866	3,737
No. of cases on MDT	78,752	468,222	699,589	1,604,927	1,751,903	2,080,998
% of total cases on MDT	1·47	8·77	14·54	32·70	45·32	55·7
No. of cases who completed MDT (cumulative total)	9,425	93,216	510,593	627,919	853,706	1,204,821

Table 4. Level of coverage for MDT in 93 leprosy endemic countries (prevalence rate of at least 1 per 10,000)

	Countries in WHO regions with MDT						
MDT coverage (%)	AFR	AMR	EMR	EUR	SEAR	WPR	Total
>76	8	12	3	0	4	12	39
51–75	7	2	1	0	3	3	16
26–50	4	4	0	0	2	2	12
11–25	8	1	3	0	0	1	13
1–10	10	0	1	0	0		11
No information	1	0	1	0	0		2
Total	38	19	9	0	9	18	93

number of registered patients in the world. This decline supports the efficacy of the WHO/MDT regimens for leprosy control and opens the possibility of major reductions. However, as shown, the world coverage with MDT for leprosy is very uneven and efforts need to be made to strengthen treatment capabilities in countries and regions where leprosy is endemic.

The coverage of MDT in 93 leprosy endemic countries is given in Table 4. Thirty-nine countries (or 42%) have 76% or more of their registered leprosy patients on MDT, and 55 countries (or 59%) have at least 50% MDT coverage of their patients.

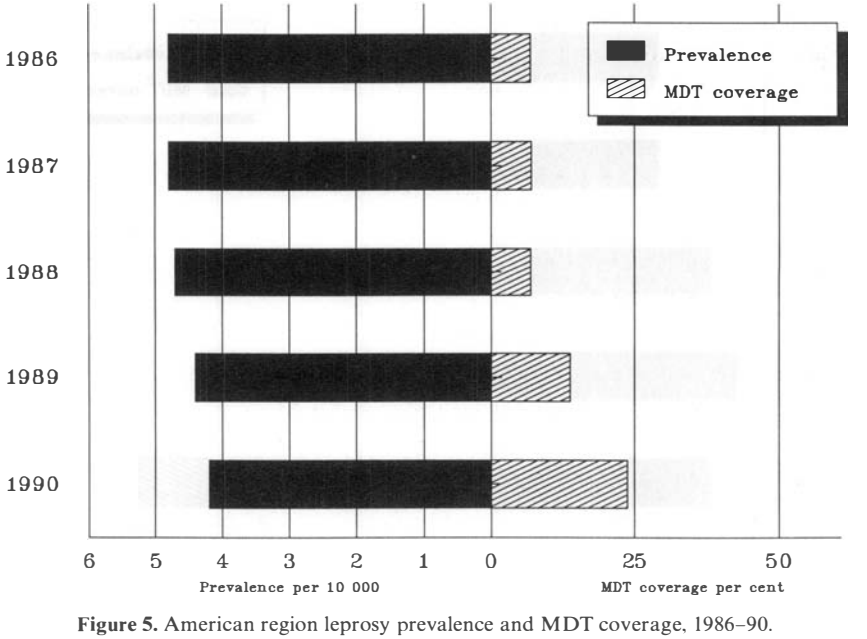

Figure 5. American region leprosy prevalence and MDT coverage, 1986–90.

Positive experiences with MDT to date

Technical

On the technical side the positive experiences include:

(a) the low frequency of drug toxicity in the field;
(b) the high level of acceptance of clofazimine discolouration;
(c) patient satisfaction with clinical response;
(d) the significant reduction in frequency and severity of ENL reactions; and
(e) very low relapse rates after cessation of treatment.

Operational

On the operational side the positive outcomes include:

(a) the marked increase in treatment compliance by patients;
(b) increase in detection of new cases through voluntary reporting;
(c) better motivation among health workers; and
(d) greater community support resulting from the recognition of MDT as effective technology.

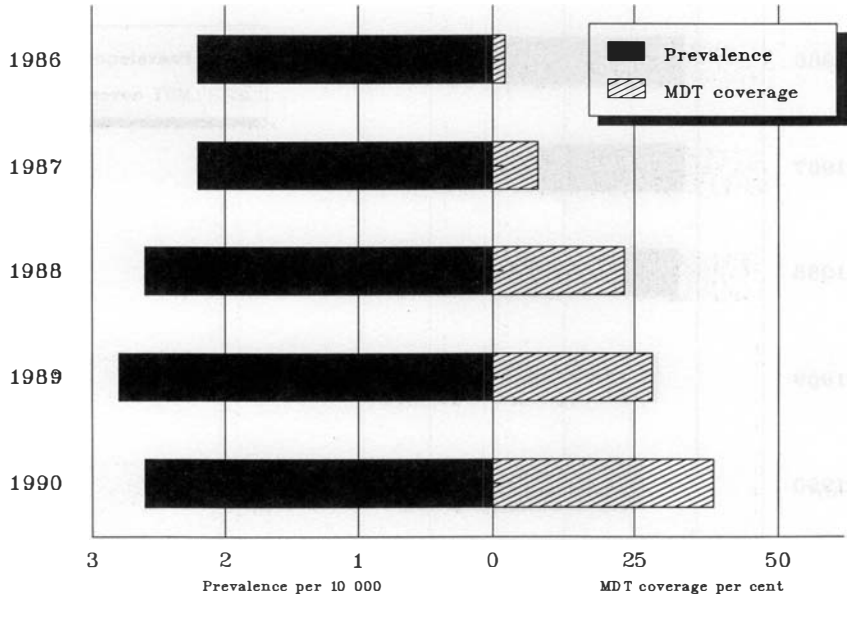

Figure 6. Eastern Mediterranean region leprosy prevalence and MDT coverage, 1986–90.

Problems relating to MDT

Technical

The technical problems experienced so far include:

(a) difficulties in classifying a proportion of patients, partly as a result of inadequate laboratory services;
(b) disappointment with the slow decrease of BI;
(c) slow clinical response following the initial period of very satisfactory response;
(d) difficulties in distinguishing between relapse and late reversal reactions in PB leprosy;
(e) lack of any impact in the deformity situation.

Operational

The operational and administrative problems include:

(a) the inability to increase the priority for leprosy in some countries as a result of other pressing health needs;
(b) poor health infrastructure to cope with MDT;
(c) inadequate resources, particularly for drugs;
(d) absence of a proper plan of action to implement MDT;
(e) inadequate training of health workers;
(f) lack of laboratory facilities for skin-smear examinations;
(g) poor referral facilities to deal with complications; and

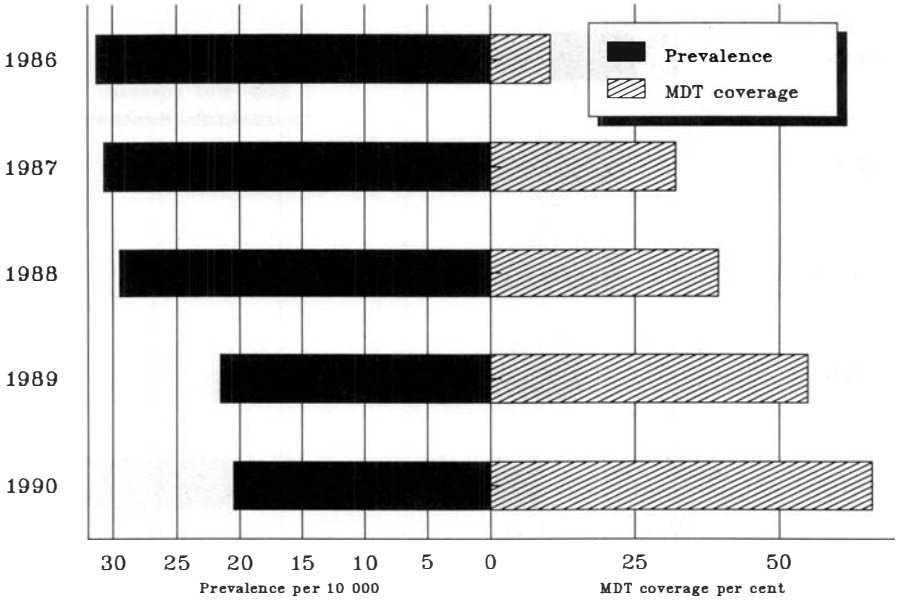

Figure 7. South-East Asian region leprosy prevalence and MDT coverage, 1986–90.

(h) insufficient patient education about what to expect from MDT so that when the time comes for stopping treatment, the decision would be acceptable to the patients.

The need for co-ordination

In spite of the current progress, leprosy control through MDT is facing a number of problems which are slowing its implementation and coverage. The most important ones are: (a) leprosy is often not considered a health priority by governments because the disease and its disability effects are not fully appreciated; (b) in many countries, awareness of and concern for people with leprosy is often restricted to a small number of health professionals (usually those working for voluntary organizations or missions) highlighting the important need for training of health workers at all levels, including district level health managers; (c) the high cost of MDT regimens *vs* dapsone monotherapy; (d) a major constraint in many endemic countries is the poorly-developed health infrastructure as well as the PHC system which make it difficult to reach target populations; and (e) lack of adequate laboratory facilities for skin smear examinations.

