better patient care and savings.¹⁷ This aspect should be addressed firstly on the basis of asking the question "Is the therapeutic ratio favourable and realistically constructed for this patient and this proposed treatment?" and not "Is it more cost effective to treat this patient than another patient?"

- 1 Senile dementia of Alzheimer's type—normal ageing or disease? [Editorial.] *Lancet* 1989;i:476-7.
- 2 Mitchell JRA. Can we really prevent postoperative pulmonary emboli? *BMJ* 1979;ii:1523-4.
- 3 Jones A. End points in cancer therapy. *Clin Radiol* 1980;31:121-35.
- 4 Kearsley JH. Cytotoxic chemotherapy for common adult malignancies: the emperor's new clothes revisited? *BMJ* 1986;293:871-6.
- 5 Lunt B, Neale C. A comparison of hospice and hospital: care goals set by staff. *Palliative Medicine* 1987;1:136-48.
- 6 Slevin ML, Plant H, Lynch D, Drinkwater J, Gregory WM. Who should measure quality of life, the doctor or the patient? *Br J Cancer* 1988;57:109-12.

- 7 Higginson I, McCarthy M. Evaluation of palliative care: steps to quality assurance? *Palliative Medicine* 1989;3:267-74.
- 8 Cassidy S. Emotional distress in terminal cancer: discussion paper. *J R Soc Med* 1986;79:717-20.
- 9 Gilhooly MLM, Berkeley JS, McCann K, Gibling F, Murray K. Truth telling with dying cancer patients. *Palliative Medicine* 1988;2:64-71.
- 10 Sutherland HJ, Llewellyn-Thomas HA, Lockwood GA, Tritchler DL, Till JE. Cancer patients: their desire for information and participation in treatment decisions. *J R Soc Med* 1989;82:260-3.
- 11 Black D, Jolley D. Slow euthanasia? The deaths of psychogeriatric patients. *BMJ* 1990;300:1321-3.
- 12 Glover J. *Causing death and saving lives*. London: Penguin, 1977.
- 13 Rachels J. *The end of life*. Oxford: Oxford University Press, 1986.
- 14 Ahronheim JC, Gasner MR. The sloganism of starvation. *Lancet* 1990;335:278-9.
- 15 Hirschfield MJ, Ziv L. When a demented patient refuses food—ethical arguments of nurses in Israel. *Palliative Medicine* 1989;4:25-30.
- 16 Smith T. Consensus on overtreatment cancer. *BMJ* 1988;297:438.
- 17 Timothy AR. Cost versus benefit in non-surgical management of patients with cancer. *BMJ* 1988;297:471-2.
- 18 Stoll BA. Choosing between cancer patients. *J Med Ethics* 1990;16:71-4.

(Accepted 12 March 1991)

Lesson of the Week

Leprosy in reaction: a medical emergency

Adam S Malin, Michael F R Waters, Suhail A Shehade, Marguerite M Roberts

The clinical course of leprosy in immunological reaction is often acute and rapidly progressive

Leprosy is a chronic granulomatous infectious disease that primarily affects the skin and nerves. The progress of the disease is often considered to be slow and indolent. However, skin or nerve lesions may suddenly flare up in a state of immunological reaction (lepra reaction), of which two main types are recognised: reversal (upgrading) reaction (type I reaction) and erythema nodosum leprosum (type II reaction). Delayed treatment of these reactions may result in irreversible nerve damage.¹ The three cases described below illustrate the difficulties in diagnosis and the problems that may ensue if lepra reactions are not promptly recognised and treated.

Case reports

CASE 1

A 26 year old Nigerian was seen by a neurologist in an outpatient department in August 1989. Two weeks earlier he had developed swelling of his right ring finger, pains in his right hand up to his elbow, and pains in his left knee and ankle. He also complained of numbness in his right hand and over his entire left leg. After one week he had developed pain and numbness in his right foot. Examination showed weakness and sensory loss in the distribution of the right ulnar nerve and swelling of the proximal interphalangeal joint of his right ring finger. In his legs there was weak dorsiflexion and eversion of the left foot. There was profound sensory impairment to pinprick in the right foot and the whole of the left leg up to the groin. Tendon reflexes were present and plantar responses were flexor. The combination of the nerve damage and the swollen small joint suggested a connective tissue disease and non-urgent admission was arranged. The patient was admitted 14 weeks later because of shortage of beds.

