

Lepra Reaction

Its Relation with Fragmentation of *Mycobacterium leprae* under Sulfone Therapy¹

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One of the aspects of leprosy which has most intrigued leprologists is that concerned with the acute reactional episodes suffered by a great majority of leprosy patients at some period in the evolution of their disease.

Ignorance of their pathogenic mechanism, and consequently of their rational therapy, leads to discrepancies in concept among leprologists, for up to the present time there has been no uniformity in criteria leading to an understanding of the lepra reaction, some leprologists limiting use of the term to lepromatous cases, while others speak of lepra reactions in cases of the tuberculoid and indeterminate forms of the disease.

It seems certain that these acute phenomena are totally different in the two types of leprosy, not only clinically but also in their etiopathogenic mechanism. No one disagrees with the idea, for example, that erythema nodosum, or its polymorphous form, occurs only in lepromatous cases and never in tuberculoid or "dimorphous" forms.

In the following pages we shall refer only to the classic lepra reaction, that is to say to those acute episodes occurring in lepromatous leprosy.

Without attempting to discuss the diverse etiopathogenic theories that have been invoked to explain the lepra reaction, we shall simply cite some of those most discussed, i.e., phenomena on an allergic or para-allergic basis (Schwartzman phenomenon⁽¹⁰⁾), adaptation illness⁽¹¹⁾, and the problem of autoimmunization. It should be

noted that in the lepromatous forms bacillemia is more frequent than the acute episodes. Why, then, does not bacillemia always produce a state of reaction?² Perhaps this may be explained by the presence of autoimmunization features and therefore the existence of agglutinins that act on the Virchow cells, their metabolites, and the host cells, and on the leprosy bacilli and their metabolites⁽⁴⁾.

The Panel on the Lepra Reaction at the VIIIth International Congress of Leprology⁽²⁾ concluded: "The acute and subacute episodes are closely linked with the immunologic process, which in turn determines the various clinical forms of leprosy. Disturbance of the immunologic equilibrium may precipitate an acute attack, with the appearance of disseminated lesions. The disease itself may become better or worse. Several factors may disturb the equilibrium between the host and the bacilli."

ROLE OF HANSEN'S BACILLUS IN THE ETIOPATHOGENESIS OF THE LEpra REACTION

M. leprae is accorded great antigenic capacity, especially because of its content of proteins and lipids, antigens thought to be liberated with the destruction of the bacillus as a result of, or without, treatment.

The presence of granules in the interior of the bacillary cytoplasm is universally recognized. These have led to controversy; some consider them as indications of bacillary degeneration, and others as resistant bodies taking part in multiplication in the manner of spores.

Imaeda⁽⁹⁾, with the electron microscope, has studied bacilli from "dimorphous" cases and claims that these granules

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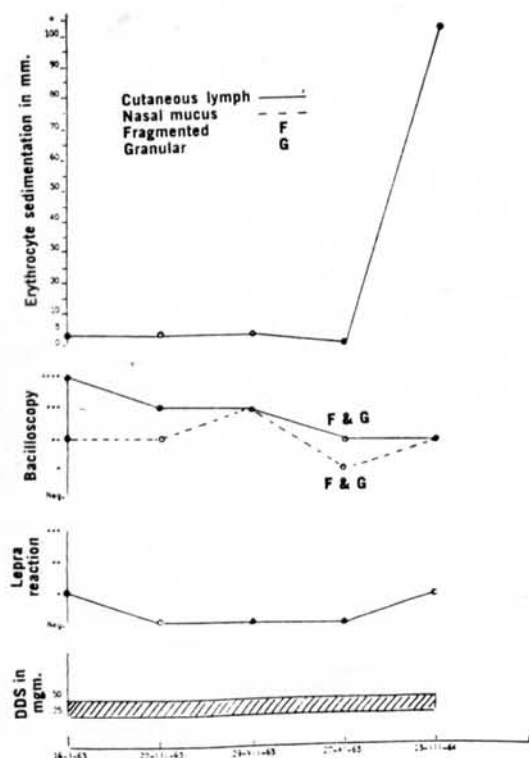


FIG. 1. Case No. 1—28 year old male, diffuse lepromatous leprosy (LLD).

might be from phosphates and poly-B-hydroxybutalates, and that the former represent degenerated bacilli.