However, over the last few years, a few leprosy endemic countries have increased their budget for leprosy control activities, based on the implementation of MDT. In addition, a substantial proportion of funds for the purchase of drugs and related operational costs come from international, bilateral and voluntary organizations, especially the International Federation of Anti-leprosy Associations (ILEP) and the Japan Shipbuilding Industry Foundation (JSIF). Considering the increased need for funds, material and

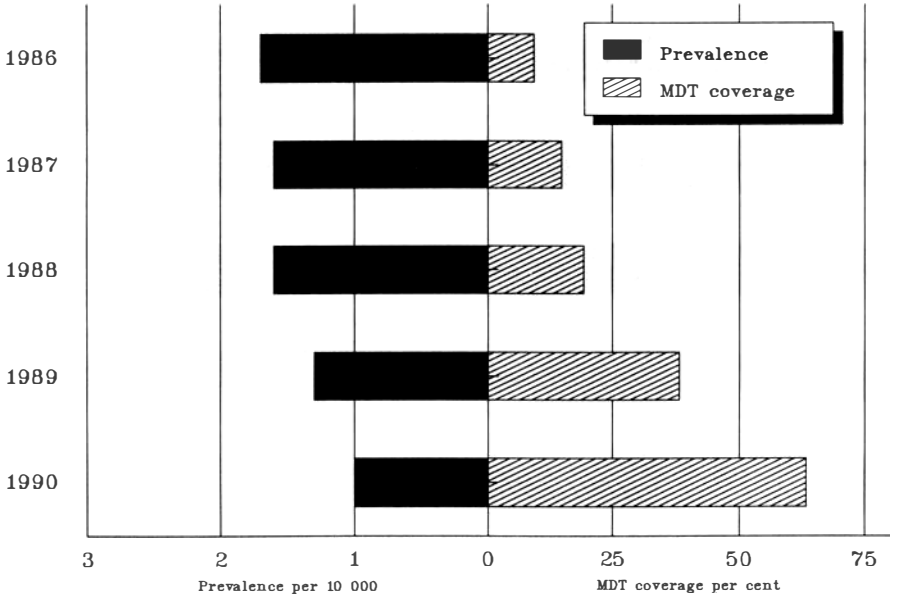

Figure 8. Westen Pacific region leprosy prevalence and MDT coverage, 1986–90.

human resources for a more rapid expansion of MDT coverage, it is important to develop mechanisms for the optimal utilization of available resources at the global, regional and national levels in addition to seeking additional resources. In this respect the WHO Expert Committee on Leprosy in its sixth report strongly advocates effective co-ordination between the national government, national and international non-governmental organizations and other international contributing agencies for optimal utilization of available resources for better leprosy control.

Disability prevention and rehabilitation

Regarding the problem of disability in leprosy, a considerable portion of the disability load is the result of failure to incorporate into leprosy control programmes activities relating to the prevention of disabilities by using simple technologies and patient motivation. While one should admit that current technologies for prevention of deformities are relatively weak, there is no justification for not putting into use what is available.

In spite of all efforts towards early detection and treatment, a proportion of patients will develop deformities and the situation cannot be ignored. Leprosy control programmes are as much medical care programmes as they are programmes for disease prevention, and the prevention and treatment of deformities are part of the medical care. However, we would like to promote rehabilitation based primarily on the involvement of the community, where emphasis will be on the participation of the individual and the family in the rehabilitation efforts.

A major problem confronting control programmes, and one that will continue to confront them for many more years in spite of an increase in the implementation of MDT, is the group of leprosy patients already disabled. It is in this connection that we would like to promote cost-effectiveness approaches such as community-based rehabilitation (CBR).

CBR is a concept closely related to primary health care (PHC). The CBR approach tries to solve the problems in a different way from the institution-based rehabilitation (IBR) hitherto advocated. The CBR approach promotes awareness, self-reliance and responsibility for rehabilitation in the community; builds on manpower resources in the community, including the disabled themselves, their families and other community members, as the disabled and their family members are called on to take an active part in the training efforts; encourages the use of simple methods and techniques which are acceptable, affordable, effective and appropriate to the local setting; uses the existing local organization and infrastructure to deliver services, especially primary health care services, and takes into consideration the economic resources of the country and thus allows for an eventual extension to provide total coverage according to perceived needs.

While there is no doubt that all components of patient care deserve attention, it is important, particularly in the light of resource constraints, that leprosy programmes invest more on those patient-care components that are clearly cost-effective and capable of complementing the implementation of MDT.

Community participation

The participation of the community is highly crucial in several of the activities in leprosy control. This is particularly so in view of the strong stigma against the disease found in many societies. The social problems relating to leprosy, however difficult that may be, can be solved only by facing them squarely and devising appropriate solutions through health education and other measures, and not by evading the issue or by developing cosmetic approaches. Social stigma, severe as it may be in many situations, is often used as an easy excuse for poor performance by health workers in leprosy, when it is quite possible to deal with it in an effective manner.

In most societies, family and community support for leprosy patients does exist, in small measure however, and what is required is to mobilize and strengthen it through community action. It is here that the primary health care approach plays a vital role in disease control which no amount of investment in high technology can replace.

Future prospects

With an increasing political commitment in many countries to deal with leprosy effectively, with the increasing appreciation of the value of MDT as a very potent technology, and with increasing international co-operation, both from the bilateral and multilateral sectors enabling additional inputs, it is not unrealistic to expect a reduction of leprosy caseload by as much as 60 to 80% in the next five to ten years, at least in countries with effective programmes. However, notwithstanding anticipated major reductions in prevalence, it should be recognized that other problems will remain for a long time to come such as disabilities among old cured patients and a continued, albeit reduced, incidence of new disease arising from infections caught several years earlier. Hence, apart from investing heavily on efforts to reduce leprosy prevalence through MDT, there is a need to plan for the future so that leprosy control becomes part and parcel of primary health care encompassing early detection, treatment, as well as disability prevention and management.

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SPECIAL ARTICLE

Setting up HIV serology for the Karonga leprosy vaccine trial in Malawi

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Summary As part of the leprosy vaccine trial taking place in Karonga District, Northern Malawi, it is essential to establish whether the presence of HIV infection in the population is affecting the incidence rate or clinical presentation of leprosy or the effectiveness of the trial vaccines. To obtain the appropriate information, a rapid and economical HIV testing protocol, which could be performed in a rural laboratory and would be robust under variable environmental conditions, had to be developed. This paper reports on the development/evaluation phase of a multitest protocol based on commercially available particle agglutination and ELISA anti-HIV antibody detection kits. The protocol was devised by first evaluating a range of kits in London using a battery of African and non-African sera and then field testing 1455 sera in Malawi, which included 184 sera from leprosy patients and 60 sera from syphilis patients to check for cross-reactivity. According to the protocol developed, all sera are screened initially both by indirect ELISA (Organon) and using a rapid and economical modification of the Serodia particle agglutination test. Positives are retested using both a competitive ELISA (Wellcome or Behring) and the standard Serodia particle agglutination test. The validity of this multitest protocol was confirmed by Western blotting a large sample of the positive and negative Malawian sera in London. Factors affecting kit selection, and problems associated with individual kits, are discussed. While the specific multitest protocol developed for Malawi might not be suitable for every project, the principle of developing economical alternatives to Western blotting is an important consideration for any field investigation of HIV.

Introduction

It is well documented that individuals with HIV infection are at increased risk of certain mycobacterial diseases, in particular tuberculosis and the so-called atypical mycobacterioses.[1,2] The possibility that HIV might affect incidence rates or clinical presentation of leprosy has been conjectured, but is still an open question.[3–5] This issue has become of

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critical importance to the antileprosy vaccine trial currently being carried out in Karonga District, Northern Malawi.[6] HIV infection has been recognized in Malawi at least since 1985.[7–12] Given that HIV infection is known to be endemic in the vaccine trail population, interpretation of the data obtained from the trial would be compromised in the absence of information on HIV infection and its implications for leprosy incidence and vaccine effect. For this reason a proposal to carry out a case-control study of leprosy and HIV infection, in the context of the vaccine trial, was submitted to the Malawi government, was approved and began in 1988. The study entails the comparison of HIV status between leprosy patients and control groups matched for age, sex and area of residence.

The case-control study involves carrying out HIV serological assays on both leprosy cases and controls selected from within the population of Karonga District. The results of this study will be reported at a later date, but this paper describes steps undertaken to set up the laboratory protocol for work carried out in Malawi. It is felt that our experience may be of help to other researchers contemplating similar studies. It should be emphasized that the samples used in the preliminary studies reported here were highly selected, hence prevalence rates should not be inferred from the frequencies obtained.

Review of methods available for HIV testing

A number of methods of detecting antibodies to HIV, the usual criterion used for infection, are currently available (Table 1). The most widely used diagnostic kits are those employing the ELISA technique. These may either be of the sandwich type where specific HIV antibodies are detected with a second labelled antiglobulin reagent (e.g. Organon, DuPont, Elavia) or of the competitive type where specific HIV antibodies compete with labelled anti-HIV (e.g. Wellcome, Behring). Western blotting works in principle as a sandwich ELISA but in this case viral proteins are separated by SDS polyacrylamide gel electrophoresis and transferred to nitrocellulose prior to incubation with test sera, so that antibodies to individual viral components may be detected (e.g. Biorad, Elavia, Du Pont). Increasing in popularity are the particle agglutination tests in which gelatin (Serodia) or latex beads (Cambridge Biosciences) are coated with viral antigens for incubation with sera. In addition to the above methods are immunofluorescence and slide tests (e.g. Karpas).

The most widely used method of determining HIV status, at least in areas of low prevalence, has been to screen sera by ELISA. Positive results may be repeated and then tested by Western blot, which has been taken as a standard.[13,14] Antibodies detected by Western blot include antibodies to core antigens p17, p24 and p55 (*gag* gene products) and to envelope glycoproteins gp41, gp120 and gp160 (*env* gene products).[15] Although diagnosis of HIV positivity is now commonly made if antibodies to both *gag* and *env* products are observed,[13,14] a serum containing anti-p24 alone may indicate HIV positivity.[13,16] In European studies seroconversion is generally found to be accompanied by the appearance of anti-p24 followed by anti-p55 several weeks after infection.[16–18] Western blots highlight changing antibody profiles with the onset of AIDS (in particular the decline of anti-core antibodies in Europeans).[15,17,19] In contrast, false-positive or 'indeterminate' sera containing only antibodies to *gag* gene products have been identified,[20–27] some by repeated sampling over a period of time[20,22] and some by a failure to culture virus.[21] Additional problems include cross-reactions between viral proteins and

Table 1. Summary of the major types, suppliers, advantages and disadvantages of kits available for the detection of anti-HIV antibodies.

