LEPR REV (1991) 62, 113–121

Editorial

REVERSAL REACTIONS IN LEPROSY AND THEIR MANAGEMENT

Introduction

One of the tragedies of leprosy, which particularly helps to maintain the fear and the outdated, unscientific stigma of the disease, is the fact that many patients may develop new prominent skin lesions and new peripheral nerve damage, with resulting increased disability, even crippling deformity, after the onset of correct chemotherapy. Some patients, especially those diagnosed early in the course of their disease, may experience a steady and uninterrupted response to treatment. Others develop one or more acute or subacute episodes of inflammation, not due to bacterial multiplication, but which are immunologically mediated, associated with the remarkable persistence of mycobacterial antigen in tissues after bacillary death.

Almost all such immunological 'reactions' fall into one or other of two aetiopathological types.1–3 (A third type, the Lucio phenomenon is rare, occurs only in polar lepromatous (LLp) 'lepra bonita' patients, is virtually restricted to Central and northern South America, and nearly always occurs before the start of treatment. Downgrading reactions in untreated or relapsing patients are controversial, and have been too little investigated.) Unfortunately, even today there is no internationally agreed nomenclature. One type, which is restricted to lepromatous, both LLp and subpolar lepromatous (LLs), and to small numbers of borderline–lepromatous (BL) patients, is usually called erythema nodosum leprosum (ENL)—although other systems of the body, as well as the skin, are commonly involved—or lepromatous lepra or Type I2 reaction. ENL has been extensively discussed in the past, especially between 1960 and 1980; valid methods of organizing double-blind clinical trials have been described and effective treatment programmes have been identified, even though (despite impressive recent research) there remain major gaps in the immunological understanding of the reaction. The second type, which is particularly common among BL, borderline (BB), and borderline–tuberculoid (BT) patients, but which also occurs in small numbers of treated LLs patients and possibly in untreated polar tuberculoid (TT) (but not in LLp, indeterminate, and treated TT patients), has many names. The WHO Expert Committee on Leprosy, in its 6th Report,4 used the term 'reversal reaction', which had been suggested by Wade5 in the early days of dapsone chemotherapy, although many workers name them Type I2 or upgrading1 reactions. This is a reaction in which, unlike ENL, high fever and severe general malaise does not occur, though mild fever and malaise may, and in which only skin and nerves are involved.
A reversal reaction (RR) can normally be diagnosed without difficulty on the clinical signs and symptoms,\textsuperscript{3} supported if necessary by histopathology\textsuperscript{1, 6, 7} and the natural history of the episode. The underlying immunological mechanisms are being increasingly identified, and are now forming a more and more coherent picture, better developed than that for ENL. Yet clinically, the reverse is true. Clinical and epidemiological knowledge of the natural history of RRs is limited. Neuritis may sometimes be dramatically acute, sometimes remarkably insidious and comparatively painless (the so-called ‘silent neuritis’), so that at either extreme severe nerve damage may occur before the diagnosis is made. Because the skin signs may develop gradually, patients may delay in returning to the clinic. There have been few reports of controlled clinical trials in the treatment of RR and no standard trial designs have emerged. Although corticosteroids remain the treatment of choice, because of the differing severity and duration of individual reactions, no generally agreed treatment schedules have been developed, either for hospital or field use.

**Definition and description**

No succinct definition of RR has been given, only clinical and histological descriptions, to which may now be added immunological findings.

**CLINICAL**

Over the course of a few days or weeks, the leprosy lesions themselves become (more) erythematous, raised, oedematous, and infiltrated. In more severe reaction, the hands and/or feet may develop oedema, especially where there are reactive skin lesions near the periphery of the limbs. Sometimes the skin may become so swollen and fragile that it ulcerates (such lesions are not uncommon on the faces of children and the resulting unsightly scarring may cause social embarrassment and impair marriage prospects). Usually in BL and BB patients, and occasionally in BT, new lesions develop, presumably due to the immunological recognition of inapparent foci of *Mycobacterium leprae*. The lesional edges become more sharply defined, so that clinically a BL patient may change to BB or even to BT, and as the reaction resolves, the lesions become drier and often have surface scales. In LLs leprosy, erythematous plaques may develop in the infiltrated skin.