Ridley⁽¹³⁾ claimed that bacilli in lepromatous were granular before the onset of erythema nodosum leprosum and that this manifestation was closely connected with the quantity of nongranular bacilli in the skin. The effect of bacteriologic relapses was to abort the onset of erythema nodosum. It seems that this fragmentation can be considered as playing an important role in the pathogenesis of the lepra reaction. His observations were considered by the panel on the reaction at the Rio Congress, and were noted as confirmed in other countries.

EFFECT OF SULFONE THERAPY ON THE FRAGMENTATION OF *M. LEPRAE*

A patient with lepromatous leprosy unshows noteworthy changes in the morphology of the bacillus, after a variable time,

including staining defects, fragmentation, and granulation, followed by disappearance of the bacilli. Imaeda⁽⁹⁾ has observed that after six months of treatment intact bacilli are not observed. Instead, there are degenerated bacilli, lying within an electron-microscope-transparent substance. The disintegration of the bacillus is manifested by coagulation of its cytoplasm. The walls of the bacillary cell dissolve only in the final stage of disintegration. Previously to this it is evident that sulfone treatment has an active effect on the fragmentation of the bacillus, regardless of the exact type of drug used.

In this respect it may be noted that the Panel on Therapy in the last International Congress, in 1963, pointed out that the bacillus-negative state in lepromatous cases takes place within three to six years in 50 per cent of cases⁽³⁾.

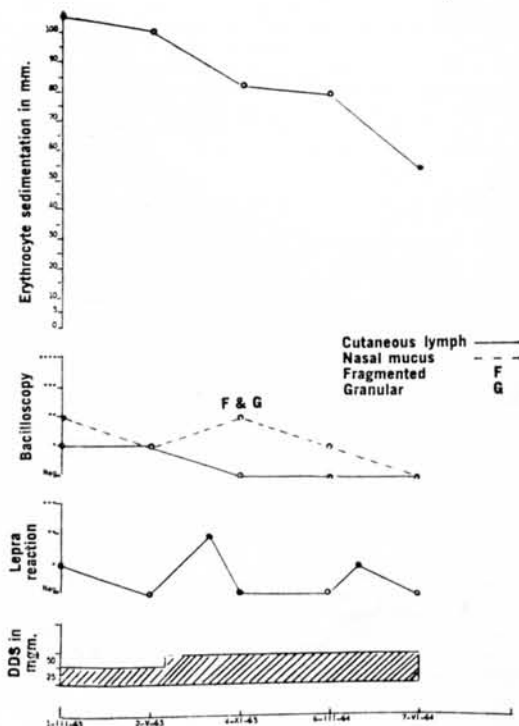


FIG. 2. Case No. 2—52 year old male, nodular lepromatous leprosy (LLN).

LEPRA REACTION AND SULFONE TREATMENT

Muir (11), Wilson, Kim and Topple (19) and many other investigators agree with the observation that the lepra reaction may appear without any apparent cause, but that it is much more frequently seen in association with chemotherapy, above all with the administration of sulfones in high dosage.

Dhople and Magar (5) state that the lepra reaction does not seem to be related with the concentration of DDS in the blood, but is definitely related to its concentration in the tissues, which might liberate an unknown active substance, which, on reaching a certain level, would lead to reactional upsets.

L. de Souza Lima (cited by Walcott (18)), observed that the lepra reaction occurred in 50 per cent of treated patients. Fernández and Carboni (cited by Floch (7)) noted it in 67 per cent, and Floch (7) in 40 per cent.

Walcott (18) reported that among 248 lepromatous patients with lepra reaction, in 7 per cent the attacks occurred before sulfone treatment and in 93 per cent after treatment was started.

