Leprosy Research Unit, which has now become the Leprosy Research Centre, an institution for teaching and research that has had great influence in all leprosy work, and been a source of inspiration for leaders as well as beginners, in that field. Dr. Cochrane has always promoted intensive teaching in leprosy, with emphasis on early diagnosis, and has campaigned constantly for a larger part for leprosy in the curricula of university medical schools. His own activity in the field is evidenced by numerous publications, including his widely used Leprosy in Theory and Practice, first published, with the aid of numerous well-known collaborators in 1939, and republished as a second edition with Dr. T. F. Davey as co-editor in 1964.

It would be impossible in any reasonable length to note his numerous contributions to the advance of knowledge and practice in the leprosy field, and the many honors he has received, from the King George VI Coronation Medical in 1937 to the Damien-Dutton Award at Careville, Louisiana in 1964. The H.A., of which The Journal is the official organ, has profited by a life long dedication. In its earliest years, 1932-1935, he served as its Secretary-Treasurer. In the succeeding years he has been repeatedly councillor and vice-president, until his election as president in 1965.

The Editor would close by noting briefly but with pleasure his intimate association with Dr. Cochrane at the Leonard Wood Memorial—Armed Forces Institute of Pathology Conference on Research Problems in Leprosy in Washington in May 1965, and the profit he derived from it. Dr. Cochrane’s part in that conference was impressive. Out of his broad experience and innate understanding has come a capacity to see as a whole the central purposes in the far flung enterprises in the study and control of leprosy. It is to be hoped that his wisdom and devotion will long be available to the Association. — E.R.L.

NODULAR PANNICULITIS AND PERIPHERAL NEUROPATHY FOLLOWING SUDDEN WITHDRAWAL OF CORTICOSTEROIDS

(Poststeroid Nodular Panniculitis) 1

Among the many potential hazards of prolonged corticosteroid therapy, given for diverse conditions, several recent reports have directed attention to a nodular panniculitis that may follow the sudden withdrawal of the drug in patients who have been receiving high doses for prolonged periods (2). This phenomenon is thus quite distinct from the better known and fairly common “rebound” effect, in which the symptoms and signs of the original pathologic condition reappear either when corticosteroids are suddenly discontinued or when the

1 My thanks are due to Dr. S. O. Egwuatu, Chief Medical Officer, Ministry of Health, Eastern Nigeria, for permission to publish this Editorial.
dosage is too rapidly decreased. The recurrent symptoms may be suppressed again by readministration of the corticosteroid.

The first report of nodular panniculitis following rapid withdrawal of prednisone after prolonged high-dose therapy (11) indicated that, while systemic evidence of "rebound" may have occurred, viz., elevation of the erythrocyte sedimentation rate and appearance of C-reactive protein in the serum, there was no recurrence of the rheumatic manifestations for which prednisone therapy had been given. Some of the patients did, however, develop numerous painful and tender discrete lesions similar to those of erythema nodosum, while others showed an acute nodular panniculitis.

A subsequent paper by Taranta et al. (21) reported the "paradoxical" finding that this nodular panniculitis could be made to disappear by reinstatement of the prednisone that had been suddenly suppressed. The panniculitis reappeared when prednisone was again stopped, to regress rapidly when the drug was readministered.

Vince (26) recorded the case of a young patient who developed a similar panniculitis when the dose of prednisone was reduced but not completely suppressed. The panniculitis, however, persisted (though in a milder form) when the dose of prednisone was increased—perhaps not sufficiently. Spagnuolo and Taranta (22) reported four more examples in which the clinical and pathologic findings were essentially similar to those described by the above workers.

Most of the patients who figure in these reports had been suffering from some form of rheumatism for which high doses of corticosteroids had been prescribed over a long period. One of them had leukemia, however, and one was suffering from nephrosis. In a patient reported by Burkinshaw (8), a condition called erythema nodosum was apparently precipitated by poliomyelitis vaccination. It was controlled by prednisolone, but reappeared after the drug was discontinued. Another episode occurred following an additional poliomyelitis vaccination. This history is reminiscent of both the "rebound" effect and poststeroid panniculitis.

Roenigk et al. (17) emphasize not only the "paradoxical" disappearance of the nodular panniculitis on readministration of prednisone, but also the absence of evidence of acute adrenal insufficiency at the time of the first appearance of the panniculitis.

