CORRESPONDENCE

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EFFECTS OF LEPRA REACTION IN LEPROMATOUS LEPROSY

TO THE EDITOR:

For many years I have maintained that lepra reactions have a beneficial effect on the later course of lepromatous cases.

In 1936 I was a joint author of an article [*Rev. brasileira Leprol.* **4** (1936) 129] in which it was asserted that: (*a*) lepra reaction is beneficial because it impedes the progress of the disease and improves the skin lesions; and (*b*) in such cases ocular lesions are less frequent than in those which never had reaction.

In 1947 I reported [*Rev. argentina Dermatosif.* **31** (1947) 506] that (*a*) lepra reactions, especially if frequent, severe, and prolonged, not only retard the progress of the disease but cause its regression; and (*b*) the influence of the reactions is greater the earlier they begin.

In 1955 I reported [*Dia Medico* **27** (1955) 527] the results of efforts to induce lepra reactions artificially for therapeutic purposes, concluding that (*a*) reactions cannot be induced artificially in all lepromatous patients; (*b*) when a reaction is induced artificially the picture, clinical and bacteriological, is the same as that observed in spontaneous reactions; and (*c*) the benefits of artificially-induced lepra reactions are similar to those of spontaneous reactions.

Because there have been very few publications on the subject, I would like to know the opinions of other leprologists on the following points:

1. Are the lepromatous patients with the most severe ill effects of the disease (blindness, deformity and mutilation) usually those who have not had lepra reactions, or only infrequent and mild reactions (without fever and of short duration)? Stated otherwise, are the lepromatous patients who have had frequent, severe and prolonged lepra reactions the ones who have not, or have only exceptionally, suffered serious progression of the disease, with the ill effects mentioned?
2. Is it believed that lepra reaction exerts a beneficial effect, the benefit the more marked the earlier the reaction occurs?
3. Is it believed that lepra reaction might be used as an adjunct measure for therapeutic purposes (except for patients who have severe involvement of the nerves or eyes)?
4. Is it believed that the lepra reactions so frequently provoked by sulfones are beneficial?

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This questionnaire was submitted directly to several leprologists who, it was thought, would be in a position to contribute. Somewhat over one-half of them responded.—EDITOR.

From Dr. J. A. Kinnear Brown, Entebbe, Uganda.—In 1930, when I first began to treat leprosy at Uzuakoli, I used Alepol, hydnocarpus oil, hydnocarpus ethyl ester, and potassium iodide. We found that if we could so control the patient's activities and the dosage that after each bi-weekly treatment there was one rise of temperature to 99° there was usually clinical improvement, although this applied more particularly to tuberculoid cases. If there was no such rise and the disease was active, the dosage was cautiously increased. Two recordings of 99° or one of 99.2°, however, were indications for reducing the dose or giving a short rest. In this sense, to keep a patient reacting on a marginal level was beneficial, but in lepromatous cases anything more than that carried a risk of a prolonged and perhaps disastrous reaction.

In Africa, when advanced lepromatous cases are seen for the first time it is not possible to discover with any certainty to what extent they have or have not had any reaction, and it therefore cannot be determined whether they have benefited from or been made worse by reaction. Of those whom we have under continual observation we can say that they generally deteriorate if they have repeated or prolonged reactions of any severity, and frequently we are hard put to it to check a reaction however it may be precipitated. There may, of course, be the individual patient who improves after a severe reaction, but this may be because some coincident cause of debility has been removed, or because although the lesions are clinically lepromatous it might be discovered histologically that they were actually dimorphous.

Dealing with Dr. Schujman's questions in order, and referring as he does only to lepromatous leprosy, my answers based on my experience in Nigeria and Uganda follow.

1. The lepromatous patients with the most severe ill effects are usually not those who have not had lepra reaction or who have had only infrequent and very limited reactions. Otherwise stated, lepromatous patients who have had frequent severe and prolonged reactions are not the ones who usually escape serious progression of the disease.

