Localized Bacilliferous Skin Lesions Appearing in Patients With Quiescent Lepromatous Leprosy[1]

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It is not uncommon for polymorphous skin lesions containing numerous *Mycobacteria leprae* to herald or accompany acute exacerbation in lepromatous leprosy. This report, however, deals with multiple papilliform lesions, teeming with *M. leprae*, which arise suddenly in patients with lepromatous leprosy still under treatment, whose routine skin and nasal smears have contained neither "solid rods" nor acid-fast bacillary debris for many months. The condition was discovered as the result of routine bacterioscopic examination of any unusual lesion appearing in the skin of patients with apparently quiescent lepromatous leprosy under observation and treatment in the Uzuakoli Leprosy Research Unit, Eastern Nigeria.

CLINICAL OBSERVATIONS

Without any local or systemic prodromata, small flat-topped nipple-like elevations about 5 mm. in diameter arise in the skin. The number may vary from a few to forty or fifty. They may appear either at once or in successive crops spread over several weeks. The suddenness of their appearance, and the rapidity with which they attain their maximum dimensions, are alike striking. Within a few days the small shot-like papules set deep in the skin become soft and succulent, rounded and elevated, and papilliform. The color of the skin overlying the papules may be unchanged, or it may be distinctly lighter in hue than the surrounding skin, a pinkish-brown or yellowish-brown in the deeply pigmented African. The distribution of the lesions follows no discernible pattern: they are mainly scattered singly or in groups on the upper part of the trunk and the proximal portions of the limbs.

No symptoms accompany or follow their appearance. The surrounding skin is unchanged. They have shown no tendency to ulcerate.

The natural history of the lesions, when left without treatment, is unknown, since four of the five patients considered in this paper continued to receive antileprosy treatment, either dapsone or B.663 (Geigy). The lesions gradually shrink until, at the end of six to twelve months, they are flush with the skin and represented only by a thin circular scar, which may be finely striated, and perhaps slightly puckered, or shiny and pigmented.

BACTERIOLOGIC OBSERVATIONS

The five patients forming the subject of this report had been under treatment for severe lepromatous leprosy (completely Mitsuda-negative) for varying periods. The initial Bacterial Index (B.I.), i.e., the average of the results taken from six skin and two nasal mucosal sites, ranged from 2.75 to 4.0, and in the five patients averaged 3.4 (maximum: 4.0, on Dharmendra's notation). The initial Morphologic Index (M.I.), i.e., the average of the percentages of "solid rods" at these eight sites, ranged from 35 per cent to 100 per cent, with an average of 59 per cent. With the gradual disappearance of "solid rods" from all sites smeared, coincident with treatment, the M.I. fell to zero, and remained at zero for at least 31 months; i.e., no "solid rods" had reappeared at any of the sites smeared at monthly intervals. Nonsolid rods and acid-fast debris had progressively diminished under treatment, the B.I. falling to zero, and remaining at zero in each patient for

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at least seven months before the sudden appearance of the lesions forming the subject of this communication.

Bacterioscopic examination of material obtained by the scraped incision technic from these acutely arising papilliform lesions revealed innumerable "solid rods" and numerous globi in each field under the oil-immersion lens. In two patients, no "non-solid rods" or debris at all could be made out, either within the globi or among the individual bacilli scattered between the cells. In another, 80 per cent of the bacilli were classed as "solid rods." In the remaining two patients, both the B.I. and the M.I. were lower.

In those patients in whom successive crops of similar lesions appeared, it was possible to follow the increase of the density of the bacterial population in these lesions by means of fortnightly smears, the M.I. remaining the same—and this, despite the continuation of treatment in four of the five patients and the resumption of treatment in the fifth. Both the B.I. and the M.I. thereafter fell gradually, at about the same rate as the average of multiple smears in patients with lepromatous leprosy of comparable severity.

