INTERNATIONAL JOURNAL OF LEPROSY Volume 57, Number 1
Printed in the U.S.A.

CLINICAL NOTES

Editor's Note: In an effort to increase the utility of the JOURNAL in continuing medical education, it has been suggested that a new feature of the JOURNAL be added on a trial basis to the Editorial Section—Clinical Notes. In this section, we welcome contributions dealing with practical problems in leprosy work. Submissions to this section will undergo minimal editorial changes and may well contain controversial points. Letters to the Editor pointing out other viewpoints are welcome.

We are pleased to begin this section with Dr. Pfaltzgraff's views, based on many years' experience, on the management of reactions.—RCH

The Management of Reaction in Leprosy

A great deal has been written about the pathophysiology of reaction in leprosy, but there is still considerable confusion about the subject. However, if we recognize the signs and symptoms resulting from reaction, it is now possible to control the process with the drugs and physical measures available to us. It is usually possible to partially reverse the complications of reaction, and frequently to return the individual to completely normal function, especially if management is begun at an early stage of active involvement.

Reactions are immunologically determined, but exactly what mechanisms are involved is as yet not fully understood. However, it is possible to have a practical working knowledge that may not be immunologically sound, but is adequate to clinically care for patients who are troubled by reactional states.

A reaction can be defined as the signs and symptoms of inflammation giving evidence of the individual's immunological response to the presence of *Mycobacterium leprae* as foreign material. A reaction is expressed as swelling, redness, heat, pain, and possibly loss of function. These signs of inflammation occur in those parts of the body invaded by the organism.

In an elementary but wholly practical way we can explain reactions as being the cellular and humoral response of the individual to antigens of *M. leprae.*

Types of reaction. Reactions may involve the skin alone, or they may only involve nerves and produce neurological evidence of pathology; most frequently they involve both skin and nerves. Less commonly, reactions may also involve the eyes, testes, joints, muscles, tendons, bones, and the kidneys.

The cellular immune response is commonly termed type 1 reaction and occurs in the borderline or central portion of the spectrum of leprosy. Humoral responses are called type 2 reactions and occur in lepromatous leprosy. Type 1 is Type IV and type 2 is Type III in the Gell and Coombs' classification of immunologically mediated mechanisms of tissue damage.

Type 1 reactions are due to activation of the cell-mediated immune (CMI) response. They are frequently subdivided into "reversal reaction" in which there is an increasing CMI, and "downgrading reaction" with decreasing CMI. Practically speaking, it is preferable to consider type 1 as synonymous with "reversal reaction." Downgrading only occurs under conditions of inadequate antimycobacterial treatment, so need not be considered as an aspect of reaction requiring anti-inflammatory or immune suppressive treatment.

The term "type 2 reaction" is frequently considered synonymous with erythema nodosum leprosum (ENL), but preferably these terms should not be used interchangeably. Erythema nodosum means "red lumps" which appear on the skin as a result of a dermal type 2 reaction. But there are no evident "red lumps" during a type 2 reac-

tion occurring in the nerves, joints, eyes, etc. Thus, it is preferable to use the term type 2 for any humoral reaction, including ENL. ENL then is reserved solely for a humoral response in the skin.

Reactions combining type 1 and type 2 occur far more commonly than is usually accepted, and this possibility should be thought of in any patient with lepromatous or multibacillary leprosy,[1] since the management of the two types is somewhat different.

The Lucio reaction is a specific immune response leading to an endarteritis and consequent necrosis of the skin. It is quite limited in its geographic distribution and will not be considered further here.

It is commonly stressed that reactions occur most frequently shortly after the beginning of treatment, but it is important to anticipate their appearance at any time in the course of the disease. Many of the most severe reactions are seen before any treatment has been given. And nowadays with the multidrug treatment of paucibacillary disease, it is not at all uncommon for type 1 reactions to occur after treatment has been fully completed.

As to their severity, a reaction may be mild and rather insignificant so far as the production of signs and symptoms is concerned, but at the other end of the severity scale, the incapacitation of the patient may be extreme. Some reactions result in what is commonly called "silent" neuritis. However, it is the patient who is silent—he is not bothered by what is happening. The neuritis is a silent process and can result in considerable pathology and ultimate disability if you do not recognize what is happening. For this reason, it is of the utmost importance to be constantly on the alert for any evidence at all of a reactional state, regardless of whether the patient complains or not. You must examine and evaluate every patient for physical signs that signal incipient or mild reactions.