By the time of admission his neurological deficit had progressed. He was unable to straighten his right ring finger and little finger, had difficulty walking, and was kept awake at night with pain in his left leg. Examination showed total right ulnar and left common peroneal nerve palsies with complete footdrop. These nerves were considerably thickened bilaterally and there was moderate enlargement of superficial nerve branches over the wrists and dorsa of the feet. He had hypoaesthetic, hypopigmented macules over his arms,

and a large area of hypopigmentation which corresponded with the anaesthesia over his leg. The clinical diagnosis of leprosy was confirmed by skin biopsy. He was transferred to the Hospital for Tropical Diseases. Slit skin smears were negative for acid fast bacilli. These findings confirmed the diagnosis of borderline tuberculoid leprosy, and the rapid development of neurological damage and the results of electromyography indicated a severe reversal reaction affecting nerves rather than skin.

Chemotherapy was started with rifampicin 600 mg daily for two days (then repeated on the first two days of each month), clofazimine 100 mg daily, and dapsone 50 mg daily. For the reversal reaction he was given prednisolone 60 mg daily. Physiotherapy was started, and he was fitted with a splint for his footdrop and given insoles and shoes to protect his anaesthetic feet.

After 48 hours the pain in his left leg disappeared and the dose of prednisolone was reduced to 40 mg daily. He gradually regained power in his left foot and by three weeks was able to evert and dorsiflex the ankle against gravity. There was no improvement in the right ulnar claw hand nor in the widespread anaesthesia. Several months later he developed a plantar neurotrophic ulcer and a metatarsal stress fracture.

CASE 2

A 30 year old Vietnamese man arrived in England in 1983. In July 1989, over one month, he developed anaesthetic skin lesions, weakness, and numbness of the hands (first the left, then the right), pain in the fingers, and weight loss. He was seen on several occasions at his local hospital but the diagnosis was not suspected until he saw a physician privately. He was referred for admission to the Skin Hospital.

Examination showed multiple papules, annular lesions, and plaques over the trunk and limbs which were anaesthetic, erythematous, and psoriasiform. Nearly all the nerves of predilection in leprosy were thickened. There was a left ulnar claw hand with considerable intrinsic muscle wasting; the right thumb was weak and there was mild thenar muscle wasting.

Results of skin biopsy of a lesion supported the diagnosis, and triple chemotherapy with rifampicin, dapsone, and clofazimine was promptly started. Despite this he continued to complain of pain in both his hands, and he rapidly developed a right sided

Hospital for Tropical Diseases, London NW1 0PE

Adam S Malin, MRCP, registrar
Michael F R Waters, FRCP, consultant leprologist

Skin Hospital, University of Manchester School of Medicine, Salford M60 9EP
Suhail A Shehade, MRCP, senior registrar
Marguerite M Roberts, FRCP, consultant

Correspondence to:
Dr A Malin.

BMJ 1991;302:1324-6

Skin lesion covering whole of left leg with clearly visible upper border (case 1)

wristdrop. He was transferred for specialist care 12 days after starting chemotherapy. By this time there were total left ulnar and right radial nerve palsies and partial right ulnar and median nerve palsies. There was asymmetrical tenderness and thickening of peripheral nerves, notably of the right radial nerve, which was palpable in the spiral groove. His skin lesions were consistent with borderline tuberculoid leprosy in reversal reaction. This was confirmed by the results of skin and nerve biopsies and slit skin smear tests.

Prednisolone was added to the chemotherapy in a dose of 60 mg daily. The tenderness of his nerves disappeared within two days. The dose was then gradually reduced to 20 mg daily over the next two months and was continued for a year. His right wristdrop and right thumb weakness improved steadily, and eventually recovered entirely. The left ulnar palsy, which was the first to deteriorate, showed only mild improvement over the next year.

CASE 3

A 26 year old Nigerian man presented to a dermatology clinic in June 1989 with extensive boils and was admitted for further investigation. He had arrived in the United Kingdom three weeks earlier. He described a six month history of recurrent boils over his face, arms, axillae, groin, and legs associated with fever, anorexia, weight loss, and intermittent pains in his large joints. His medical history included treatment for a skin problem in 1987. On examination he had a temperature of 38°C, axillary lymphadenopathy, scars from previous boils, and multiple nodules and pustules over both forearms measuring 1-2 cm in diameter. Investigations showed a normochromic, normocytic anaemia (haemoglobin concentration 100 g/l), a normal white cell count ($9.6 \times 10^9/l$), and negative results on bacteriological swab culture from two pustules. A tropical differential diagnosis was considered, and he was transferred for specialist management.