The apparently normal skin between the lesions participated not at all, or but slightly, in the recrudescence of bacillary activity. In three patients, all sites smeared—apart from the lesions themselves—remained clinically normal and bacterioscopically negative. In one patient, small numbers of bacilli of morphologically normal aspect began to reappear in apparently normal skin; and in the remaining patient "non-solid rods" and bacillary debris made their appearance in the ear lobes. In these two patients, bacilli and debris at these sites disappeared much more rapidly than in the papilliform lesions themselves.

PREVIOUS TREATMENT

Four patients were actually receiving regular dapsone therapy when the lesions appeared: two were having 300 mgm. twice weekly, one 100 mgm. twice weekly, and one 50 mgm. twice weekly. The other patient, having been for a considerable time in chronic exacerbation which flared up seriously whenever dapsone was given, even in as low a dose as 10 mgm., had been receiving a maintenance dose of 5 mgm. of prednisolone daily; no dapsone had been given for eight months.

SUBSEQUENT TREATMENT

With the possibility of true dapsone resistance in mind, the first two patients in this series were given B.663 (Geigy) at a dose of 100 mgm. daily. Their subsequent progress has been excellent, the skin lesions subsiding rapidly and the M.I. and B.I. falling satisfactorily. With a view to ascertaining if the bacilli were dapsone-resistant, bacillary emulsions prepared from whole lesions from these patients, excised with aseptic precautions and flown on ice to the Medical Research Council, London, were injected into the foot pads of mice that were receiving dapsone in the diet. In both cases, bacillary growth was inhibited by dapsone, but multiplication occurred in mice not receiving dapsone. Thus, the bacilli present in the acute lesions, one of which was in a patient taking 100 mgm. dapsone twice weekly, and the other in a patient who had been having dapsone until eight months previously, were not resistant to dapsone.

Bacillary emulsions from a third patient (the last of the five), who had made excellent clinical and bacteriologic progress for 52 months on 50 mgm. of dapsone twice weekly, have been recently inoculated into mouse foot pads. The results are awaited with interest, since, on analogy with other diseases, the possibility exists that small doses of dapsone may tend to induce drug-resistant bacillary mutations.

HISTOLOGIC APPEARANCES

I am indebted to Dr. D. J. Harman, of the Leprosy Study Centre, London, for the following report:

"Histological Report on an Acute Papilliform Lesion. The tissue is fixed in formalin, and includes most of the thickness of the dermis. In sections stained with TRIFF stain ([7]), three sweat glands are visible free from cellular infiltrate. The majority of the neurovascular bundles show some infiltrate within and around them. In the middle layer of the dermis towards the centre of the section, there is a more exten-

sive infiltrate especially around the neurovascular bundles associated with hair follicles. This infiltrate has the appearance of burgeoning from the reticular layer of the dermis upwards towards the epidermis, causing some flattening of the rete pegs; it is separated from the basal layer of the epidermis by a clear zone. Masses of similar infiltrate are seen around small neurovascular bundles in the upper dermis on either side of this main central mass of infiltrate. Beyond this, the infiltrate is very scanty.

"The infiltrating cells are mainly histiocytes, with lymphocytes and a few plasma cells. There is some degree of foamy vacuolation of the cytoplasm of the histiocytes, modified by cell shrinkage in this formalin-fixed tissue.

"The nerves are completely clear of intraneural cellular infiltration.

"Acid-fast bacilli in solid staining form are seen in considerable numbers within the nerves, which are surrounded by infiltrate. There are also numerous bacilli in the histiocytic infiltrate. These are nearly all single rods or grouped in twos and threes, but there are some clusters and a few small globi. A few clumps of histiocytes are present in the main central mass of infiltrate; in this situation, a large proportion of the organisms show some irregularity in staining, but elsewhere practically all the organisms are in solid rod form.

"Conclusion. This is a biopsy from an infiltrated and slightly elevated lesion of active lepromatous leprosy, showing some unusual features. Firstly, the area involved is strictly delimited. There seems to be a bacillary exacerbation in progress, which is confined to a few nerve branches in the dermis and their area of distribution. Secondly, the relative freedom from infiltrate of some of the sweat glands and of the surrounding dermis is particularly striking in a lepromatous case where there is generally evidence of previous bacillary dissemination and cellular infiltration."