Some reactional involvement is merely transient inflammation with no resultant permanent damage, such as reactions in the skin, joints, muscles, tendons, and bones, but when reactions involve nerves, the eyes or the testes, they readily lead to permanent damage and loss of function. Therefore, always consider reaction involving these structures as severe. Silent reactions are sometimes termed "quiet" since the onset and progression are insidious and may easily go unnoticed by both the patient and the medical observer.[2]

By far the most important type of reaction is that involving nerves with resultant sensory, motor, and autonomic deficits. Evidence of reaction may not be very dramatic initially and so there is a tendency to ignore its presence. The patient may think it is an inevitable result of the disease and not mention it to the attending physician. But the ultimate disability can be very destructive.

A general statement that can be made about reaction is that whenever something happens rapidly in leprosy, it is almost surely due to reaction. However, it is important to be aware of the "silent" type of reaction. One needs to be constantly on the alert for evidence of changes that may be signs of a reactional state, whether they take place rapidly or slowly, with many signs and symptoms or with few.

During the recent XIII International Leprosy Congress, reaction and neuritis and, more specifically, the insidious "silent" type of neuritis that furtively destroys nerves was discussed in five of the Pre-Congress Workshops. At last it appears that this subject is getting some of the attention it deserves. The discussion of this problem in the Workshops on Prevention and Management of Impairment and on Rehabilitation made more specific reference to the slowly progressive, quiet type of neural involvement and suggested that some specific measurable way of determining the progression of nerve damage should be established.

A quantitative evaluation of alteration in protective sensation would be the best procedure for general adoption. This can be done by using a single nylon bristle that just begins to bend when the tip is subject to 10 g of "end-on" pressure. Any bristle can be used after determining what length of the fiber will just start to flex when pressed

[1] Cleazy, J. K. A. Simultaneous type 1 and type 2 reactions. Int. J. Lepr. **51** (1983) 413.

[2] Srinivasan, H., Rao, K. S. and Shanmugan, N. Steriod therapy in recent "quiet nerve paralysis" in leprosy. Lepr. India **54** (1982) 412–419.

against the pan of a scales subjecting the tip of the bristle to 10 g of pressure. Any area of the patient's extremities—hands or feet—that demonstrate inability to feel this pressure should be recorded. Repeated measurements of the size of the area to determine increase or decrease can be recorded. Then, any increase in the area of insensitivity is an indication to immediately apply measures to suppress the immune response—corticosteroids, physical measures, clofazimine, thalidomide, etc., as discussed below. If for some reason, measurements cannot be carried out with some degree of accuracy, and if there is any doubt as to the presence of reaction or progression of nerve pathology, treat the patient as if it is, in fact, reaction. This policy will lead to less harm than if one waits to see what happens until after the process has become obvious and begun its downhill course.

The nerves more commonly involved in neuritic reactions, in the usual order of frequency of occurrence, are the ulnar, median, facial, common peroneal, posterior tibial, and the radial. But be aware of the fact that there are other nerves which may occasionally be affected. The nerves in which there is most potential for reversal of the process and return to normal function are the radial, posterior tibial, common peroneal, facial, ulnar, and the median.

Management of reaction. The four principles that need to be considered in the management of reaction are: 1) control neuritis in order to prevent anesthesia, paralysis, and contracture; 2) halt damage to the eye, preventing blindness; 3) control the patient's pain; and 4) kill bacilli and stop the progression of disease. Setting down these principles in this way does not imply that Number 1 is more important than Number 2 but, rather, that all of these aspects of care need to be implemented at the same time. These principles apply regardless of the type of reaction. There may be differences in the types of reaction, but the important difference is in the degree of severity.

As a new patient is introduced to the management of his disease, it is of the utmost importance to advise him of the potential for reaction occurring during the course of his treatment so that he knows and can anticipate what may happen. It is vital that he realize that during reactions his disease may appear to get worse, but this never should lead to cessation of the specific attack on the disease itself. It is important that we consider reaction not as a component of the disease but rather as a complication which, in all instances, can and should be prevented. And every effort should be made to halt every reaction at the earliest possible stage. Reaction, neuritis, and disability are not aspects of leprosy that require action only after treating the basic infection. They need to be considered immediately when the diagnosis of leprosy is established, and provision made to provide proper treatment.

