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 ([7]). 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

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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 ([21]) 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.* ([23]) reported the "paradoxical" finding that this nodular panniculitis could be made to disappear by reinstitution 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 (6). 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 Roenigk *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. Roenigk *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 (5) 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 overrapid reduction in corticosteroid dosage or complete supression of the drug; and dramatic control of the symptomatology on reinstitution 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-

allels 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.*, [13] Rodriguez [16], and Ridley [15], 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 rareties as subacute migratory nodular hypodermatitis, periarteritis nodosa, and similar conditions well summarized by Van Laethem and Boncoin-Beeckman [25].

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 [26], 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 mutiple ulcerations are sometimes the portal of invasion of staphylococci, resulting in a septicemia 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 [9]. Balina *et al.* [2] consider that a severe and uncontrollable reactional 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 [19].

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, 24].

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.

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