Clinical features.—The clinical features of poststeroid nodular panniculitis consist first of erythema-nodosum-like lesions, acuminate or macular rose spots situated in the skin of the limbs, the trunk and the face, and second, of a diffuse nodular panniculitis affecting a more or less extensive area of the subcutis in the same situations. The actual dose-level of corticosteroids and the period of administration both appear to be of slighter consequence than the rapidity of withdrawal. The severity of the condition varies within wide limits. The milder lesions may disappear spontaneously; the more severe are amenable to the readministration of corticosteroids, and thereafter tend to disappear gradually.
In published reports, emanating mainly from the United States of America, the predominance of colored patients is noticeable, but this may be coincidental. A true predominance, if it indeed exists, may be a further instance of the known tendency of the deeply pigmented skin to respond exuberantly to such challenges as Mantoux testing, framboesial infection, chronic irritation, etc., and to drugs inducing fixed eruptions (4). When they have completely subsided, the lesions in skin or subcutis leave no evidence of deep fibrosis, such as depressed scars. The dark staining of a localized postinflammatory hypermelanosis is all that indicates the site of a previous lesion.

Histologic appearances.—The histologic appearances have been fully reported by Taranta et al. (23) and Roemig et al. (17). Portions of tissue removed during the acute stage showed either acute or subacute inflammation of the fatty layer of the subcutis. Round cells and polymorphonuclear neutrophils predominated in the earlier lesions, while giant cells and histiocytes were present at later stages. Both the interlobar septa and the blood vessels were relatively free from inflammatory exudate. Roemig et al. (17) reported needle-shaped clefts within fat cells, with infiltration of the fat lobules by a variety of chronic inflammatory cells and the presence of foreign-body giant cells.

LEPROTIC PANNICULITIS

Leprologists familiar with the typical manifestations of erythema nodosum leprosum and its protean variations in the skin and subcutaneous fatty tissue (4) will at once sense some important resemblances between poststeroid nodular panniculitis and the conditions they are familiar with. They will also recognize the sequence: suppression by corticosteroids, recurrence of the original symptomatology on over rapid reduction in corticosteroid dosage or complete suppression of the drug; and dramatic control of the symptomatology on reinstatement of the anti-inflammatory therapy. They will be in some doubt as to whether the phenomena they are acquainted with are to be regarded, in the light of the work reported above, as part of a "rebound" phenomenon, or as an example of nodular panniculitis of the type now associated with suppression of corticosteroids.

The clinical appearances of the lesions, their natural history, their distribution, the residual staining, and the absence of depressed scars, all plead in favor of similarity if not of virtual identity between the panniculitis of erythema nodosum leprosum and poststeroid nodular panniculitis, and against Weber-Christian disease (relapsing febrile nodular nonsuppurative panniculitis), and similar conditions.

The localization of the lesions in nodular panniculitis (and the accompanying polymorphic erythema nodosum) is very similar in the poststeroid condition to that occurring in the acute exacerbation of lepromatous leprosy, i.e., the forearms, arms, thighs, trunk and face, approximately in that descending order of frequency. Similar par-
alleles may be found in the sites of predilection of the chronic, irregularly diffuse panniculitis of progressive lepra reaction, with its accompanying chronic inflammatory changes in the overlying skin. Since recent work has shown that the chemical composition of the body fat in the individual is remarkably constant and stable whatever the site (14), it appears likely that the distribution of the panniculitis depends on a sensitization of the tissues by localized deposition of circulating antigen.

The histopathologist familiar with the work of Fernández and Mercau (10), Pepler et al., (11) Rodriguez (15), and Ridley (16), may well recognize the familiar microscopic pictures of polymorphonuclear infiltration of the fat lobules and a minimal involvement of interlobular septa and blood vessels, although the latter appears to be variable and dependent at least partly on the age of the lesion examined. The histologic findings in the specimens of poststeroid panniculitis emphasize these resemblances, and exclude from the differential diagnosis such rarities as subacute migratory nodular hypodermatitis, periarteritis nodosa, and similar conditions well summarized by Van Laethem and Boncoeur-Beeckman (20).

Another interesting parallel between the generalized tissue hypersensitivity occurring in lepromatous leprosy in exacerbation and poststeroid nodular panniculitis, lies in the acute ulceration that may supervene in either condition (1), recalling the characteristic multiple ulcerations occurring in Lucio leprosy. Similar skin ulcerations may sometimes develop in corticosteroid-dependent patients with lepromatous leprosy in chronic reaction in whom the dose of corticosteroids is reduced too rapidly. These multiple ulcerations are sometimes the portal of invasion of staphylococci, resulting in a sepsis that yields to a combination of suitable antibiotics and sulfonamides, together with corticosteroids in adequate and enhanced dosage. In lepromatous leprosy, the reappearance of panniculitis upon over-rapid reduction in corticosteroid dosage has not infrequently been urged as a serious contraindication to their use to control episodes of acute exacerbation (1). Balina et al. (1) consider that a severe and uncontrollable reactive state may sometimes supervene as a result of their indiscriminate use.

There seems to be no constant bacterioscopic counterpart of acute exacerbation as manifested in erythema nodosum leprosum and accompanying panniculitis. Morphologically normal bacilli may or may not be present; they may or may not reappear, degenerate bacilli may or may not increase before, during or after the acute episode. Experimentally, corticosteroids appear to facilitate multiplication of M. leprae in the mouse foot pad (15).