2. An early severe reaction does not necessarily indicate the ultimate course of the disease. Often enough, and particularly in children, early reaction is not a good omen unless, of course, the exciting factor can be recognised and removed. It may be that early reaction leads to early investigation and treatment or, in the case of patients not in institutions, to early and protective slowing down of their activities.

3. It is possible that in some cases maintenance for periods on the marginal level described above may be beneficial, but with the modern advances in therapy the need to rely on that method is less, and one has to weigh the risk of precipitating something that may easily get out of control.

4. For the reasons stated, I do not think that severe reactions provoked by sulfones, or for that matter by anything else, can be of themselves beneficial.

It is possible that in other races, where the frequency of lepromatous disease is greater, the balance between the various types, groups and phases is different, and the incidence of intercurrent debilitating conditions is less, other opinions may be justifiable.

From Dr. R. Chaussinand, Paris, France.—It is known that in lepromatous leprosy the state of reaction, properly speaking, which must not be confused with erythema nodosum leprosum, may result in death. It is also known that the state of reaction, properly speaking, and even the erythema nodosum condition, frequently provokes the appearance of ocular lesions and persistent neuritis.

It is, therefore, beyond doubt that for the patient it is of great importance to try to avoid, as much as possible, the appearance of a state of reaction, properly speaking, and even the erythema nodosum, by prescribing the sulfone treatment in small and gradually increasing doses (maximum dose: 2 mgm/kgm).

From Dr. Felix Contreras, Madrid, Spain.—There is always much interest in this question, to which many conflicting answers have been given. This has been done even by Schujman himself—the most outstanding proponent of the beneficial effect of lepra reactions, "especially when they are frequent, severe and prolonged"—when he collaborated with Fernandez in an article [*Revista de Leprologia de São Paulo* **2** (1934-1935) 79-86], in which it is said that reactions "will obscure the prognosis of the disease," and that "it cannot be denied that when [the reaction] is violent or prolonged, its effects are harmful. . . ."

With reference to lepromatous leprosy, we are nearer to the latter opinion than to that repeatedly advanced by Schujman. In that form of the disease there are at least two types of reactions, the erythema nodosum or multiforme type and the genuine lepra reaction.

Leprosy infection, like tuberculosis, syphilis, rheumatism, Nicholas Favre disease, Lipschutz ulcer, etc., and including some drugs, frequently causes or precipitates a type of reaction known as erythema nodosum or multiforme, the etiology of which is still unknown. It remains uncertain how these different diseases can give rise to the same syndrome. Reactions of that type may cause deterioration in leprosy, tuberculosis and other diseases, but it is more common that they increase the reactive capacity and enhance the defensive mechanisms. In many instances the exanthematic outbreak may have an esophylactic protective function, according to the concept of Hoffmann.

This esophylactic criterion is not acceptable in genuine lepromatous lepra reaction, because it does not limit itself exclusively to skin eruptions but may involve the nerves, eyes, and other organs; and histologically one can find in the nodule an acute perifocal inflammation with numerous polymorphonuclears, greatly dilated vessels, and diapedesis of plasma and leucocytes. In most of the cases receiving no active treatment, lepra reaction causes manifest deterioration.

In considering the inquiry of Schujman we must bear in mind previous experience in the use of cortisone, because if we succeed in arresting the lepra reactions these cases will have no merit in the evaluation of the influence of reactions on the course of the disease. Some of these cases may have favorable evolution, not because of the reaction but because of the [cortisone] treatment, which—combined with the sulfones used in the treatment of the disease—is very probably useful even in the absence of lepra reactions, in analogy to the results obtained when cortisone is combined with specific drugs in the treatment of tuberculosis.

From Drs. A. R. Davison and R. Kooij, Pretoria, South Africa.—In reply to the queries raised by Dr. Salomon Schujman we submit the following comments. We recognise the following reactions: (1) erythema nodosum leprosum, (2) neuritis, and (3) iridocyclitis. These are reactions which occur late in the disease and have deleterious effects on the patient. There is, however, a kind of reaction, (4) acute lepromatous infiltration, which occurs early in the disease and has a beneficial effect.