In some patients, the RR is only manifest in the skin. Frequently, however, nerves are also involved, sometimes only one, sometimes several; most commonly the ulnar, but any of the nerves of predilection, including branches of the facial, may be involved. The patient may develop paraesthesiae in the distribution of the affected nerve, nerve tenderness may be noted, and in the more acute severe reactions, nerve pain. On occasion, however, all that may be complained of is increasing functional loss, whether increasing anaesthesia, or more commonly, muscle weakness. The latter may come on almost imperceptibly, but sometimes acute foot drop, or an acute facial paralysis\textsuperscript{6} may develop over 24–36 hours, or even acute wrist drop over 3–4 days\textsuperscript{8}. If careful records have been made, undoubted increase in the size of the affected nerve may be detected, together with nerve tenderness, and appropriate new skin anaesthesia. Voluntary muscle tests (VMT) will reveal increasing weakness. Sometimes reactional neuritis may occur without any skin manifestations.
The timing and duration of RR depends to some extent on the type of leprosy. Inflammation in untreated BT leprosy (and presumably in untreated TT, although this has been little studied) is due to RR, and most typically occurs at a time when nonspecific depression of cell-mediated immunity (CMI) ends, for example, about 6–8 weeks postpartum or on recovery from intercurrent infection. BT lesions already mildly inflamed on diagnosis may, within a few day of commencing MDT, go into reaction. The majority of BT RRs develop in the first 6 months of treatment, but they are not rare during the second 6 months, and with increasing rarity, may undoubtedly occur during the 2nd, 3rd, or 4th\textsuperscript{6} years (possibly even later; research is required on this point). It is relevant that Pattyn and his colleagues have found persisting granuloma (and therefore presumably persisting antigen) as long as 4 years after diagnosis in a small proportion of PB leprosy patients whose treatment included rifampicin.\textsuperscript{9} In BB leprosy, RRs usually begin within a few weeks or months after commencing MDT. In BL leprosy, reactions commonly commence after 1–12 months, but may occur in the 2nd or 3rd years, and occasionally in the 4th and 5th\textsuperscript{6} years. In LLs leprosy which has recently downgraded from borderline and which clinically still resembles BL, RR may occur within a few months, but in established LLs patients, RR may occur later, perhaps 1–5 years after commencing treatment.

The duration of a RR, although also very variable, usually only lasts a few (say 3–9) months in BT, but may last as long as 15 months in BL or even 2 years in LLs leprosy. This individual and type variability makes the laying down of standard regimens very difficult. Sometimes, second reactions are seen in the same patient.\textsuperscript{6}

All too few studies have been made on the frequency of RR. To a large extent the reported frequency depends on whether an author works in a hospital or in a control area. Main referral centres may report a high frequency, from the very nature of the patients which attend there. In Malaysia and London, over 20 years ago during the era of dapsone monotherapy, it was found that about one third of all BL patients developed RR in the 1st year, and perhaps one half over 5 years, and 10\% of histologically classified LLs patients.\textsuperscript{10} Recently in the Karonga trial area of Malawi, where the control work is very intensive and many patients are actively detected at a very early stage, RR was diagnosed during the 1st year after completion of WHO paucibacillary MDT in 4 of 39 self-reporting BT and TT patients, but in only 1 of 153 patients obtained by active case-finding.\textsuperscript{11}

**IMMUNOLOGICAL**

The universal finding that many (though not all) RR patients ‘upgraded’ their leprosy classification towards tuberculoid, both clinically and histologically, suggested that the underlying mechanism was due to an increase in CMI and delayed type hypersensitivity (Gell and Coombs Type IV reaction). This was confirmed experimentally by Rees & Weddell,\textsuperscript{12} who obtained RR in thymectomized, irradiated, lepromatous mice 1–2 weeks after giving transfusions of syngeneic lymphocytes. Shortly afterwards, it was shown that a marked rise occurred in the level of lymphocyte transformation during RRs, especially in BT leprosy, the response subsiding, but often to a higher baseline level than beforehand, on the ending of the reaction,\textsuperscript{13} even though the change in classification was maintained. Interestingly, Barnetson et al.\textsuperscript{14} found that the lymphocytes of patients suffering from skin RR responded best to stimulation by whole \textit{M. leprae} as antigen, whereas lymphocytes from cases of nerve RR responded best to \textit{M. leprae} sonicate; if both
Table 1. Immunological parameters in reaction skin lesions