Type	Suppliers (e.g.)	Advantages	Disadvantages
Sandwich ELISA		Printed records, suitable for plasma.	Requires a plate reader.
	Organon Teknika	Uses dilute samples, suitable for filter papers.	
	Diagnostics Pasteur (ELAVIA)	Control well for each sample, different viral isolate (LAV).	
	Abbott		Bead technology—requires specialized equipment.
Competitive ELISA		Printed records.	Uses more sample, may not detect all variants (e.g. HIV2).
	Behring		
	Wellcome	Suitable for filter papers.	False negatives with plasma, peroxidase problems, supply problems.
Particle agglutination		High sensitivity, negative control for each sample.	No printout of results.
	Cambridge Biosciences		No UK agent.
	Fujirebio (Serodia)	No major equipment required	Not advised for testing plasma samples.
	Edgware modification of above	Low cost.	Requires centrifuge, limited lifespan of particles.
Slide tests	Karpas		Background problems with African sera.
	Organon		Requires a fluorescent microscope.
Western blot		Gives qualitative information.	High cost, difficult to interpret, nonspecific bands.
	Biorad, DuPont, Diagnostics Pasteur		

The various comments in this table obtained from the literature and by observation of the kit instructions are meant as rough guides only, and should be interpreted in the context of specific applications envisaged.

antibodies to other retroviruses or to other proteins in the HIV preparation.[28] Advice as to the appropriate protocol for testing such sera has varied.[26,29]

The available tests differ in the number of false positives they detect and in their ability to detect seroconverters and diseased individuals. These differences are associated with the virus preparation and methodology employed.[22,23,30,31] However, as techniques have become more sensitive,[32,33] in some cases even more sensitive than the Western blot, it is becoming accepted practice for other tests to replace the Western blot for confirmation. This has been proposed both for Europe/USA[32,34] and for Africa.[35–37] A combination of two tests based on different methodologies (e.g. ELISA and particle agglutination tests) reduces the chance that nonspecific factors will interfere with both tests and result in a false positive.[33] Some studies have given equal weight to each test.[32] Alternatively, an

initial screen using the most sensitive test can be followed by a second highly specific test on positive samples only. Problem sera (e.g. positive by the more sensitive test, negative by the more specific test) may then be analysed by Western blotting.[36,38]

Western blots are not ideal for Africa,[30,39] where the incidence of HIV is high, because of their cost (e.g. Biorad costs £12.80 per sample) and because blot profiles of positive African sera may differ from those of Western sera.[40] False-positive or uninterpretable results associated with apparent anticore antibodies and nonspecific weak bands have been identified.[35,40,42] Many evaluations of ELISA and particle agglutination tests have been reported (e.g. [32,43–49]), giving details of sensitivity, ability to detect seroconverters[33,50] and specificity together with reactions with panels of problem sera.[22] However, these surveys, carried out using sera from Europe and America, have not always reached similar conclusions. Since most commercial kits are still evolving (e.g. the use of recombinant peptides is now increasing at the expense of whole virus preparations), reported evaluations are not necessarily appropriate to current kits. Whereas there has been much discussion as to the suitability of various tests for Africa,[30,39,40,42,51] there have been few comprehensive evaluations.[35–37,52–55]

Selection of tests for evaluation

Our selection of tests to be evaluated for HIV testing in Malaŵi was determined in part by the circumstances in which the work was to be carried out. The project laboratory in Chilumba has carried out routine microscopy on slit skin and sputum smears, sputum culture, and syphilis serology for several years. Located in a rural area, many reagents must be shipped from London. Distilled water is available, but electricity is generated for only 8 to 9 hours per day. Ambient temperature in the laboratory varies between 28°C and 36°C, resulting in suboptimal performance of refrigerators and freezers. The technicians had very limited experience in techniques relevant to HIV testing.

The following specific issues were considered when selecting and evaluating tests (see Tables 1 and 2):

1 We reviewed the literature on HIV tests employed in countries in Central, East and South Africa and found that a variety of tests had been used: 'Organon' in Tanzania[56] and Rwanda,[57–59] 'Wellcome' in Zambia[4,60] and Uganda,[61,62] and 'Abbott' in Zimbabwe[63] and South Africa.[64] In Malaŵi itself the larger hospitals in the South had used a 'Wellcome' test alone.[12] However, smaller hospitals generally have had access only to the 'Serodia' particle agglutination test. We decided to evaluate all tests used in neighbouring countries, except for Abbott kits which use a bead technique requiring additional specialized equipment. All evaluated tests can be read either by eye (particle agglutination tests) or using a Multiskan (Flow Laboratories) 96-well platereader (ELISAs) purchased for the Chilumba laboratory.

2 A variety of antigen sources were considered. Many companies grow HIV for ELISAs and Western blots in H9 cells, but these cells may be a source of cross-reactions with African sera.[42] In contrast, the virus used in ELAVIA kits is both an independent isolate (LAV) and is grown in the CEM cell line. For this reason, the Elavia ELISA was evaluated to provide an alternative antigen source to that used in Organon and Wellcome kits. Use of recombinant antigens may alleviate some of the problems of cultured virus.

Table 2. Selected characteristics of the five serological tests evaluated.

Nature of test	Organon Sandwich ELISA	Elavia Sandwich ELISA	Wellcome Competitive ELISA	Edgware Particle aggln.	Serodia Particle aggln.
Negative control per sample	no	yes	no	yes	yes
Recommended for plasma samples	yes	yes	(yes)	no	(no)
Recommended for heat-inactivated samples	no	no	yes	yes	yes
Recommended incubation temperature	37°C	37°C	45°C	RT	RT
Test readable by eye	yes	no	yes	yes	yes
Printed record of results	yes	yes	yes	no	no
List price per test January 1990	£1.50	£1.02	£1.45	£0.09	£0.85

3 Tests employing several different techniques were to be included in the evaluation. Both indirect and competitive ELISAs were included, since these form a potentially useful combination of tests.[39,51] Indirect ELISAs may be prone to false positives due to cross-reactions,[39] but competitive ELISAs may be too specific to pick up newer variants of HIV in Africa.[30] Competitive ELISAs might be more likely to give false negatives, e.g. from washing problems,[51] but may be capable, like particle agglutination tests, of detecting IgM antibodies.[50,51,65]

4 Reported sensitivities (true positives/(true positives + false negatives)) and specificities (true negatives/(true negatives + false positives)) were considered from studies in which many different samples had been tested as well as from those in which end-point titrations had been assessed.[35,36,43–45,47–49,54,66] Tests were usually reported to be both highly sensitive and highly specific (i.e. > 98%) on European sera. It was noted that the reported sensitivity of particle agglutination tests was particularly high[46,50,53,55,65,67,68] as was the sensitivity of tests incorporating recombinant antigens.[69,70] However, there were relatively few evaluations carried out using sera from Africa,[35–37,52,54,71] and hence we were hesitant to place too much emphasis on reported estimates of sensitivity and specificity.

5 Kits were evaluated if they had features likely to enhance specificity. ELAVIA kits, for example, incorporate an uncoated well for every antigen-coated well to serve as a blank for each sample.[30] Organon kits require substantial (1/34 or 1/100) dilutions of sera prior to testing, thereby reducing interference by nonspecific factors.[51] Problems with a peroxidase inhibitor, resulting in false positives, are known to occur with at least two of the three generations of Wellcome kits.[51,54,66,72–75] This problem has not been reported for the Behring competitive ELISA.[74]

6 HIV-2 has not been reported from Malawi to date. However, to have an initial anti-HIV-1 screening test which could also detect at least a proportion of HIV-2 positive sera was considered important. No combined anti-HIV-1 and HIV-2 detection kits were available at the time of this evaluation, although in 1990 several kits are appearing on the market (e.g. Peptilav[76]). An indirect ELISA with whole HIV-1 viral antigen may detect up to 70% of HIV-2 positive individuals, whereas competitive ELISAs may pick up less than 50%.[54,70,77–79] Cross-reactivity between HIV-1 and HIV-2 is mainly associated with core proteins.[77] Western blotting against both sets of viral antigens is necessary to differentiate between HIV-1 and HIV-2. Particle agglutination tests for detection of anti-HIV-1 are not suitable for the detection of anti-HIV-2.[53,67] The efficiency with which sandwich ELISAs using recombinant HIV-1 antigens will detect anti-HIV-2 appears to depend on

the nature of the antigens.[69,70,79] The Organon sandwich ELISA included in our evaluation uses whole HIV-1 viral antigen and is reported to detect cross-reacting antibodies in more than 50% of HIV-2 infected individuals.[77]

7 Most of the blood samples to be used in the Malawi study are drawn by venepuncture. However, we wanted the option to use whole blood collected on filter paper. Some of the control specimens would be recalcified plasma. The Wellcome competitive ELISA has been used successfully to test sera dried on filter paper,[80] and Litton Bionetics,[81] ElectroNucleonics,[81] Cellular Products[82] and Organon Vironostika[83] tests have been used successfully for testing dried whole blood on filter paper. The Wellcozyme recombinant ELISA gives false-negative results at the recommended incubation temperature of 45°C if plasma is used instead of serum.[84] The Serodia particle agglutination test is also not recommended for use with plasma. We also considered reports of using heat inactivated sera[80,85] and filter paper dried bloodspots[83] and whether any problems were found using haemolysed samples, or using stored or frozen-and-thawed sera.[35,45,81,85,86]

8 Choice of kit was also influenced by cost (e.g. see Table 2), reliability of supply, and the shelf life given for the kits at the time of supply. Supply problems were encountered only with Wellcome, which resulted in test evaluations being carried out on first-generation kits in London but on third-generation kits in Malawi. Shelf life was of particular interest for particle agglutination tests, where HIV-coated particles have only a limited lifespan after reconstitution.