DISCUSSION

This rather uncommon clinical phenomenon, disclosed by routine bacterioscopic examination of the acutely developing lesions, is reported not because of its practical importance but rather because of its intrinsic pathologic interest. The lesions are to be distinguished, on the one hand, from the early signs of relapse in the patient in whom lepromatous leprosy has been quiescent for some years and who is currently not receiving treatment; and, on the other hand, from the well-recognized transient reappearance of morphologically normal *M. leprae* in patients under treatment with various antileprosy drugs, such as dapsone, thiambutosine, thiacetazone, etc.

In the five patients under review, discrete papilliform lesions, replete with morphologically normal *M. leprae*, suddenly made their appearance in patients under treatment with dapsone (or, in one case, in a patient who had been under treatment with dapsone until eight months previously). The apparently normal skin, the ear lobes, and the nasal mucosa did not show any bacillary activity in three patients, and only slight activity in two. The bacilli remained sensitive to dapsone, as shown by mouse foot pad inoculation experiments in two patients, and by clinical evidence (with dapsone treatment continuing) in two patients. It is too early to assess the response of the fifth patient. In all five patients, no acid-fast bacilli or debris had been seen in the routine monthly smears for at least seven months beforehand. The lesions in four patients responded well to treatment, the "solid rods" disappearing at the usual rate, and the B.I. falling satisfactorily.

It might be imagined that the sudden appearance of these succulent papilliform lesions might herald clinical and bacteriologic relapse. But four out of five patients were under adequate dapsone treatment at the time, the organisms were sensitive to dapsone in four cases, and in these four the acute lesions did, as it transpired, regress under treatment.

Several important questions remain unanswered. For instance, where do these *M. leprae* come from? The histologic picture gives no certain clue: the bacilli were found in enormous numbers in macrophages (whatever their origin), in cells that might be degenerating Schwann cells, and free between cells in the dermis; they were particularly numerous between the

fibers of the ramifying nerves in this situation. It is well known from the work of Weddell ([6]), Rees *et al.* ([4]) and others, that "solid rods" of *M. leprae* may remain unaltered for years at such sites as the following: between nerve fibers, in endothelial cells, in the media of arterioles, and in the arrectores pilorum muscles.

In the present cases it would appear that the bacilli were derived from *M. leprae* that were not only inaccessible to dapsone but were able to multiply for some time unhindered by concentrations of fixed or circulating dapsone that eventually, in at least four out of the five, proved inhibitory. Shepard ([5]) failed to grow *M. leprae* that had been obtained from patients who had received more than two weeks' antileprosy treatment. He surmised that viability might be affected before demonstrable morphologic changes became apparent in bacilli stained by conventional methods.

Another question is: why do they seem suddenly to multiply? Some locally acting agent would appear to stimulate their sudden multiplication, perhaps by removing an inhibiting factor. Given the slow generation time of *M. leprae*, it seems incredible that so many bacilli could become demonstrable in so short a time by standard staining technic. Within a few days of the patient's first noticing them, the individual lesions have attained their maximum dimensions. The rapid increase in size of the lesion may be only partly accounted for by a bulky subacute inflammatory exudate and intracellular edema. In the case of one patient, the possibility cannot be ruled out that long-continued corticosteroid therapy (about five years in all) was not unrelated to the reappearance of the morphologically normal bacilli. If this is so, the virtual limitation of localization of the bacilli to the acute lesions under discussion, is noteworthy.

A useful conception, admitted in respect to *M. tuberculosis* ([1]), is that certain bacilli may remain dormant for prolonged periods before reemerging into activity. There is some evidence that L-forms exist for *M. leprae*, as for other mycobacteria. If such bacilli persist in subcutaneous pockets, as, for example, in nerves, they might, when the microenvironment becomes propitious, begin to multiply and evoke a localized tissue response of lepromatous nature. It has been noted by Rees and Waters ([2]) and by Rees and Garbutt ([3]), that *M. lepraemurium* in culture may suddenly, for some unknown reason, begin to multiply after many months of quiescence. It is suspected that *M. leprae* may also exhibit this kind of activity in the human host.