Examination showed multiple lesions typical of pustular erythema nodosum leprosum over his forearms, thigh, and forehead. His left ulnar nerve was tender and considerably thickened. Other peripheral nerves were non-tender and moderately thickened. Additional features of erythema nodosum leprosum were present including synovitis of the left wrist and generalised lymphadenopathy. There were no signs of orchitis or iridocyclitis. He had a symmetrical glove and stocking peripheral neuropathy. There were no anaesthetic skin lesions. The signs were consistent with a diagnosis of lepromatous leprosy complicated by pustular erythema nodosum leprosum, which was

confirmed by results of slit skin smear tests, histological examination, and electromyography. At this point he admitted that he had been diagnosed as having leprosy in Nigeria 18 months previously and had been taking three drugs ever since. Eight months after starting antileprosy chemotherapy his "boils" had begun to appear in crops.

Treatment was resumed with rifampicin 600 mg on the first two days of each month, dapsone 50 mg daily, and a high dose of clofazimine at 300 mg daily. Thalidomide was added in a dose of 200 mg twice daily. Within 48 hours his fever, synovitis, and ulnar nerve tenderness disappeared and there was great improvement in his skin lesions.

Discussion

Leprosy must always be considered in patients who come from an endemic area and have an undiagnosed peripheral neuropathy.² In cases of leprosy further careful examination will usually show one or more characteristic skin lesions which may be anaesthetic because of involvement of dermal nerves. The skin changes in case 1 were not apparent initially. The main skin lesion, which covered the whole of the left leg, may have been so large that it was missed. At the time of admission the clearly visible upper border corresponded to a change from normal sensation (pigmented area) to anaesthesia (hypopigmented area), which virtually confirmed a diagnosis of leprosy (figure).

In case 2 leprosy was diagnosed soon after presentation and appropriate chemotherapy was started. Although the importance of rapid neurological deterioration associated with tender nerves was not fully appreciated, prompt transfer of the patient permitted rapid treatment and recovery of the radial nerve palsy, which had developed just before he started taking corticosteroids. His right hand, which had become weak just before diagnosis, also recovered full motor power, but the left ulnar nerve, which had been functionally damaged for over two months, showed only mild recovery.

Cases 1 and 2 are examples of reversal reactions in which there is an increase in cell mediated immunity resulting in rapid neurological deterioration.^{3,4} Early recognition allows the inflammation to be halted by corticosteroids before irreversible damage develops.^{5,6} Reversal reactions may also be more insidious, with gradual neurological deterioration—the so called silent neuritis. Clinical features include nerve tenderness, increasing anaesthesia, and decreasing muscle strength. Other features of reversal reactions include swelling and erythema of old leprous skin lesions and new oedematous skin lesions.¹

Case 3 is a good example of erythema nodosum leprosum. The acute inflammatory response is believed to be due to tissue deposition of immune complexes with vasculitis and polymorphonuclear infiltrate (Arthus type reaction).⁴ It commonly occurs in lepromatous patients, especially in the first year of treatment.⁷ Erythema nodosum leprosum is characterised by crops of painful, erythematous papules or nodules, which may form ulcers or sterile pustules. The patient is often systemically unwell with fever and may have a painful neuropathy and lymphadenopathy. Other complications include iridocyclitis, epididymo-orchitis, synovitis, large joint arthritis, and an immune complex type glomerulonephritis.⁸ Erythema nodosum leprosum rapidly responds to thalidomide 400 mg daily in divided doses.^{1,9,10} Steroids are also effective, but the reactional state may require long term suppression, resulting in side effects that could be avoided with low maintenance doses of thalidomide.¹ Clofazimine is a useful adjunct and acts as an anti-

inflammatory agent at the higher dose of 300 mg daily but may not be effective for several weeks or months and can also cause unacceptable facial pigmentation.¹

Patients with undiagnosed leprosy are referred to specialists according to the predominant clinical feature—in these three cases to specialists in neurology and dermatology. In case 1 the neurological lesions were well documented but hypopigmented macules were not mentioned. In case 2 the importance of the rapidly changing neurological signs was not fully appreciated. In case 3 neither the sensory loss nor the nerve thickening were identified, although the diagnosis was made difficult by the patient's failure to provide a complete medical history. In the other instances patients have been referred to rheumatologists; orthopaedic surgeons; ear, nose, and throat surgeons; and ophthalmologists.^{2 11 12} Frequent misdiagnoses include nasal allergy (lepromatous involvement of the nose), fungal skin infections, psoriasis, and syringomyelia.

In conclusion, an unexplained rash or peripheral neuropathy in patients from an endemic area should alert the clinician to the possibility of leprosy. Furthermore, although leprosy may follow an indolent, chronic course, it also may present in reaction with severe, rapidly progressive and, with erythema nodosum leprosum, potentially fatal disease. Rapid neurological deterioration is often reversible with anti-inflammatory

drugs. If all clinicians were to remain alert to these facts many cases of irreversible nerve damage could be prevented.

We thank Dr A D M Bryceson for his helpful advice and permission to report case 1 and Mrs Jean De Luca for help with preparing the manuscript.