Remember, reaction and its sequelae are only the evidence of the immune response to the basic infection by *M. leprae.* They are not necessarily relieved by antileprosy therapy until the infection is fully eradicated and the immune response "turned off." So, as symptoms, they demand symptomatic relief. Thus, it stands to reason that it is never possible to provide a "predetermined course" of treatment. Rather, management of reaction is to provide whatever is required to alleviate the patient's complaints, relieving signs and symptoms. Frequently, it is stated that a "course" of corticosteroid (or other immunosuppressive measure) has not provided relief. In that case the therapy was simply inadequate. Either the steroid dose needs to be increased or it should be supplemented by other measures in order to provide optimum relief of signs and symptoms.

There are four aspects of treatment and care that need to be implemented in a practical approach to the control of reactions. These are: a) anti-inflammatory therapy primarily to reverse nerve damage; b) analgesia to control the patient's pain; c) physical measures to prevent or reverse contractures; and d) anti-bacterial therapy of the disease itself.

There is considerable confusion regarding the management of reactions, in that frequently arbitrary statements are made that there are contraindications to combining various modes of treatment or of drugs that have differing actions. However, it is so important to control reactions that every measure possible should be used at the same time. There are no contraindications to us-

ing any or all of the drugs and physical measures concurrently. In fact, some seem to have a synergistic effect.

Several workers have devised practical measurements to be used to evaluate the extent of nerve damage. This is set out by Fritschi in his book on surgical reconstruction,[3] and also in a brief article in *Leprosy Review.*[4] This is also presented in excellent detail by Brandsma.[5, 6]

For practical purposes, both in describing reactions and in determining principles of management, reactions are best divided into those that are mild and those that are severe. Mild reactions may be either of type 1 or type 2 in which there is pain or edema in the skin or an increase in erythema of skin lesions, but there is no significant systemic disturbance, nor any subjective or objective evidence of nerve involvement. Most importantly mild reactions never lead to permanent sequelae.

Severe reactions are: a) those in which there is evidence of neural involvement. These are more common early in the course of tuberculoid disease but may take place later in the course of lepromatous disease as well; b) spontaneous ulceration of the skin; and c) involvement of the eye or the testes in type 2. All of these are indications for urgent anti-inflammatory treatment in order to prevent permanent disability.

Drug therapy. In mild reactions aspirin is the best and most economical non-steroidal drug used to control both inflammation and pain—600 mg to 1200 mg may be given up to every 4 hours or 4–6 times daily. Another inexpensive anti-inflammatory agent with a weaker response is chloroquine given as 150 mg chloroquine base up to 3 times daily. There appears to be some synergistic value in combining these two drugs. Antimonials have some anti-inflammatory effect, the basis for which is unknown. The organic trivalent antimonials are less toxic, and the one most frequently used is stibophen in a dosage of 2–3 ml intramuscularly on alternate days for 5 or 6 doses. The only type of reaction for which stibophen has unique value is for bone pain. Rare patients seem to be afforded relief by no other non-steroidal drug.

If thalidomide is available it can be used for mild type 2 reactions. It has no effect in type 1 but can be used for type 2 freely in male patients and female patients not of child-bearing age. For mild reactions 200 mg on a daily basis would help the patient be more comfortable. Mild reactions do not lead to disability, so this is merely for symptomatic relief.

For severe reactions in any patient in whom there is a potential for permanent damage to nerves, eyes, or testes, corticosteroids are definitely indicated. Prednisone or prednisolone given in a single daily dose is usually adequate. It is impossible to give a fixed schedule of dosage for corticosteroids, but most patients can be adequately cared for by the initial use of 60-80 mg daily. However, in those patients with really severe neuritis, up to 120 mg daily may be required.

Preferably one should err on the side of beginning with a higher dose than necessary because the vital thing is to suppress the acute phase of the neuritis and then taper off after the initial episode has been relieved. Acute symptoms should have started to subside within 24 hours, and in 5–7 days one should begin to reduce the dose. Another way of saying this is that the treatment should be reduced upon the indications. There may be times when one has given an inadequate dose and it may be necessary to increase it, but it is better to begin with sufficient drug in order to start reducing the inflammation from the first dose. This may be especially true during the period following the initial treatment when one is attempting to taper off and has reduced the dose too quickly. The beginning dose can likely be reduced by half in less than a week, reducing after that by 10 mg weekly over a prolonged period. Most patients will be improved adequately by the use of corticosteroid for up to 6 months, although occasionally it is necessary to continue for a longer period of time. It has been

[3] Fritschi, E. P. *Surgical Reconstruction and Rehabilitation in Leprosy.* 2nd ed. New Delhi: The Leprosy Mission, 1984, pp. 30–48, 165–181.