Horta (8) in Mexico gave the following figures: lepra reaction was seen in 34.4 per cent of lepromatous cases; in only 35 per cent of these had there been treatment with DDS; in contrast, figures varied from 50 to 70 per cent in patients treated with thioureas and with sulfomethoxypridazine.

STUDIES BY THE AUTHORS

On the bases set forth above, our investigation has been directed to two points:

1. Effect of DDS treatments on the fragmentation of *M. leprae*.
2. Influence of this fragmentation on the occurrence of reactional attacks.

MATERIAL AND METHODS

Review of records. A review was made of 834 records of leprosy patients who attended the Centro Dermatológico Pascua of the City of Mexico from 1958-1963. From these, in turn, 542 were separated out, whose disease corresponded with the lepromatous type, and from them 429 who had

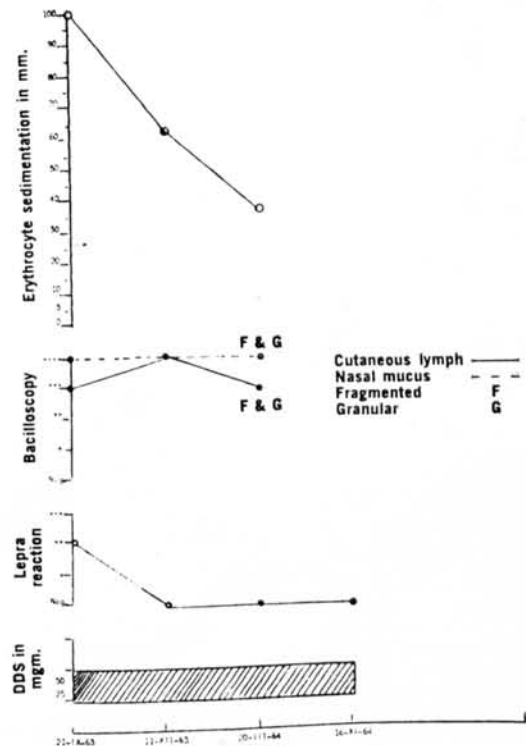


FIG. 3. Case No. 8—47 year old male, nodular lepromatous leprosy (LLN).

been treated with DDS were selected for study.

Investigation was made of the treatment and dosages, and the reactional episodes, from the point of view of number, date of appearance, intensity and clinical form. Clinical, bacteriologic, and histopathologic aspects, as observed before and during treatment, were reviewed and correlated, with emphasis on the appearance of the bacilli.

Study of patients. Ten previously untreated lepromatous patients were chosen for special investigation. Clinical, bacteriologic, and histopathologic studies were made on these, and treatment with DDS was started, in doses from 25 to 50 mgm. per day.

Clinical and bacteriologic examinations were made each month and at three months respectively, with special attention to manifestations of lepra reaction, appearance of the bacilli, and erythrocyte sedimentation,

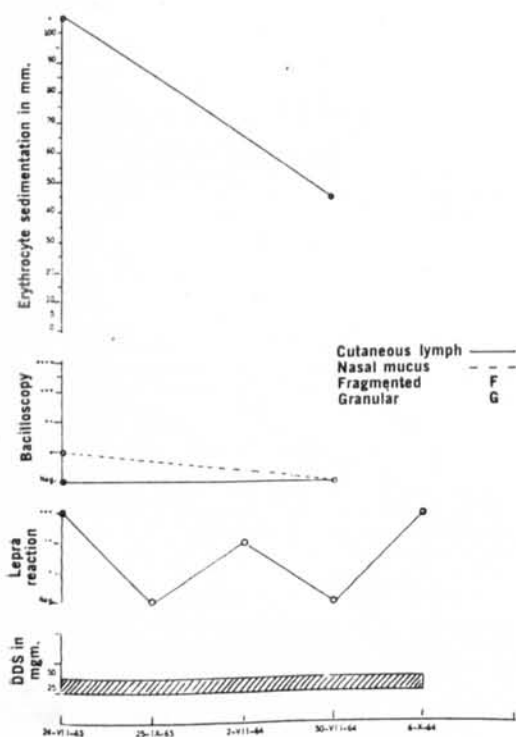


FIG. 4. Case No. 7—39 year old male, nodular lepromatous leprosy (LLN).

i.e., data on the basis of which correlative data were elaborated, and from which we record here the most clearly illustrative (Figs. 1-4). The period of observation varied from eight to 22 months.