The possibility remains that viable *M. leprae* in unknown numbers may actually have been present in these patients in some form that was not rendered visible by the standard technics of fixation and staining, only becoming detectable when their tinctorial properties changed. There is at present no direct evidence for this rather attractive hypothesis.

On the assumption that the bacilli have almost certainly not developed resistance to dapsone, it would probably be justifiable in the future to continue to treat patients who develop such lesions, with dapsone in standard doses.

The real though limited epidemiologic importance of transient bacillary reactivation in a patient with supposedly quiescent lepromatous leprosy needs no stressing, and indicates the desirability of regularly examining such patients and their intrafamilial contacts.

The frequency of occurrence of this phenomenon is unknown, but it might not be suspected in situations where facilities for bacterioscopic examination are not always available or utilized. Also, the continued efficacy of dapsone in ensuring repression of the lesions might allay any suspicions of localized bacillary "relapse."

It is unknown whether similar foci of morphologically normal bacilli do indeed suddenly appear elsewhere in the skin in such subjects, though the fact that some thousands of such smears are made annually in Uzuakoli, in randomly selected skin sites, as well as in the neighborhood of quiescent lepromatous lesions, without disclosure of any such foci, indicates that this is unlikely.

SUMMARY

Five examples are reported of papilliform skin lesions containing numerous morphologically normal *M. leprae*, which ap-

peared suddenly in patients who had had several years of treatment for lepromatous leprosy and who were clinically quiescent. No "solid rods" had been seen in routine monthly smears for at least 31 months, and no acid-fast debris for at least seven months. The unaffected skin remained bacteriologically negative in three patients, and became only slightly positive in two.

In four patients the bacilli were not dapsone-resistant, as was proved by mouse foot pad inoculation with material obtained from two patients, and by continuing dapsone treatment in two others. In four patients the lesions regressed with treatment. The questions raised by this finding are discussed.

RESUMEN

Se informa de cinco casos de lesiones papiliformes de la piel que contienen numerosos *M. leprae* morfológicamente normales, que aparecieron repentinamente en enfermos con lepra lepromatoso, que habían recibido tratamiento durante varios años, y en quienes la enfermedad estaba clínicamente inactiva. No se observaron "bastoncillos completos" ("solid rods") en los frotis de rutina mensuales, por lo menos, en 31 meses ni restos acido-resistentes en siete meses mínimum. La piel sana continuó negativa en tres enfermos y se hizo ligeramente positiva en dos.

En cuatro enfermos los bacilos no eran resistentes a la dapsona, como se probó mediante la inoculación de material obtenido en dos enfermos en la almohadilla plantar de ratones y la continuación del tratamiento con dapsona en otros dos pacientes. En cuatro enfermos las lesiones volvieron atrás con el tratamiento. Se discute y comentan las preguntas a que da origen este hallazgo.

RÉSUMÉ

Cinq exemples sont ici relatés de lésions papilliformes de la peau contenant de nombreux *M. leprae* morphologiquement normaux. Ce type de lésion était apparu brusquement chez des malades qui avaient été traités pendant plusieurs annés pour une lèpre lépromateuse et qui étaient cliniquement quiescents. Aucun "bâtonnet solide" n'a été observé au cours des frottis mensuels de routine durant 31 mois et plus, et on n'a pas noté de dèbris acido-résistants pendant sept mois ou plus. La peau non atteinte est restée bactériologiquement négative chez trois malades, et n'est devenue que faiblement positive chez les deux autres.

Chez quatre malades les bacilles n'étaient pas résistants à la dapsone, ainsi qu'on a pu le mettre en évidence d'abord par des inoculations dans la sole plantaire de la souris avec du matériel obtenu chez deux malades, ensuite par l'effet de la poursuite du traitement chez deux autres. Chez quatre malades, les lésions ont régressé à la suite du traitement. On discute les questions qui ont surgi à la suite de cette observation.

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