<table>
<thead>
<tr>
<th>Cell type</th>
<th>ENL</th>
<th>Reversal reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>T CD4+ : CD8+ ratio</td>
<td>Rises (slightly)</td>
<td>Rises</td>
</tr>
<tr>
<td>T CD4+ memory: naive cells</td>
<td>Rises (6:1)</td>
<td>Rises (9:1)</td>
</tr>
<tr>
<td>T CD8+ cytotoxic: suppressor</td>
<td>1:3</td>
<td>2:1</td>
</tr>
<tr>
<td>CD3+ gamma delta T cells</td>
<td>Unchanged (3%)</td>
<td>Increase (22%)</td>
</tr>
<tr>
<td>IFN-gamma mRNA cells</td>
<td>0.05% (mild increase)</td>
<td>1% (marked increase)</td>
</tr>
<tr>
<td>DR-Ia + keratinocytes</td>
<td>±</td>
<td>+</td>
</tr>
</tbody>
</table>

skin and nerve RR were present, the lymphocytes responded to both types of antigen. There is a great need to repeat this work, using the cytoplasmic15 and cell wall16 M. leprae antigenic fractions now available.

Over the last 5–6 years, several groups of workers, in particular Modlin and Rea in Los Angeles, have studied intensively the immunological parameters in reaction skin lesions.17–20 Their findings are summarized in Table 1, in which the findings in RR are compared with those in ENL. There is a rise in the proportion and number of T helper (CD4+) compared with T suppressor (CD8+) lymphocytes. The ratio of T CD4+ memory to naive cells also rises, as does the T CD8+ cytotoxic: suppressor cell ratio. It has recently been claimed that gamma delta T cells show a dramatic increase in RR lesions,21 although this finding awaits confirmation by other workers. Interferon-gamma messenger RNA cells also increase in RR skin lesions. It must be remembered that these very intensive studies involve relatively small numbers of patients, and it is not always clear how many BT, BB and BL patients are involved. But the overall picture of the mechanisms of RR is convincing, even if the basic question, namely, what is the initial happening which precipitates the reaction, remains unsolved. Nor have simple tests been devised to enable a clinician to anticipate when a patient is about to develop a RR, although it has recently been shown that a smear-negative (PB) BT patient who is PGL-1 antibody positive is significantly more likely to develop a RR than one who is PGL-1 antibody negative.22 Does this mean that there is more available antigen to be recognized in such BT patients, or that ‘recognition’, by both B and T lymphocytes is ‘better’ in those who develop a RR?

Management

The development of a RR can be a very frightening and damaging experience for a patient, which may make him or her lose faith in the leprosy workers. A patient may think that the leprosy has ‘got worse’, that MDT has proved a failure, and therefore he goes for traditional medicine, only returning to the clinic some months later when it is too late to expect return of nerve function under treatment. Therefore, the management of reversal reaction should begin at the time of diagnosis, and continue until the patient is released from post-MDT surveillance.
PATIENT EDUCATION

It is important to warn newly diagnosed BT, BB and BL patients of the possibility of RR developing after the start of treatment. Nonfrightening, culturally acceptable language is essential. For example, patients may be told that their lesions will soon start to go down under MDT. With this good treatment, their bodies may start to fight the disease better, which is a good thing, but sometimes they start fighting it too hard. Then it is rather like a boxer punching himself; the lesions may become swollen and red again, and new lesions may appear where dead germs were hidden, and nerves may become inflamed. The patients are reassured not to be anxious, but rather at the first suspicion of any such happening to return rapidly to the clinic, so that additional good treatment can be given to 'slow down the fight'. A short time spent thus in education may save the patient from permanent disability (and the clinic from many hours or years of needless work).