[4] Fritschi, E. P. Field detection of early neuritis. Lepr. Rev. **58** (1987) 173–177.

[5] Brandsma, W. Basic nerve function assessment in leprosy patients. Lepr. Rev. **51** (1981) 161–170.

[6] Brandsma, W. Nerve function testing and evaluation. The Star **43** (1983) 2–3, and **44** (1984) 8–10.

conclusively determined that the use of a longer course of corticosteroid results in less nerve damage.

Several workers have recommended the use of a standardized "course" of steroids that can be given at the discretion of paramedical staff on an out-patient basis. This has been proposed by Kiran, *et al.*,[7] and more recently satisfactory control of reactions on an out-patient basis by paramedical workers in Ethiopia has been reported from ALERT.[8] Out-patient administration using a standardized regimen is certainly to be preferred to not using corticosteroids at all. However, in order to attain optimum results in preventing permanent damage from neuritis, the patient should ideally be admitted to a hospital where the administration of corticosteroids can be regulated by close observation of the reactional state.

Severe type 2 reactions are best controlled by the use of thalidomide. However, corticosteroids usually should initially be combined with the thalidomide in order to get the most rapid reduction in nerve swelling and inflammation. The corticosteroid can be reduced quite rapidly as the thalidomide begins to take effect. However, it is often necessary to continue a 10–20 mg dose of corticosteroids, since thalidomide does not fully control the neural component of the reaction. In many instances during a type 2 reaction, there is also a type 1 component which is not affected by the thalidomide, making some corticosteroid essential.

Remember that although drugs are invaluable in combating the infection by *M. leprae,* ultimate eradication of all bacilli is dependent upon the host immune response. Corticosteroids suppress the immune response, and with their use there is potential for encouraging multiplication of bacilli. Therefore, whenever corticosteroids are used, an effective bactericidal drug should also be given. It is possible for tuberculosis, strongyloidiasis, or amebiasis to be activated in patients on long-term corticosteroid treatment. Chest X ray and stool examination should be carried out in order to check for these potential complications, and then to treat them if need be.

Certain complications may arise from the drugs used to control reaction and neuritis, but if used as recommended in this presentation, they will only arise infrequently.

Aspirin and other non-steroidal anti-inflammatory agents occasionally cause symptoms of peptic ulceration and even bleeding. If this happens, the offending compound must be discontinued and another of that group of drugs may be tried as an alternative.

Chloroquine can cause insomnia, tinnitis, and visual difficulty, but these side effects are transient and of no significance with short-term use.

Stibophen is a somewhat toxic drug and should not be used in someone who has had any untoward reaction to its use previously.

All of the side effects of corticosteroid use are well-known: peptic ulceration, Cushing's syndrome, steroid dependency, etc. Prior to the availability of clofazimine, these were a problem. When clofazimine became available, it was no longer necessary to keep patients on long-term, high-dose corticosteroids. So now these complications are unusual.

Clofazimine itself has a few, usually minor side effects. Skin pigmentation is the most common, but is no real problem, and patients usually are willing to put up with the temporary discoloration because of the relief from neuritic pains that it affords. Clofazimine also causes dryness and fissuring of the skin, especially in lesions and also pretibially. This can be controlled with oils or emollients. Following long-term use, a patient rarely may develop gastrointestinal intolerance with cramps and diarrhea. If this persists, even with a lower dose, then the drug should be discontinued.

Because reactions produce neuritis which may lead to permanent disability when managed incorrectly, all patients with either type of reaction should only be given those antileprosy drugs which do not aggravate or incite reaction during periods when there is a relatively high risk for them to occur. Therefore, in either type of reaction clofazimine should be used as the sole antilepro-

[7] Kiran, K. V., Stanley, J. N. A. and Pearson, J. M. H. The out-patient treatment of nerve damage in patients with borderline leprosy, using a semi-standardized steriod regimen. Lepr. Rev. **56** (1985) 127–134.

[8] Becx-Bleumink, M. ALERT Annual Report, 1986–1987. Addis Ababa: ALERT, 1987, pp. 87–92.

tic temporarily. It has been proven beyond doubt that this is of value in the management of type 2 reactions and helps to a certain extent in type 1 as well. Even though this may not be dramatic, in conjunction with other anti-inflammatory measures it aids in the preservation and restoration of maximum function.