- 1 Waters MFR. Leprosy (Hansen's disease/hanseniasis). In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford textbook of medicine*. 2nd ed. Oxford: Oxford University Press, 1987:5:305-13.
- 2 Myers B, Bryceson ADM. Leprosy—an important cause of peripheral neuropathy in Asian immigrants. *Practitioner* 1987;231:637-8.
- 3 Ridley DS. Reactions in leprosy. *Lepr Rev* 1969;40:77-81.
- 4 Waters MFR, Turk JL, Wemambu SNC. Mechanisms of reactions in leprosy. *International Journal of Leprosy* 1971;39:417-28.
- 5 Pearson JMH, Ross WF. Nerve involvement in leprosy: pathology, differential diagnosis and principles of management. *Lepr Rev* 1975;46:199-212.
- 6 Pearson JMH. The use of corticosteroids in leprosy. *Lepr Rev* 1981;52:293-8.
- 7 Waters MFR, Rees RJW, Sutherland I. Chemotherapeutic trials in leprosy. 5. A study of methods used in clinical trials in lepromatous leprosy. *International Journal of Leprosy* 1967;35:311-35.
- 8 Bullock WE. Immunobiology of leprosy. In: Nahmias AJ, O'Reilly RJ, eds. *Immunology of human infection*. New York: Plenum Press, 1981:369-90.
- 9 Iyer CGS, Languillon J, Ramanujam K, et al. WHO coordinated short-term double-blind trial with thalidomide in the treatment of acute lepra reactions in male lepromatous patients. *Bull WHO* 1971;45:719-32.
- 10 Parikh DA, Ganapati R, Revankar CR. Thalidomide in leprosy—study of 94 cases. *Indian J Lepr* 1986;58:560-6.
- 11 Powell S, McDougall C. Clinical recognition of leprosy: some factors leading to the delay in diagnosis. *BMJ* 1974;i:612-3.
- 12 McDougall AC, Archibald GC. Lepromatous leprosy presenting with swelling of the legs. *BMJ* 1977;i:23-4.

(Accepted 19 March 1991)

A PAPER THAT CHANGED MY PRACTICE

Classic and convincing study

The Norwegian study of timolol in patients who had had an infarct was one of those rare trials in which everything seems to have gone right. A total of 1884 patients who had survived a myocardial infarction for between seven and 28 days were randomly allocated to treatment with timolol 5 mg, increasing to 10 mg twice a day, or matching placebo, and they were followed for a mean of 17 months. The fatality rate in the placebo group was 16.2%, while among the patients treated with timolol it was 10.4%—a relative risk reduction of 36% which was statistically highly significant.

This was the first β blocker trial to give a totally convincing result. There had been studies of propranolol, oxprenolol, and alprenolol which claimed to show that active treatment was superior to placebo, but all were too small to form a basis for a wholesale change in clinical practice. A large trial of practolol had just about produced a positive result, but practolol itself had been withdrawn because of side effects and doubts lingered about the long term safety of β blockers in general. Until the timolol trial was published I did not use any β blocker for secondary prevention of myocardial infarction.

Since the timolol trial there have been several large and excellent multicentre studies of different therapies in cardiovascular disease, but the Norwegians published a classic study that all have since had to copy. For the first time in a cardiovascular trial the Norwegians maintained a register of all patients who might have been considered for inclusion in their trial, and it was thus possible to see how these included patients related to the general population of survivors of an infarct. Patients withdrawn from treatment

were followed until the end of the study and their outcome was described separately from that of those who continued to take the treatment allocated: both "intention to treat" and "explicative" analyses were possible—and both indicated a marked benefit from active treatment. The trialists were perhaps "lucky" in finding a fatality rate in the placebo group higher than in any other such trial of β blockers, and also in finding a similar fatality rate in patients who continued to take, or were withdrawn from, placebo treatment. These made the results look clean and totally believable.

There have been many more β blocker trials on patients who have had an infarct in the past decade, and marked benefits have been shown from propranolol, metoprolol, and atenolol. Overviews, or "meta-analysis," have suggested that all β blockers have similar effects, but I am dubious about basing clinical practice on such studies. Clinicians cannot prescribe " β blocker three times a day" to all patients who have had an infarct: they have to choose a particular drug and opt for a particular dose. I do not use timolol for any other purpose, but for the secondary prevention of myocardial infarction I still routinely prescribe "timolol 10 mg twice a day." Now that the attention of trialists has turned away from β blockers I doubt if there will ever be another study of a drug of this group that will make me change my practice again. —JOHN HAMPTON, professor of cardiology, Queen's Medical Centre, Nottingham

Norwegian Multicentre Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981;304:803-7.