ANTICIPATION

Some BT patients on first diagnosis are already in reaction. Other patients whether BT, BB, BL or LLs, have rather red, mildly oedematous lesions, and are likely to develop undoubted reaction shortly after starting MDT; such patients require careful watching. Two other groups of patients also need special care. Pregnant women are particularly prone to develop RR 4–12 weeks after delivery. Children and adults who have large plaques on the face are especially liable to develop RR with involvement of the facial nerve, leading to lagophthalmos. Finally, any BT, BB, or BL patient found on diagnosis or later to have one or more tender nerves must be suspected of developing RR neuritis, and should be considered for a course of corticosteroids; if there is evidence of corresponding nerve damage developing over the previous 3–6 months, then a course of corticosteroid therapy is mandatory.

MEDICAL TREATMENT

Mild reactions, consisting of mild erythema and oedema of skin lesions with or without the appearance of new lesions, and/or mild nerve tenderness, but without nerve pain or loss of function, will usually resolve over a few weeks, and may be treated conservatively with analgesics (Aspirin or Paracetamol; some workers also like to give chloroquine), and by rest to any affected limb. Antileprosy treatment is continued, the patient is seen every 2 weeks if possible, and is asked to return at once if the reaction becomes more severe.

Severe reactions. If there is undoubted fever or discomfort, if there is oedema of the hands or feet, if there is nerve pain or paraesthesiae or increasing loss of nerve function, or even marked nerve tenderness alone, or if a mild reaction persists for more than 6 weeks, the RR is graded as severe and the patient should be treated with corticosteroids. As for mild reaction, antileprosy treatment is continued, and special attention must be paid to affected nerves, splinting limbs appropriately if main nerve trunks are involved.

The principles of corticosteroid therapy are straightforward. The initial dose should be sufficient to suppress rapidly the inflammation either in skin or in nerves. The improvement in skin lesions is visible, that in nerves has been confirmed within a few days by motor conduction velocity studies. Then the dose has to be cut in stepwise manner until a suitable suppressive maintenance dose is reached. This is continued until the
reaction begins to settle, when the dose is once again cautiously cut, and eventually tailed-off and stopped.

An initial dosage of 40 mg prednisolone (or prednisone) daily is successful in most adults, although rarely patients may require 60 mg prednisolone for the first 4 days; Jacobson, working in a referral centre in the ‘First World’, prefers routinely to commence with 60 mg daily. The dose may be cut by 5 mg every 1–2 weeks until a maintenance dosage of the order of 20–25 mg daily is reached. This needs to be continued for several months, the duration depending upon the severity of the reaction and the type of leprosy; ultrashort courses lasting only 6 weeks have yielded much less satisfactory results than longer courses, although there have been very few controlled studies.

During this period, a further gradual improvement in motor nerve conduction velocity may occur over several months, which has been attributed to remyelination. During the tailing-off period, the dose is cut by 5 mg daily every 2–8 weeks. Should the reaction recur during this period, the breakthrough is usually mild and occurs slowly; the dose of prednisolone should be raised by 10–15 mg above the dose at breakthrough, until the relapse is completely suppressed, and then maintained at 5–10 mg above that at breakthrough for 2–4 months, before once again being cautiously tailed-off. Our experience over the total duration of corticosteroid antireactional treatment is similar to that of Naafs et al., namely, that most BT patients require 4–9 months, BB patients 6–12 months, and BL patients 6–24 months. Most workers tend to give longer courses in neuritis than in skin reactions, partly from experience, partly because nerve damage is more difficult to monitor (although regular VMT examinations are essential, nerve conduction velocity studies are available at very few centres), and partly because there may be very little functional reserve left in a nerve and a slight increase in damage may have a disproportionate effect on function.