Apart from these various practical considerations it was also important to bear in mind when carrying out our evaluation that the presence of high levels of antibodies and immune complexes associated with infectious diseases common in Africa, such as malaria, syphilis and leprosy, may reduce the specificity of HIV tests.[42] In earlier studies,[87–89] for example, prevalence of HIV was found to correlate with the magnitude of the anti-*P. falciparum* antibody response, even though no cross-reactivity between retroviruses and *P. falciparum* could be demonstrated.[87–90] False positives have also occurred with sera from leukaemic patients who have received multiple blood transfusions,[46] and with sera containing anti-HLA antibodies,[49,91–93] Drugs which are in common use in Africa must also be considered when HIV testing, since these may also interfere with antibody screening. Although these factors did not influence the choice of kits evaluated, they would need to be taken into account in interpreting results obtained.

After considering points 1 to 8 above, the kits (Table 2) we chose to evaluate for use in Malawi were: the sandwich ELISA tests Organon Vironostika anti-HTLVIII (='Organon') and Diagnostics Pasteur ELAVIA Ac-Ab-Ak1 (='ELAVIA'); the competitive ELISA Wellcozyme anti-HTLVIII (='Wellcome'); and the particle agglutination assays Fujirebio Serodia. HIV (='Serodia'), and a rapid economical modification of the Serodia test developed[67] at the North London Blood Transfusion Service (='Edgware').

Evaluation of tests in London

1 FAMILIARIZATION WITH THE TESTS

The first evaluation of these kits in London was performed on a small panel of well-defined samples: UK Public Health Laboratory Service (PHLS) positive, weak and low positive, and negative plasmas; and Malawian sera from known HIV positives and

negatives, from an AIDS patient, from an HIV negative syphilitic, and from an HIV negative leprosy patient. This was primarily to familiarize ourselves with the kit protocols, and to test them under simulated field (e.g. varying incubation temperatures) conditions and with variable sample preparation (e.g. heat inactivation) methods.

All tests performed accurately according to their manufacturers' internal quality control criteria. In addition, when used strictly according to kit protocols, most tests gave the predicted results, even the Serodia test despite the fact that it is not recommended for use with plasma samples. Its Edgware modification did give false positives with plasmas at low dilution, and the Elavia kit gave readings between the negative and positive cut-off values (in what is classified as a 'negative but for repeat' category) for the weak and low positive control plasmas. Titrations using the known Malawian positive sera showed that the Serodia and Edgware particle agglutination assays were at least five times as sensitive as the Organon and Wellcome ELISAs. Hence, the Edgware test would provide a cheap and sensitive first screen test in a multitest screening protocol. Except for one nonrepeatable false positive by Edgware, no cross-reacting antibodies were detected by any test for the leprosy and syphilitic positive sera.

Heat inactivation (3 hours, 56°C) interfered with ELISAs but did not affect performance of the particle agglutination assays. The Wellcome ELISA failed to detect one low positive plasma when carried out at 37°C rather than the recommended 45°C, although 37°C has been reported as a suitable incubation temperature for the recombinant kit when using plasma.[84] The Edgware particle agglutination assay was found to work well at temperatures ranging from 4°C to 37°C and thus would be robust under variable field conditions. It was necessary, however, to use particles freshly reconstituted or stored at 4°C for a maximum of two weeks. Particles stored in the freezer became sticky and frequently gave false positive results.

Plates from the Organon and Wellcome (but not Elavia because of the use of the uncoated blank well) ELISAs could be read by eye, which would be useful in the event of equipment failure. There is, however, little information concerning the sensitivity and specificity of visual readings,[94] and the results read by eye would not be quantitative. Similarly, results of the particle agglutination assays are read by eye and provide only +/− data.

Following this initial screen, all test incubations were performed at 37°C and we decided not to heat inactivate any samples. The next step in our London evaluation was to test a larger panel of Malawian sera to establish that there were no additional problems with the assays specific to this population, and to see if we could establish a cheap and reliable multitest screening protocol for use in the Chilumba laboratory.

2 TESTING MALAWIAN SAMPLES IN LONDON

The second evaluation in London was carried out on 114 Malawian sera selected from a patient group we suspected would contain both HIV positive and HIV negative samples. These were screened initially using the Organon and Edgware tests. One hundred were negative by both methods. A sample of 34 of the 114 sera (including all Organon and Edgware positives) were tested by Wellcome, Serodia and Elavia methods. Of these 34 sera, six were positive by all five methods, and eight were positive by one or more but not all assays (Table 3). The remainder of the 34 were negative by all assays. Western blotting (Elavia HIV1 Blot and Biorad Blot) was performed on the eight variable result sera, but this did not completely resolve the problems which fell into three different categories:

Table 3. Detailed results of eight sera which showed anomalous results.

	Organon	Edgware	Wellcome	Serodia	Elavia	Elavia blot (HIV-1)	Biorad blot
3460	– –	+ –	–	+	–	–	–
3491	– –	+ –	–	+	–	–	
3495	– –	+ –	–	+	–	–	(–)
3511	– –	– –	–	–	+ +	(–)	(+)
3516	– –	– –	–	–	(+)+	(–)	
3528	– –	– –	–	–	(+)+	(–)	(–)
3440	– –	– +	+ +	–	– –	–	–
3509	– –	(–)+	(–)–	+	–(+)	(–)	(+)

( ) ELISA (Wellcome and Elavia) = results within 10% of cut off.
( ) Particle agglutination tests = doubtful result (see text) (Edgware and Serodia).
(+) Western blotting = weak anti-core and anti-envelope activity.
(–) Western blotting = indeterminate (i.e. anti-core or anti-envelope only).
Two results indicate that the samples were tested twice.

1 Three sera were clearly positive by particle agglutination tests but negative by ELISA and Western blotting (see Table 3). Since Western blotting may not be the most sensitive technique,[32,33,50] a negative Western blot result does not rule out a positive HIV response. Repeat sampling, which is exceedingly difficult in the project area, would be required to determine whether these were false positives or seroconverters.

2 Some problems were specific to the Elavia ELISA test kit. This is demonstrated by examination of the distribution of test OD/cut off OD values for the ELISA tests (Figure 1), which indicates the segregation of positive and negative values.[47] The clearest separation of positive and negative values was given by the Organon kit. Three samples were over the cut off by the Elavia test (Figure 1) but failed to react by other tests (Table 3). Indeterminate results were obtained when these 3 sera were incubated with Elavia HIV1 blot strips (Table 3) and, when blotted against Elavia HIV2 Western blot strips (not shown), they showed reactivity only against core proteins—an inconclusive result. These results were reminiscent of the problems we had encountered earlier with weak and low positive control plasmas, and we decided not to include Elavia kits in further development of the routine screening protocol.

3 One sample (3440, Table 3), which was positive only by Wellcome ELISA, was HIV negative when the Wellcome test was performed as a sequential ELISA adding serum prior to the addition of conjugate. This was consistent with previous observations[66,72–74] of false positives due to the presence of a peroxidase inhibitor in the serum.

Establishment of an HIV multitest protocol

On the basis of these two evaluations, the following multitest protocol for HIV testing was developed for use in the Chilumba laboratory:

1 All samples to be screened initially by two tests based on different principles—the

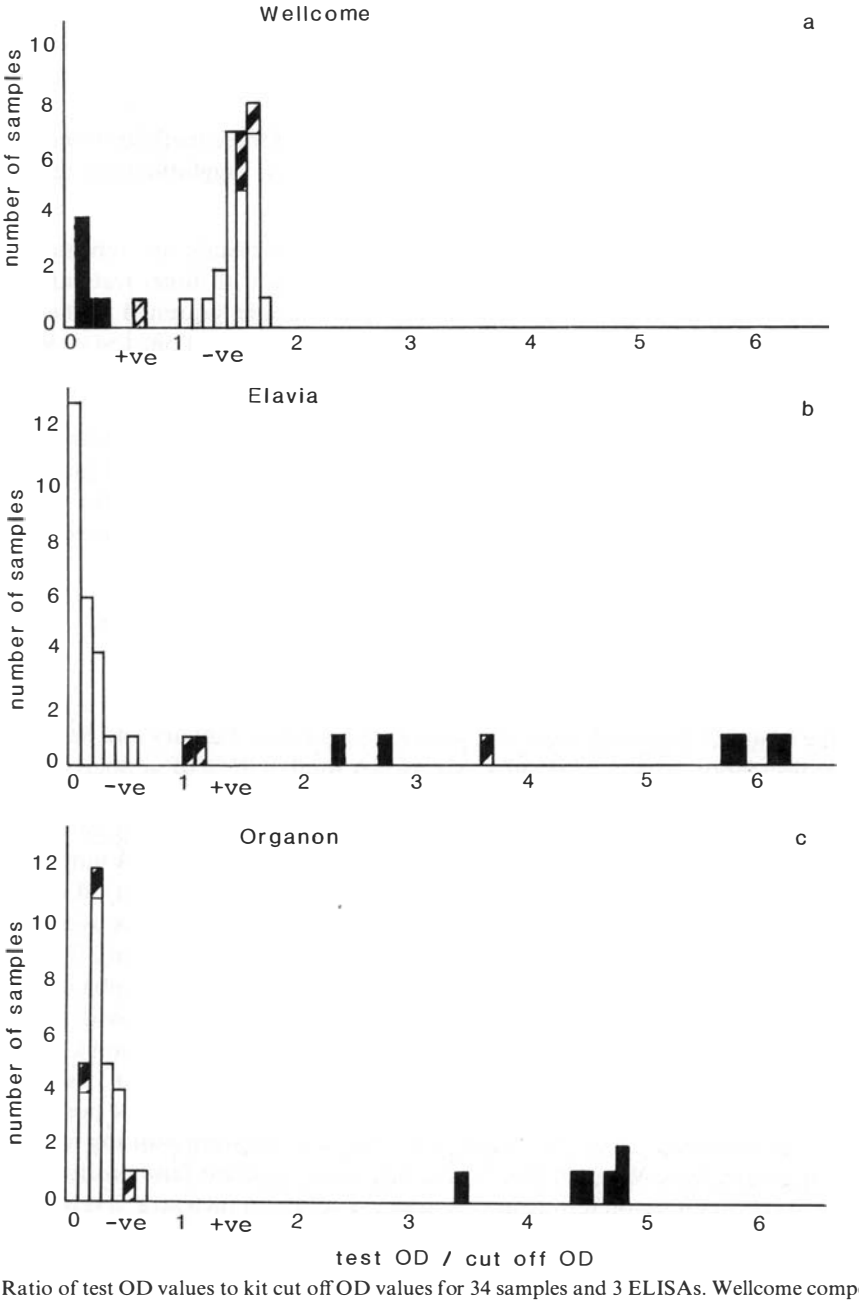

Figure 1. Ratio of test OD values to kit cut off OD values for 34 samples and 3 ELISAs. Wellcome competitive ELISA (a): HIV negative = test OD/cut off OD > 1. HIV positive = test OD/cut off OD < 1. Elavia sandwich (b) and Organon sandwich (c) ELISAs: HIV negative = test OD/cut off OD < 1. HIV positive = test OD/cut off OD > 1.