The effect of iodides in precipitating or exacerbating erythema nodosum leprosum is well recognized. Iodides may also apparently precipitate exacerbation in Weber-Christian disease (1, 25).
The multiple deep nodules of Weber-Christian disease also may respond to corticosteroid therapy and reappear when that therapy is discontinued, as in the type recently reported by Beerman et al. (3), but other authors fail to find that corticosteroids exert a favorable influence on the disease (Van Laethem and Boncoin-Beeckman (25)). It may be that the age of the lesion has an important bearing on its susceptibility to the anti-inflammatory agent.

POSTSTEROID PERIPHERAL NEUROPATHY

Another parallel between leprosy and a pathologic condition evoked by sudden withdrawal of corticosteroids is the peripheral neuropathy occurring in patients suffering from rheumatoid arthritis, and reported by Pallis and Scott (12). Some workers have considered the neuropathy as a complication of rheumatoid arthritis, while others attribute it to some obscure action of the corticosteroids (11, 18). However precipitated, this condition, like that of the accompanying rheumatoid arthritis, may be relieved by increasing the dose of the steroid that may have precipitated it. The mechanism is far from clear; it may be related to the histologic disturbances in the mesenchyme and blood vessels consequent on the sudden withdrawal of cortisone, reported by Slocumb as long ago as 1953 (20).

The peripheral neuritis of rapid appearance that is a frequent feature of the acute exacerbation of lepromatous leprosy may be associated clinically with precisely those manifestations of allergic sensitivity that are seen in poststeroid panniculitis. In both, administration of corticosteroids may be followed by symptomatic relief; that is, whether the peripheral neuritis is a local manifestation of the peculiar hypersensitive state existing in the acute exacerbation of lepromatous leprosy, or whether it is a “rebound” effect in rheumatoid neuropathy, the nonspecific anti-inflammatory action of the corticosteroids leads to the same therapeutic result.

As in the acute exacerbation of lepromatous leprosy, amelioration of the symptoms in poststeroid panniculitis and in poststeroid peripheral neuropathy, may be spontaneous, especially when of slight degree. More frequently, however, dramatic improvement awaits the readministration of corticosteroids, and subsequent freedom from symptoms is assured by maintaining for a variable period the optimum dose of the drug, and then reducing this dose by extremely small steps until the patient is eventually weaned from dependence (4). Reductions of the order of 1 mgm. of prednisolone (or equivalent) every two or even every four weeks, may be the most rapid that the patient will tolerate.

While the connection, if any, between poststeroid panniculitis and poststeroid peripheral neuropathy on the one hand, and the panniculitis and neuropathy of lepromatous leprosy on the other, remains obscure, further investigations by leprologists in their special
clinical realms should shed more light on various aspects of local tissue sensitivity and its relation to cortisone and its synthetic analogs.

—S. G. Browne

REFERENCES


SUBTITLE FOR THE JOURNAL AND CHANGE IN FORMAT

Within recent months the Editorial Board of The Journal and the Council of the International Leprosy Association have approved certain changes in the cover and format of The Journal, to take effect with the first issue for 1966, i.e., Volume 34, Number 1, for the months January-March.

The scientific investigation of leprosy has always profited from advances in the understanding of pathogenetic factors and the clinical course of other diseases caused by microorganisms of the genus *Mycobacterium*. The utilization in leprosy of staining procedures, epidemiologic methods and chemotherapeutic drugs used successfully in tuberculosis, and the leads obtained for investigation of *M. leprae* through an understanding of the unique growth requirements of the etiologic agent of Johnse's disease, are cases in point. Many other examples could be cited. Disease of mycobacterial origin occurs in mice, rats, cats, cattle of wide variety, fish and other cold blooded animals, birds of many species, and numerous other forms of life. In not a few of these the histopathologic picture in affected tissues bears some resemblance to that of leprosy. Thus, however illogical it may be, and annoying at times to expert leprologists, such terms as rat, cat, and bird leprosy, and lepra babalorum, have crept into leprosy literature, confusing some issues, as well as calling attention to some factors in common. Currently infections by *Mycobacterium ulcerans* and *Mycobacterium balnei* evoke increased interest, partly because of the necessary differential diagnosis from leprosy in some areas of the world. As a matter of fact, besides their shared staining characteristics, certain other attributes, including optimum temperature requirements for growth of the etiologic agents, are reminiscent of factors believed to play a role in the multiplication of *M. leprae*. With such facts in mind, and a practical interest in increasing circulation of The Journal by bringing in an audience of wider interest, members of the Editorial Board constituting a majority of the Council, meeting in Washington, D. C. in May 1965 in connection with a research conference on leprosy problems sponsored by the Leonard Wood Memorial and the U. S. Armed Forces Institute of Pathology, recommended that the subtitle “and other mycobacterial diseases” (in