RESULTS AND DISCUSSION

Leptra reaction occurred in 237 patients, or 55 per cent of the lepromatous cases treated with DDS. Among these, 32.4 per cent showed some acute disturbance before the treatment was commenced, and 22.6 per cent during its course. Sulfone treatment thus does not seem to be the principal cause of lepra reaction in our patients.

Among the 237 patients with lepra reaction, bacillary fragmentation was encountered in 73.9 per cent; in 26.1 per cent it was not observed. Among the patients not suffering lepra reaction 18.2 per cent showed fragmented bacilli; in 81.8 per cent fragmentation was not noted. Thus bacil-

lary fragmentation is present in the majority of cases of lepra reaction.

Bacillary fragmentation was evident before DDS treatment in 45 per cent of patients, and occurred during treatment in 56 per cent. Thus bacillary fragmentation occurs spontaneously without relation to treatment, although some role of treatment in the phenomenon is unquestionable.

Among the ten patients specially studied, nine had already had lepra reaction before treatment, and none of these exhibited bacillary fragmentation.

This fragmentation coincided in one case only with an acute attack; fragmentation was observed before the attack in four cases. In three patients the reactional attack was not associated, before or after, with bacillary fragmentation.

Bacillary fragmentation occurred during treatment in seven of the ten cases; in three it was not observed.

Although fragmentation of bacilli was observed more often during sulfone treatment, it did not occur solely as a result of treatment, and although the fragmentation was noted several times before the acute disturbance, reaction could occur without fragmentation. On the other hand, the latter could occur without an acute reactional episode.

That is to say, a cause and effect relation between fragmentation and lepra reaction cannot be established, and it might be conceived also that these acute reactions did not serve as an inciting factor in fragmentation of the bacilli.

SUMMARY

On the basis of the concept originally expressed by Ridley on the probable effect of fragmentation of bacilli in the occurrence of acute reactional attacks in lepromatous patients, a review was made of 429 clinical records of patients in the Centro Dermatológico Pascua of the City of Mexico, and a study was made of ten lepromatous patients treated with DDS.

It was observed that sulfone treatment is not the sole, nor fundamental cause of fragmentation of bacilli, and a cause and effect relation cannot be established between fragmentation and acute reactional attacks,

for the latter can occur without evidence of this fragmentation.

RESUMEN

Basados en la idea originalmente expuesta por Ridley acerca de la probable acción de la fragmentación bacilar en la aparición de brotes agudos reaccionales en enfermos lepromatosos, se realizó una revisión de 429 expedientes de enfermos del Centro Dermatológico Pascua de la Ciudad de México y se estudiaron 10 pacientes lepromatosos tratados con DDS.

Se observó que el tratamiento sulfónico no es la única causa, ni la fundamental, de la fragmentación bacilar y que no se puede establecer una relación de causa efecto entre dicha fragmentación y los brotes agudos reaccionales, pues éstos pueden presentarse sin observarse dicha fragmentación.

RÉSUMÉ

En base à l'idée originale de Ridley à propos de l'action probable de la fragmentation bacillaire sur l'apparition des pousses aiguës réactionnelles chez les malades lépromateux, 429 dossiers de malades du Centro Dermatológico Pascua ont été révisés. On a aussi étudié 10 malades lépromateux traités avec DDS.

On a observé que la fragmentation bacillaire n'est pas uniquement due au traitement sulfonique. On ne peut établir une relation de cause à effet entre cette fragmentation et les pousses aiguës, puisqu'elles peuvent se présenter en absence de cette fragmentation.

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