Key	Wellcome	Elavia	Organon	Edgware	Serodia
□	–	–	–	–	–
▨	+	–	–	–	–
◪	–	+	–	–	–
■	+	+	+	+	+

Organon sandwich ELISA (which may also detect cross reacting antibodies to HIV2) and the Edgware particle agglutination test (which is the cheapest test available, quick to perform and very sensitive). Samples negative by both Organon and Edgware methods to be scored HIV negative.
2 Confirmation of positives detected by either or both of these methods to be carried out by Wellcome competitive ELISA and Serodia particle agglutination test. Samples reacting by all 4 methods to be scored HIV positive.

Where practical, tests on samples showing anomalous results are repeated. Samples positive (preferably repeatedly) by one or more (but not all four) tests are examined further in London by Western blotting, and a repeat sample requested. If the HIV status remains indeterminate, i.e. with anomalous results on more than one test or where either of the ELISA results clearly differed from the results of the other 3 tests, these cases are assigned to an indeterminate category for epidemiological analysis.

The major equipment purchased for the Chilumba laboratory to implement the above protocol comprised a Damon IEC Centra4B centrifuge, together with plate carriers, a Flow Multiskan plus MkII platereader, a Flow Handiwash plate washer together with pump, and a selection of Labsystems Finnpipettes. The total cost of this equipment was approximately £9000.

HIV testing in Malawi

Using the multitest protocol, 1455 sera were tested between January and September 1989 at the project laboratory in Chilumba, Malawi. A total of 95% of samples screened gave unequivocal results on initial testing: 14% positive and 81% negative. The remaining 5% of samples required repeat or additional tests. A major problem in the early testing was due to samples which gave values over the cut off in the Organon ELISA but were negative by other tests. These sera gave OD values between 1 and 2 times the cut-off values, falling between negative (test OD/cut off OD < 1) and multitest confirmed positives in which the test OD/cut off OD ratios ranged, for the first 100 samples tested, from 2·3 to 16 (Figure 2). In the majority of cases a second Organon testing (either at Chilumba or in London) gave a negative result, but the occasional sample showed a persistent weak reaction. This problem was at least in part associated with batch variation in Organon kits, a problem also reported by others.[47] Western blotting (Biorad Blot) in London of 15 samples which had shown weak positive reactions by Organon revealed 4 with weak positive Western blot profiles. However, since the Organon ELISA and Western blotting are based on a similar principle, these Western blot results may also represent false positive reactions.[23] Since most repeat Organon testing gave a negative result on such sera, it is highly unlikely that these samples are true positives. This problem may only be resolved by longitudinal repeat testing of the individuals concerned.

During 1989, 22 samples gave positive reactions with one or both of the particle agglutination tests, but were negative by ELISA. This was similar to the pattern of reaction we had observed for some sera in the first screen of Malawian samples in London, and has been reported by others.[50,52] Western blotting of 18 of these revealed only 2 positives. Repeat venepuncture specimens were acquired from 5 individuals which proved negative by repeat particle agglutination testing. Sensitivity and specificity values

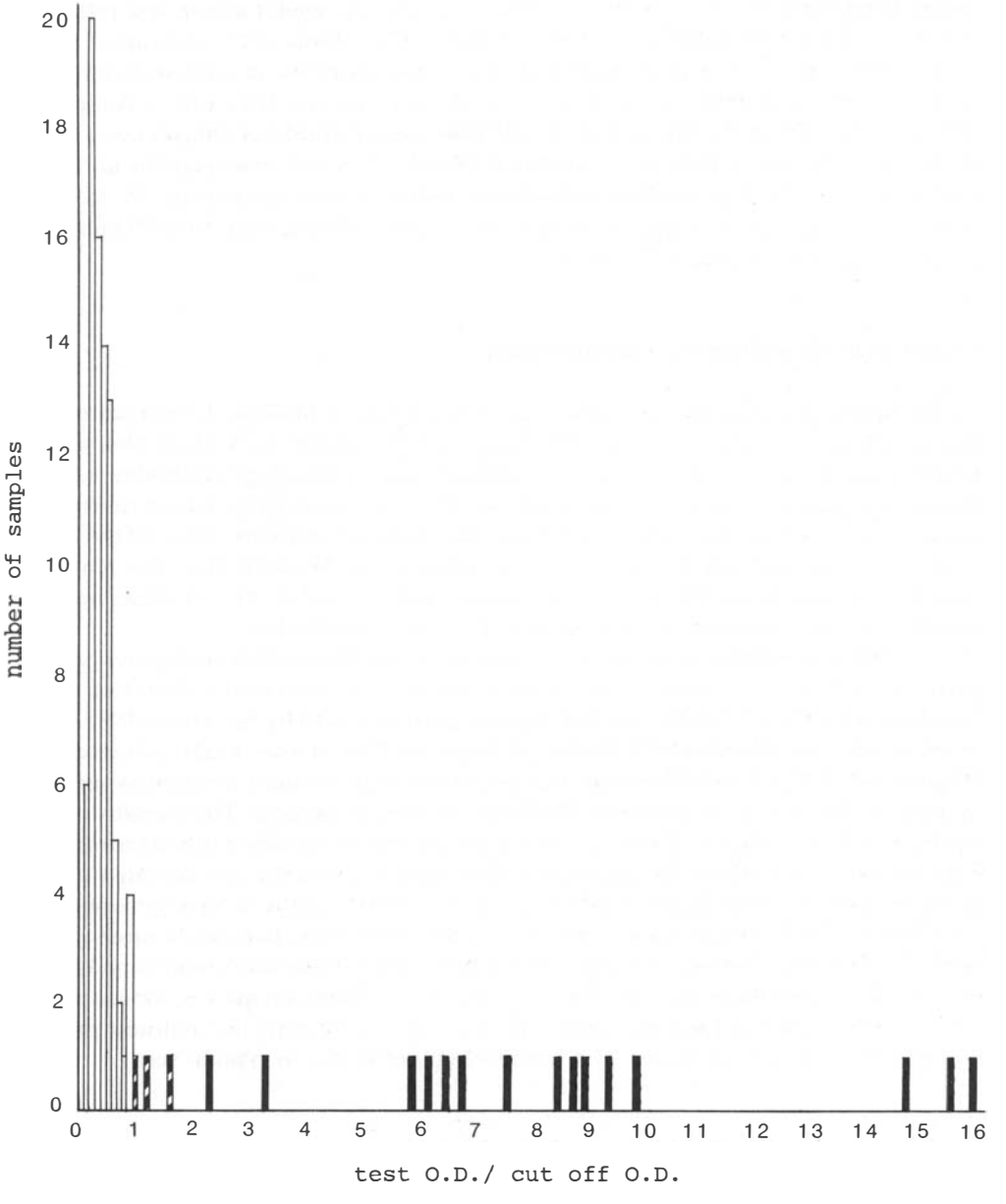

Figure 2. Ratio of test OD values to kit cut off OD values for the first 100 samples tested in Malawi by Organon ELISA. □ negative; ◪ low positive; ■ positive.

cannot be calculated for this series of tests since not all tests were performed on all samples. However, the possibility that particle agglutination tests show low specificity cannot be proved without extensive resampling of patients, since the sensitivity of these techniques is particularly high. Occasionally both control unsensitized particles and sensitized particles reacted with the sample. We did not absorb these sera with

unsensitized particles prior to repeat testing, but particle agglutination test results for such sera were not included when determining the HIV status of the individual.

The Wellcome ELISA performed well as a confirmatory test in our hands. However, supply problems required that we change from Wellcozyme anti-HTLVIII to Wellcozyme HIV recombinant, and at the end of March 1989 supply problems obliged us to replace Wellcome tests with a Behring competitive ELISA. This test was used for all further studies. Due to the high ambient temperature in the Malawi laboratory (28–36°C) the time for development of colour in the Behring test was reduced from 30 to 20 minutes to fulfill quality control criteria for the kits.

Validation of the multitest screening protocol

As one means of validating the multitest protocol set up in Malawi, 32 sera scored HIV positive by all tests and 52 scored HIV negative were applied to Western blot strips in London. Of the 32 positives, 30 had both anticore and antienvelope antibodies, i.e. were positive by standard criteria.[13,14] One of the two Western blot negatives was a tuberculosis patient who may have had clinical AIDS and thus reduced antibody titres. Of the 52 sera negative by the multitest protocol, 51 were 'negative' by Western blot. The remaining sample could not be scored due to high background. A total of 20% of these 'negative' samples showed significant levels of anti-p24 anti-core antibodies.

It was also important to establish that sera from syphilitics and from leprosy patients, particularly those from lepromatous patients, did not cross react in any of the tests to give false positive results.[95] Of 184 sera from leprosy patients tested by September 1989, only 4 were not clearly resolved as HIV positive or negative. These 4 were weakly positive by the Organon ELISA and their frequency was no greater than amongst nonleprosy sera. One of these samples was also reactive by Wellcome and one by Serodia. The majority of these leprosy cases are tuberculoid and therefore have low leprosy specific antibody titres.[96] The requirement that samples be reactive by four tests before they are accepted as HIV positive should provide accurate information on the HIV status of leprosy patients.