Such individually tailored treatment schemes may be possible in many referral centres. But often patients refuse to leave their homes, especially if the referral centre is not close by, and sometimes beds are not available for the initial period of treatment. Yet under field conditions, standard steroid regimens are required, as they are often administered by senior paramedical workers (PMWs). The standard 12-week prednisolone treatment regimen for field clinics used at ALERT, Addis Ababa, proved very useful, but because of the significant numbers of relapses that occurred during the tailing-off and immediate postcorticosteroid periods, the course was lengthened to 20 weeks for BL and other multibacillary leprosy (MBL) patients. These simple regimens are:

For paucibacillary (PB) patients with severe RR or recent nerve damage, the regimen consists of a 12-week course:

- prednisolone 40 mg daily for 2 weeks, followed by
- prednisolone 30 mg daily for 2 weeks, followed by
- prednisolone 20 mg daily for 2 weeks, followed by
- prednisolone 15 mg daily for 2 weeks, followed by
- prednisolone 10 mg daily for 2 weeks, followed by
- prednisolone 5 mg daily for 2 weeks, and stop.

In MB, BL and BB patients, the regimen consists of a 20-week course:

- prednisolone 40 mg daily for 2 weeks, followed by
- prednisolone 30 mg daily for 4 weeks, followed by
prednisolone 20 mg daily for 4 weeks, followed by
prednisolone 15 mg daily for 4 weeks, followed by
prednisolone 10 mg daily for 4 weeks, followed by
prednisolone 5 mg daily for 2 weeks, and stop.

The patients are instructed to take the prednisolone as a single dose in the morning after a meal. Slightly modified courses with an initial dose of 30 mg prednisolone daily are prescribed for pregnant women.

During a 5-month period in the first half of 1989, 70% of 510 severe reactions cases were treated with prednisolone in the field, and 30% referred to hospital, although these overall figures included some cases of ENL; 75% of those with loss of nerve function showed some or good recovery. We conclude that a majority of severe RR patients can, if necessary, be treated at home by doctors and senior experienced PMWs with standard regimens akin to the ALERT regimens, although a significant minority still require hospital admission and/or corticosteroid regimens of individual length. After stopping corticosteroids, all patients who have suffered from reactional neuritis should continue to have VMT’s, performed every month for several months, when they attend for their supervised MDT.

SURGERY

The place of surgery in the management of RR neuritis remains uncertain. Some centres subject many patients complaining of nerve pain and loss of function, especially of the ulnar nerve, to longitudinal nerve slit through the epineurium; some surgeons may also transpose a very thickened nerve to in front of the medial epicondyle of the humerus. In other centres, very few operations indeed are performed.

Workers are agreed that should a nerve abscess develop in a BT or TT patient, then surgical evacuation of the caseous material is required. Most workers would consider a ‘nerve slit’ operation should the patient continue to suffer from significant nerve pain despite several weeks of corticosteroid therapy. Whether a ‘nerve slit’ operation helps nerve function recovery in addition to the improvement obtained by a full course of corticosteroids is uncertain. A controlled trial of surgery is currently being planned by the ILEP Medical Commission.

Future outlook

Further work is required on the epidemiology and overall incidence of RRs in whole leprosy populations. Steroid regimens need to be further refined, and risk factors for RR more precisely identified. A major multicentre trial on the epidemiology and medical treatment of RRs has now reached an advanced stage of planning by the ILEP Medical Commission. Unfortunately, no new drugs to replace or augment corticosteroids have been identified as likely candidates for widespread use, as prednisolone and prednisone are cheap, relatively nontoxic to most patients in the dosages recommended for RRs, and are familiar to all doctors. But small pilot studies of new drugs could be justified to develop alternatives for patients in whom corticosteroids are relatively contra-indicated. Simple immunological tests, both to make the early diagnosis of RR, and to indicate when
a reaction has settled, rather than being merely suppressed, would be of considerable value to clinicians.

Nevertheless, the early diagnosis of RR, brought about by patient education and by anticipation and increased awareness by the leprosy control staff, associated with the monthly patient contact required by MDT, should lead to early effective treatment, and largely prevent additional nerve damage after the diagnosis of leprosy has been made. In this way, the fear and stigma of leprosy can be further reduced.

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