There is now good evidence that the World Health Organization (WHO) recommended multiple-drug therapy (MDT) does not usually aggravate reaction, contrary to what I had reported in my Letter to the Editor in 1982.[9] At that time it was not recognized that larger doses of corticosteroids need to be used while giving rifampin. There seems to be a significant reduction in the number and severity of both types of reactions when patients are given MDT. However, in any instance where there is a threat to the integrity of the nerves, it is important to continue the bactericidal treatment of the disease with clofazimine alone temporarily. A dose of 400 mg in divided doses should be used for a period of 2 weeks, reducing to 300 mg for 1 month, 200 mg for 2–6 months, and then 100 mg can be used for a period of several years if necessary as the reactional state is subsiding. However, usually after a few months of treatment with clofazimine alone it is preferable to return to the standard course of MDT as recommended by WHO.

It has been found that with the implementation of MDT for paucibacillary leprosy, reactions occasionally appear after treatment has been terminated. When this happens and the reaction is severe (with potential for producing disability), corticosteroids must be given. Although the immune response of the individual may have cared for the infection adequately, at present we have no way of knowing absolutely if there are residual viable *M. leprae* or not. So it is better to combine an effective bactericidal drug (preferably clofazimine) with the corticosteroid, treating the patient just as if this were a new infection.

Analgesic therapy to control the patient's discomfort is best done just as for its anti-inflammatory use. Thus patients in reaction should be given aspirin and chloroquine as recommended above to control their pain as well as to suppress the inflammation. A persistence of pain is an indication that thalidomide or corticosteroid dosages are inadequate.

Intraneural injection is not indicated in any circumstance for management of inflammation or control of nerve pain.

There are two other drugs that might be considered for the management of reactional states: 1) Colchicine has been used for type 2 reaction with good results. However it is a toxic drug and should only be used with caution. 2) Antimetabolites and immunosuppressants have also been tried by a few individuals. There is considerable danger of untoward side effects, and their use is not indicated when such good results can be obtained with corticosteroids used properly.

Physical measures. During episodes of neuritis there is an increase of edema and swelling which constricts the blood supply to nerves, and for this reason, if adequate corticosteroid therapy does not begin to relieve the pain and loss of nerve function in 48 hours, nerve surgery should be considered. However, this should be done in the simplest manner possible, with the least amount of trauma, merely incising the nerve sheath to release the constriction, without any attempt to dissect up the nerve. If there is an abscess, it should be incised and drained. However, small abscesses (less than 2–3 cm across) will resolve spontaneously and need not be opened. Of course oral corticosteroid therapy should be continued in adequate doses during the course of the surgery and recovery.

Physical measures are of importance to prevent disability and deformity in conjunction with the drug therapy mentioned above. This includes immobilization of affected limbs by careful splinting. During immobilization splints must be removed daily in order to put the splinted joints through passive range of motion by a trained physiotherapist. Heat applied by the use of a paraffin wax bath aids in the more rapid restoration of mobility by making the superficial tissues of the hands more pliable and promoting the return of sweating. As

[9] Pfaltzgraff, R. E. Short-term, multidrug chemotherapy of leprosy and type 1 reaction. Int. J. Lepr. **50** (1982) 365–367.

the symptoms subside and function begins to return active exercise should be cautiously instituted. Splints must be made in such a way that trauma to the anesthetic part is avoided, and they must be kept in place for 24 hours a day except during periods of exercise and massage. As improvement takes place, active exercises are increased until normal function has been restored, or until it is evident that no more improvement will occur.

Three points should be made about antileprosy therapy during the course of reaction: a) Patients who present for the first time with tender or enlarged nerves should be treated initially with clofazimine alone since it seems less prone to aggravate reaction than does the use of dapsone and/or rifampin. b) Some patients with borderline disease develop severe reaction shortly after starting treatment with dapsone and rifampin. It is wise in such instances to change to clofazimine alone temporarily, allowing corticosteroids to be withdrawn sooner. c) A bactericidal antileprosy drug must always be continued during reaction. The only one that definitely does not increase the inflammatory response is clofazimine.

Summary. Reaction and the subsequent development of neuritis is the basis for the majority of the disabilities and deformities that occur in leprosy. All possible means to prevent, to treat, and to reverse every reaction should be employed in an all-out effort to ultimately effect as ideal a functional status for the patient as can be attained.

—Roy E. Pfaltzgraff, M.D.

Consultant
Program and Training
American Leprosy Missions
One Broadway Place
Elmwood Park, New Jersey 07407, U.S.A.