Of 60 syphilis positive sera tested by September 1989, three had one or more positive agglutination results but were negative by ELISA. One of these was found to be Western blot positive (described above). This frequency of problem samples is similar to that occurring amongst total samples tested. Hence, our results using the multitest protocol are unlikely to be compromised by cross-reacting antibodies in syphilis sera.

Quality control and further kit evaluation in Malawi

Routine quality control procedures were established in the Chilumba laboratory using a panel of high/weak/low/extra low positive and negative plasmas, and a quality control panel, obtained from the Public Health Laboratory Service at Colindale. These samples were transported to Malawi freeze-dried, reconstituted, aliquotted and stored frozen (-20°C) for future testing. Since we had noted batch variation in Organon test kits, it was stipulated that these samples should be tested by all methods on arrival of new Organon kits in Malawi (approximately every 3 months). Once the initial screening was underway in Malawi, a pool of Malawian positive sera was made for inclusion in the quality control

test panel. This pool was titrated both in London and in Malawi, with endpoint titres in good agreement.

To ensure that any problems can be tracked down at the time of data analysis, the date, technician identity, laboratory temperature and, for Organon, the kit batch number, are recorded for each individual test. All printouts of ELISA results are stored and all patterns on particle agglutination plates drawn by the technicians.

In view of the batch problem with Organon kits, the Du Pont HIV ELISA and the second generation Du Pont HIV-1 recombinant ELISA have since been evaluated alongside the routine four test regime as possible alternative sandwich ELISAs. In Malawi, 210 and 241 samples, which had produced clear positive or negative results by the four test protocol, were tested by the two Du Pont ELISAs respectively. The Du Pont HIV ELISA had a sensitivity of 78% and a specificity of 73%, and the Du Pont HIV-1 recombinant ELISA had a sensitivity of 82% and a specificity of 62%, when compared to the established testing regime. These values are not comparable with reported sensitivity and specificity values since the Western blot has not been used as a 'gold standard' (see below). In addition, the recombinant kit tested in Malawi failed to show the sensitivity observed in London on titration of the known positive pool. Thus, in our hands, these tests did not perform in Malawi to the same standard as other tests and have not been considered for inclusion in our multitest protocol.

Conclusion

Different protocols for establishing HIV status will be appropriate in different contexts. A hospital diagnostic laboratory or blood bank may have requirements which differ from those of a research project. Kit selection will inevitably be based upon many considerations, such as cost, availability of equipment, and staff expertise, in addition to the performance of the test. Test performance will itself be a function of other variables, such as the quality of samples collected, the presence of HIV-2 in the population, and the presence of other infections or drugs which may affect test specificity.

It is important to evaluate the sensitivity and the specificity of whatever tests are to be utilized, in the actual context in which they are to be used. These parameters will be dependent at least to some degree upon the conditions in which the tests are applied. Thus the values cited in this paper, reflecting the performance of tests in our hands, need not obtain universally. It is also important to recognize that the ultimate predictive value of a test protocol—defined as the proportion of test positives which represent true HIV infections—will be a function not only of test sensitivity and specificity, but also of the prevalence of HIV infection in the population. Thus the proportion of false positive results will be inversely related to the prevalence of HIV infection—and should therefore decline as the prevalence of HIV in the community increases. Algebraic formulations of the relationship between predictive value and test sensitivity, test specificity and infection prevalence, are found in several publications (e.g. Burgess *et al.*[96]).

Given that the motive of our work in Malawi is primarily to investigate whether there is an association between HIV infection and clinical leprosy, it was important that our HIV testing protocol have high sensitivity, in order that we may be confident of recognizing the presence of HIV in the study population. Of equal importance, however,

was the requirement for high specificity, as the presence of false positive results would bias the observed relative risks towards unity.

On the basis of the investigations discussed in this paper, we ultimately decided upon a two-stage protocol incorporating four tests: an initial screen involving a sandwich ELISA together with a cheap modified particle agglutination test, followed by confirmatory testing with a competitive ELISA and a particle agglutination test. The order was determined by the requirement that the initial screen in the protocol have extremely high sensitivity (in order to minimize false negatives), and that the confirmatory assays have high specificity (in order to minimize false positives). Even such a battery of tests turns out to be cheaper and easier than the employment of Western blots.

Initial evaluation of several tests, and using more than one test at screening and confirmation stages, has highlighted problems associated with individual tests. The Western blot has, in this instance, been used only as an alternative test to shed light on problems but not as a 'gold standard'. We thus have refrained from calculating estimates of sensitivity and specificity. Effort has been made to validate the above procedure, with respect to more widely used testing regimens and with respect to particular diseases endemic in Malawi, and also to establish quality control routines.

As kits detecting anti-HIV antibodies are further developed, it is likely that recombinant antigens will largely replace use of whole virus. Such kits require extensive evaluation to confirm that their apparent high sensitivity on Western samples is similar for samples of other origins and that their high specificity still allows detection of antibodies to all strains of HIV.

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La préparation d'une sérologie de HIV pour l'essai du vaccin contre la lèpre à Karonga, Malawi

M A SHAW, A C TURNER, J M BLACKWELL, P E M FINE ET J M PONNIGHAUS

Sommaire - Comme partie de l'essai d'un vaccin contre la lèpre qui procède en ce moment au district de Karonga, au nord du Malawi, il est essentiel d'établir si la présence dans la population du HIV

(virus d'immunodéficience humaine) est en train d'influencer le taux de fréquence ou la présentation clinique de la lèpre ou l'éfficacité des vaccins sous essai. Pour obtenir l'information nécessaire il fallait développer un protocole d'analyse de HIV rapide et économique qui pourrait être exécuté dans un laboratoire rural et qui serait résistant aux conditions ambientales variables. Cet article rapporte sur l'étape développement/évaluation d'un protocole d'essais multiples basé sur des kits d'agglutination de particules et kits ELISA de détection d'anticorps anti-HIV disponibles dans le marché. Le développement initial du protocole consistait en l'évaluation à Londres de plusieurs kits avec une série de sérums provenant de l'Afrique et ailleurs, avant de soumettre 1455 sérums aux essais sur le terrain à Malawi. Ces sérums comprenaient 184 provenant de patients de lèpre et 60 de patients de syphilis pour vérifier s'il y avait des réactions croisées. Suivant le protocole développé, tous les sérums sont analysés initiellement avec l'ELISA indirect (Organon) et avec une modification rapide et économique de l'essai d'agglutination de particules par Serodia. Les sérums positifs sont re-analysés avec un ELISA compétitif (Wellcome ou Boerhing) et l'essai normal d'agglutination de particules (Serodia). La validité de ce protocole d'essais multiples a été confirmée par l'utilisation (à Londres) de la technique "Western blotting" sur un grand nombre de sérums positifs et négatifs provenants de Malawi. Des facteurs qui influencent la sélection des kits, et les problèmes associés avec des kits individuels sont discutés. Bien que le protocole d'essais multiples développé spécifiquement pour le Malawi pourrait bien ne pas être valable pour chaque projet, le principe de développer des alternatives au "Western blotting" qui soient économiques doit être une consideration importante pour n'importe quelle enquête sur le terrain concernant le HIV.

La preparación de una serología del HIV para el ensayo de una vacuna contra la lepra en Karonga, Malawi

M A SHAW, A C TURNER, J M BLACKWELL, P E M FINE Y J M PONNIGHAUS

Resumen - Como parte de la prueba de una vacuna contra la lepra que esta teniendo lugar en el distrito de Karonga, al Norte de Malawi, es esencial el determinar si la presencia en la población del HIV (virus de inmunodeficiencia humana) afecta el índice de frecuencia o la presentación clínica de la lepra o la eficacia de las vacunas en prueba. Para obtener la información adecuada, hizo falta desarrollar un protocolo rápido y económico de prueba de HIV, que se pudiera hacer en un laboratorio rural y que resistiera condiciones ambientales variables. Este artículo informa acerca de la etapa desarrollo/evaluación de un protocolo de pruebas múltiples basado en equipos de aglutinación de partículas y equipos ELISA de detección de anticuerpos anti-HIV disponibles en el mercado. Este protocolo se desarrolló inicialmente probando varios equipos en Londres con una serie de sueros provenientes de Africa y de otros lugares y después llevando a cabo pruebas sobre el terreno con 1455 sueros en Malawi, que incluían 184 sueros de pacientes de lepra y 60 de pacientes sifilíticos para comprobar si había alguna reacción cruzada. Siguiendo el protocolo desarrollado, se prueban todos los sueros utilizando el ELISA indirecto (de Organon) y una modificación rápida y económica de la prueba de aglutinación de partículas de Serodia. Los sueros que den resultados positivos se vuelven a examinar utilizando un ELISA competitivo (de Wellcome o Boehring) y la prueba normal de Serodia de aglutinación de partículas. La validez de este protocolo de pruebas múltiples se confirmó en Londres utilizando la técnica de "Western blotting" sobre un gran número de sueros positivos y negativos procedentes de Malawi. Se discuten los factores que influenciaron la selección de los equipos, y los problemas que hubo con equipos individuales. Mientras que el protocolo de pruebas múltiples desarrollado específicamente para utilizar en Malawi puede no valer en todos los casos, el principio de desarrollar alternativas económicas al "Western blotting" es una consideración importante en todo estudio del HIV llevado a cabo sobre el terreno.

Lepr Rev (1991) **612,** 105–106

Letters to the Editor

COUNSELLING HIV POSITIVE LEPROSY PATIENTS

Sir,

Although the current evidence shows that HIV infection is not a risk factor for newly diagnosed clinical leprosy,[1,2,3] leprosy research workers will want to carry out further investigations. In the course of such work, and sometimes during routine leprosy control work they will increasingly be faced with the task of having to counsel HIV positive leprosy patients. The objectives for counselling HIV positive patients are: 1, to reduce transmission of HIV infection; but also 2, to help the HIV infected patient to come to terms with his or her reduced life expectancy.

Counselling is frequently a very difficult task. A case history may illustrate this; a young woman approximately 30 years old was found by us with a leprosy relapse. She had been treated for a lesion on her leg with DDS monotherapy from 1977 to 1983 and had recently developed a new lesion (BT leprosy) on her forehead. On testing she was found to be HIV positive. During a preliminary discussion she told us that she had married in 1979, had had children in 1980, 1982 and 1986. The last child, born in 1986, died while young. Her husband had worked as a labourer in the capital city from 1980 to 1989 but had come home every year during his annual leave.

We assumed that it was the husband who had become HIV infected in the city and that he had infected his wife. However, on testing, the husband was found to be HIV negative.

This result complicated the issue of counselling. Revealing the results to wife *and* husband would lead to divorce and (likely) misery for the two children. In addition, the woman would probably re-marry somewhere else and spread the infection further. Not revealing the results would lead (sooner or later) to the infection of the husband. Under these circumstances we thought it would be best not to disclose the results to the couple.

In view of the likelihood of having to face such dilemmas we would like to encourage leprosy workers everywhere to stimulate and join the discussion in their areas concerning counselling and its ethical considerations and difficulties.

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Malawi

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ILLUSTRATIONS IN HEALTH EDUCATION

Sir,

I would like to add the following to the special article by A C McDougall and G D Georgiev entitled, 'Educational material for the patient with leprosy' (*Lepr Rev*, 1989; **60:** 221–8).

It correctly underlined the importance of the local development of educational material for health education purposes. Our experience in Karigiri shows that misinterpretation of illustrations, particularly if they are proxy cartoons, is common among semi-literate patients and the public who are the main target. In such situations, we suggest the use of only straightforward cartoons. One such cartoon in the South Indian context and Tamil cultural milieu is given below:

R PREM KUMAR

SLR & TC
Karigiri 632 106
Via Katpadi, T.N.
India

Lepr Rev (1991) **62,** 107–112

Teaching Materials and Services; News and Notes

Slit-skin smear in leprosy

This is the title of an article published in the *International Journal of Dermatology*, **29,** No. 1, 1990, and written by Virendra N Sehgal and Joginder from the Department of Dermatology and Venereology, Maulana Azad Medical College and GB Pant Hospital, New Delhi, India. It covers all aspects of the subject and, with 116 references, is almost certainly the most comprehensive review published in recent years. The final paragraph reads as follows:

'In conclusion, therefore, slit-skin smear examinations should form an integral part of leprosy diagnosis, treatment, and prognosis. Laboratory services in most of the control units, however, are unsatisfactory. Classification of a MB case into PB is a serious repercussion of relying upon slit-skin smears for treatment. Not only may the treatment of such cases be inadequate, but it also may be a perpetuating factor for drug resistance. Therefore arrangement should be made for regular training and supervision of laboratory workers and checking of their equipment. A system of quality control by random checking of smear results by establishing regional reference laboratories should be instituted.'

Partners: a magazine for paramedical workers in leprosy

Partners is published twice yearly by the Leprosy Mission International, 80 Windmill Road, Brentford, Middlesex TW8 0QH, England and edited by Jane Neville. As far as possible it is distributed through local agencies rather than direct from London. Where possible, interested readers should contact their local ILEP representative. For India, Nepal, Sri Lanka and Burma contact: The Leprosy Mission Health Education Centre, Naini Leprosy Hospital, PO Naini, Allahabad District, UP 211008, India.

A French edition, *Associés*, is available from La Mission Evangelique contre La Lèpre, chemin de Rechoz, 1027 Lonay/VD, Switzerland.

Issue No. 21 (received February 1990) carries articles by experienced authors on: Multidrug therapy; MDT update—Zambia; Tuberculosis (diagnosis); Health education in leprosy work; patient education in tuberculosis; relapse and reactions after MDT. A list of teaching and learning materials for leprosy and tuberculosis is also included. *Partners* is now distributed to 24,750 people and is also translated into Indonesian.

Leprosy and the eye

The following is reprinted from the 10 March 1990 issue of the *Lancet* by king permission of the Editor:

Lewallen and colleagues lately described their research on ocular autonomic dysfunction and intraocular pressure in leprosy during the examination of 241 patients and 135 controls in South Korea.[1] Noting that pupil size is a reliable measure of ocular dysfunction in diabetes,[2] they decided to use this method in their study. Intraocular pressures were measured with a Perkins applanation tonometer, taking readings in both upright and supine positions. In the leprosy patients, mean intraocular pressures were significantly lower and pupil size significantly smaller than in controls.

Although there was no correlation between pupil size and intraocular pressure in this series, the results confirmed the presence of autonomic dysfunction in leprosy. However, the findings did not support a previous suggestion[3] that such dysfunction is the primary cause of low intraocular pressure in leprosy. ffytche, commenting editorially on the subject of early diagnosis of ocular leprosy, drew attention to the potential importance of tests such as those used by Lewallen et al., and the need to develop others, so that patients at risk can be identified as early as possible and singled out for long-term ophthalmic care. That multiple drug therapy with combinations of dapsone, clofazimine, and rifampicin, as recommended by the World Health Organization in 1982,[4] may well reduce the incidence of ocular complications does not diminish the importance of constant vigilance by leprologists, paramedical workers, and the patients themselves. ffytche also noted that in some patients with lepromatous leprosy the eye may continue to harbour antigen, or perhaps even living organisms, long after the completion of a satisfactory course of chemotherapy. In lepromatous (multibacillary) leprosy, damage to the eye is a result of invasion of anterior segment structures and ensuing inflammatory reaction; in paucibacillary forms of the disease there may be impairment of sensation in the cornea and conjunctiva together with paresis of the orbicularis oculi muscle and damage to extraocular structures.

Ophthalmologists and clinicians with experience of leprosy have long recognized another potentially damaging feature of the disease—the occurrence of episodes of ocular inflammation in lepromatous patients long after the disease is deemed to be inactive by standard criteria, including the finding of negative skin smears from numerous body sites.[5] Such episodes, affecting one or both eyes, may occur in patients who show no signs of clinical activity, or of adverse immunological reactions (cell-mediated or humoral) or any other part of the body. Although tuberculosis may affect the eye after episodes of bacteraemia,[6] such events are rare and, as Hansen observed in 1873, 'There is no disease which so frequently gives rise to disorders of the eye, as leprosy does.'[7] *Mycobacterium leprae* seems to show a preference for cooler body sites and the relatively low temperature of the anterior part of the eye (there is a gradient of no less than 6°C between the cornea and retina in laboratory animals)[8] may well favour the lodgment, growth, and perhaps the persistence of bacilli in anterior segment structures. However, the affinity of this organism for the eye has yet to be fully explained. As Lewallen and colleagues note: 'Studies of ocular autonomic function will help clarify the ocular pathophysiology of this disease. Furthermore, studies of intraocular pressure in patients with ocular autonomic dysfunction may help to explain the role of ocular autonomic nervous system in intraocular pressure regulation in healthy eyes'. Not for the first time in recent years, ophthalmology is spreading new light on an ancient disease.

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German Agency for Technical Cooperation

The German Agency for Technical Cooperation (GTZ) is commissioned by the Government of the Federal Republic of Germany to undertake specialist technical planning and implementation of measures for technical cooperation with developing countries. This mandate is based on a General

Agreement with the Federal Government. The guidelines for development policy are formulated by the Federal Ministry for Economic Cooperation (BMZ) as the department responsible. The Agency employs the facilities available in both the private and public sectors, provided this is conducive to the expedient and cost-effective fulfilment of its obligations.

The foremost tasks of the GTZ are:

- specialist planning and implementation, control and monitoring of Technical Cooperation projects and programmes with partners in developing countries;
- the provision of advice to other bodies likewise engaged in development schemes (e.g. organizations in the Federal Republic of Germany or abroad and also private organizations);
- recruiting, selecting, preparing and assigning expert personnel and attending to their professional and personal affairs during their period of assignment;
- planning the technical details of the material and equipment for the projects, also purchasing this equipment and dispatching it to the developing countries;
- examining all the conditions for the granting of nonrepayable financing contributions from the Technical Cooperation funds, disbursing these grants on the basis of an agreement, according to the progress of the project, monitoring the use of the grants and providing specialist advice, if required, to the project executing organization in the developing country.

For further information write to: Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ) GmbH, PO Box 5180, Dag-Hammarskjöld-Weg 1 + 2, D 6236 Eschborn. Telephone (061 96) 79-0. Telex 407501-0 gtz d. Fax No. (061 96) 79-11 15.

World Neighbors, USA

World Neighbors is a people-to-people, non-profit organization working at the forefront of worldwide efforts to eliminate hunger, diseases and poverty in Asia, Africa and Latin America.

It affirms the determination, ingenuity and inherent dignity of all people. By strengthening these primary resources, people are helped to analyse and solve their own problems. Success is achieved by developing, testing and extending simple technologies at the community level, and training local leaders to sustain and increase results.

Programme priorities are food production, community-based health, family planning, water and sanitation, environmental conservation and small business.

Founded in 1951 and rooted in the Judeo-Christian tradition of neighbour helping neighbour, World Neighbors is a non-sectarian, selfhelp movement supported by private donations.

This Organization has developed a filmstrip and slide projector which may be of interest to those who have teaching responsibilities. The 'Illustrator' filmstrip and slide projector is a newly designed and tooled projector designed to meet the needs of development educators everywhere.

Using a new high-tech lamp—12-volt 20-watt ESX Tungsten Halogen with a multifaceted Dichroic reflector—the 'Illustrator' provides an incredibly bright image. And the low-watt bulb makes it possible to power the 'Illustrator' with our 12-volt solar-chargeable gel-type battery. Using the optional AC power module, the 'Illustrator' can also be used at home or office by plugging into either 110- or 220-volt electricity.

Made of high performance plastic and aluminium, the 'Illustrator' is small and lightweight—easy to carry over the shoulder or in your back pack. The 'Illustrator' kit includes the projector, horizontal and vertical filmstrip adapters, slide inserter and carrying case. Weight: 1 lb, 7 oz, bulb: 20 watt, power: 12-volt rechargeable gel-type battery, 12-volt car battery (110- or 220-volt with optional AC power module).

They also have a wide range of training materials, details of which are available from a catalogue: World Neighbors, 5116 North Portland Avenue, Oklahoma City, OK 73112, USA.

Manual of epidemiology for district health management. Eds *J P Vaughan* and *R H Morrow*

This book fills the need for a simple, practical, step-by-step guide to the use of epidemiology as a tool for improving the management of health services. Addressed to general health workers, the book uses clear definitions, analogies, examples, checklists, sample forms and calculations, and abundant illustrations to demystify the methods of epidemiology and show how they can work in concrete situations. Particular emphasis is placed on the simple knowledge and skills needed to collect and then use epidemiological data to monitor health problems commonly found in developing countries.

The book has 14 chapters. Readers are first introduced to the main tasks involved in the management of district health services and the types of information that can contribute to more effective management. The second chapter shows how a four-phase epidemiological approach, involving descriptive, analytical, intervention, and evaluation epidemiology, can supply virtually all the information needed to pinpoint health problems, design targeted interventions, and define reliable indicators for monitoring progress. Basic definitions of incidence versus prevalence, of numbers versus rates, and of episodes versus attendances are also set out in an effort to simplify the concepts of epidemiology and prevent common errors in the design or interpretation of studies. Other chapters offer guidance in the collection of demographic data, the conduct of routine health surveillance, the use of epidemiology to control an epidemic, and the design of special surveys to collect additional information. Details range from a formula for estimating crude birth rate, through examples of diagnostic criteria useful when developing case definitions, to advice on the use of cluster samples and the determination of sample size. Readers are also alerted to problems in the use of questionnaires and the strict need for confidentiality when conducting investigations.

The second half of the book concentrates on the analysis, presentation, and use of results. Topics covered include the use of record forms and coding, methods of data processing and analysis, and the presentation of health information in tables and figures, graphs, frequency histograms, bar charts, pie charts, scatter diagrams and maps. Guidelines for the preparation of health reports, including a model outline, are also provided. The final chapter, which constitutes the core of the manual, shows how the knowledge and skills previously described can be used to formulate plans for the management and monitoring of district health services.

The book concludes with a series of six appendices offering further details on methods outlined in the manual. Following a list of ethical principles to follow during epidemiological investigations, readers are shown how to estimate sample size for a prevalence study, use random numbers, organize an epidemiological survey, assess the validity and predictive value of screening and diagnostic tests, and use age-specific rates and direct age standardization to protect against incorrect conclusions.

Available from: WHO Publications, 1211 Geneva 27, Switzerland. 1989, pp 198 (available in English; French in preparation); Sw.fr. 35.–/US$28.00; Order no. 1150335.

Royal Tropical Institute, Amsterdam

The Koninklijk Instituut voor de Tropen (Royal Tropical Institute) is active in the field of development cooperation. The basis of all the Institute's activities is the collection and dissemination of knowledge on tropical countries.

The publications of the Royal Tropical Institute reflect the Institute's policies and expertise in anthropology, history, tropical agriculture and tropical hygiene. Its present publications policy focuses on multidisciplinary research, both basic and applied, in the field of:

(a) rural development; (b) health and development; (c) tropical hygiene; (d) culture, history and anthropology.

A brochure is available with a list of publications. Those under tropical hygiene include: 'Mycobacterial disease: development in serodiagnosis and therapy' (Proceedings of a 1988 Symposium); 'Intermediate technology and ophthalmology' (1985); and 'Patient compliance with dapsone administration in leprosy' (1980). Further enquiries: Publications Department, Royal Tropical Institute, 63 Mauritskade, 1092 AD Amsterdam, The Netherlands.

Leprosy and the polymerase chain reaction

The following is extracted from 'Opinion' in the *British Medical Journal*, No. 6707, Volume 299 (1989):

'A sensitive and specific method for the detection of *M. leprae* would add an unbiased criterion to the available means of diagnosis and it might allow diagnosis at a very early stage, before the appearance of clinical signs,' write Rudy Hartskeerl and colleagues in the current issue of the *Journal of General Microbiology* (1989; **135:** 2357). If the organism could be identified rapidly leprologists could be far more discriminating in investigating such cardinal issues as the sources of infection, numbers of infected individuals, the clustering of infectious reservoirs, the risks of infection and disease, and the effect of prophylactic treatment within a population.

Existing methods are certainly far from satisfactory. *M. leprae* can be grown in armadillos—but only slowly, expensively, and in modest quantities. It can be stained for microscopic examination—but not specifically. It is detectable by serological tests—but only just. Relatively insensitive at present, serology will remain forever useless (even if vastly improved) as a means of detecting infection before the onset of the immune response. Likewise, monoclonal antibody probes are insufficiently sensitive for the purposes for which they are required.

Hartskeerl and his coworkers at the Royal Tropical Institute in Amsterdam have now come up with the answer: the polymerase chain reaction. One of the most recent products of the burgeoning craft of applied molecular biology, this is an elegant and highly efficient means by which particular segments of DNA can be amplified by many orders of magnitude. Although devised little more than two years ago by Randall Saiki and colleagues at the Cetus Corporation in California, it is already being applied with spectacular power to tasks as diverse as cloning immunoglobulin genes, detecting latent viruses, and diagnosing cystic fibrosis in utero.

The key component is the enzyme known as DNA polymerase. Provided with DNA building blocks, plus one of the two strands of the DNA molecule as a template and a short segment of the other strand as 'primer', the enzyme will synthesise a new strand complementary to the template by extending the primer. If two primers are added, one from each strand, which lay on either side of a targeted region of DNA, then that sequence—that is, the one which runs between the two primers—can be selectively copied. The copies themselves can then serve as templates for further copying. The process requires a sequence of temperature changes, allowing in turn the two DNA strands to separate, the primers to stick to their complementary sequences, and then the polymerase to do its work. Repeated cycles over two or three hours amplify the targeted sequence a million or more times.

The Amsterdam team chose as a target the gene coding for the so called 36 kDa antigen of *M. leprae* and then made primers flanking this region of DNA. Adding DNA polymerase (and DNA building blocks), they found that the technique worked a treat. It was not only capable of detecting *M. leprae* in armadillo tissue as well as in a purified state, but it did so down to the level of a single bacillus. The enormous potential of this technique for diagnosis, follow up, and epidemiology surely now means that *M. leprae* is truly in retreat.

Robert Cochrane Fund for Leprosy

The Fund, in memory of the great leprologist Robert Cochrane, is administered by the Royal Society of Tropical Medicine and Hygiene. It is to be used to finance up to three travel Fellowships each year, to a maximum value of £1500 each. The Fund will support travel for:

Leprosy workers who need to obtain practical training in field work or in research.
Experienced leprologists to provide practical training in a developing country.

There is no restriction on the country of origin or destination providing the above requirements are fulfilled.

Application forms are available from the Society and completed forms must be received by the Society at least six months ahead of the proposed visit. All applications must be sponsored by a suitable representative of the applicant's employer or study centre, and agreed by the host organization. A two-page report on the travel/study should be submitted to the Society within one month of the recipient's return.

Health for no one by the year 2000. David Werner

Adapted from a talk given by the author at the annual meeting of the National Council for International Health (NCIH), a group of US NGOs involved in international health and development. A controversial exposé of how global power structures consistently place profit ahead of human welfare. Includes appendix detailing the destruction and human suffering being caused by eight powerful multinational 'killer industries' that have targeted the Third World as their newest, fastest-growing, and most vulnerable market. These industries include alcoholic beverages, tobacco, illegal narcotics, pesticides, infant formula, non-essential medicines, arms and military equipment, and international banking (money-lending for profit).

The cost is US$3.00 and its available from: The Hesperian Foundation, PO Box 1692, Palo Alto, California 94302, USA.

Disabled people in developing countries; horticulture and agriculture

At a recent meeting of Action Health 2000 (The Bath House, Gwydir Street, Cambridge, England) Mr Chris Underhill, Director, Action on Disability and Development, 23 Lower Keyford, Frome, Somerset, BA11 4AP, England, spoke on the training and rehabilitation of disabled people in developing countries, using horticultural and agricultural activities. He emphasized the high level of success which has been attained by his own and other organizations in the training of disabled people for market and domestic gardening, and light agriculture. This approach has been described in detail in an article entitled, 'Skills for survival' by Chris Underhill and Peter Lee published in *Growth Point Magazine* by Horticultural Therapy and Third World Group for Disabled People, 16 Bath Street, Frome, Somerset BA11 1DN, England.

Mycobacterial diseases

This new publication, 'gives dermatologists, microbiologists, immunologists, dermatologists in training, registrars in other specialities and interested family practitioners a concise appraisal of some recent developments in various aspects of mycobacterial skin diseases. The up-to-date information will contribute an enhanced ability to diagnose and treat this important and widespread group of conditions.

The chapters dealing with bacteriology, pathology and immunology at the beginning of the book provide the necessary conceptual framework for the later sections on clinical aspects. Subjects covered include leprosy, tuberculosis and environmental (atypical) mycobacterial skin diseases.

The editor is Marwali Harahap, Professor of Dermatology, University of North Sumatra Medical School, Rumah Sakit Pirngadi, Medan, Indonesia. Price: £30.00 (US$52.50); 142 pages. It can be obtained from any medical bookshop or Kluwer Academic Publishers, Falcon House, Queen Square, Lancaster LA1 1RN, England, or the Sales Department, POB 989, 3300 AZ, Dordrecht, The Netherlands.

Editorial notice

For this issue 'Teaching Materials and Services' and 'News and Notes' have been combined and reduced to save space. Future issues are to be larger, at no extra cost, to accommodate the increase in manuscripts suitable for publication.

Instructions to Authors

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