There are two other conditions which are not lepromatous reactions but which are beneficial if they occur. They are: erysipelas, and exfoliative dermatitis, the latter probably due to the drug being administered.

From Dr. H. Floch, Cayenne, French Guiana.—In briefest form, my answers to Dr. Schujman's questions are as follows:

1. No.
2. Lepra reactions are very different from each other, from the point of view in question, and that is what one should consider first.
3. No, at least for the present.
4. It is difficult to tell exactly, in lepra reactions during sulfone treatment, to which the observed improvement should be ascribed. In my opinion it goes first to the sulfones.

It is, however, beyond dispute that certain reactions are beneficial, but to me there are also certain ones that are not beneficial. We have discussed this matter in an article [Floch, H. and Mailloux, M. Should lepra reactions be induced for therapeutic purposes? Arch. Inst. Pasteur Guyane Française et Inini **17** (1956) Publ. No. 410 (October)] [See abstract in this issue.] There we pointed out that there are three kinds of reactions in lepromatous leprosy, (1) acute lepromatization or lepromatous leprosy in reactions; (2) eruptions of erythema nodosum or multiforme type, and (3) the kind variously called pseudo-exacerbation (de Souza Lima), or acute infiltration (Tajiri), or reversal reactions (Wade); and that the first of these three—the true lepromatous reactions—aggravate the disease, the effects of the second of them are variable, while the third are beneficial.

We admit that not infrequently acute episodes in lepromatous cases have rapidly produced strikingly beneficial results, but often they are harmful and may even result in death. Consequently we cannot, at present, recommend the artificial precipitation of reactions in lepromatous cases for therapeutic purposes.

From Dr. Yoshinobu Hayashi, Tokyo, Japan.—I think that several kinds of reactions are included under the generic term "lepra reaction." These are: (1) erythema nodosum leprosum (ENL), which occurs frequently in the course of lepromatous leprosy, especially in the absorption stage; (2) acute infiltration (Tajiri), with tuberculoid structure, occurring acutely in the quiescent stage of lepromatous leprosy; (3) relapse of the tuberculoid macule, appearing acutely, intensely and relative extensively in the quiescent stage of tuberculoid leprosy; and (4) exacerbation of neurologic symptoms, appearing acutely, intensely and relative extensively without any skin eruption. I understand that, of these several reactions, the inquirer is concerned with the ENL kind, and therefore I confine my reply to that condition.

1. Most of the cases of lepromatous leprosy with extremely severe residual conditions, such as blindness, deformities or mutilations, must have experienced the development of ENL. Acute iridocyclitis or scleritis frequently occurs in that reaction, hence visual disturbance or loss of eyesight may follow. Acute neuritis may also occur in ENL, resulting frequently in severe neurologic disturbances. Although the condition of the patient usually becomes stationary for some time after the progress of ENL, the residual symptoms may frequently be severe.

2. It is a question whether ENL may have a beneficial effect upon the course of leprosy. I think it a kind of side effect observed when certain beneficial effects occur as a result of treatment, or sometimes spontaneously. According to my observations, ENL occurred in about 63% of the cases treated with chaulmoogra oil, and is seen in about 73% of those treated with promin. Although there are relatively few cases of recovery without ENL having occurred, I think it preferable that recovery be attained without the occurrence of ENL.

Development of ENL has a close association with treatment, occurring largely (in about 50%, in my experience) within a year after the treatment is started. Moreover, it has a relationship with the degree of the disease, i.e., it appears more frequently in severe cases than slight ones. In this connection, when the patient is treated earlier, the development of ENL is also seen earlier because of the greater effect of the treatment. However, this means that the ENL may break out as a secondary effect of the treatment, following the essential effect on the leprosy. Consequently, I do not believe that the leprosy symptoms recover as a result of the appearance of ENL.

3. Is it believed that any procedure of inducing ENL might be used as an adjunct measure for therapeutic purposes? Although I cannot give a definite answer to this question, because of lack of experience with any special measure of inducing ENL, I always endeavor as much as possible to avoid the ENL that might appear in the treatment of leprosy.

4. I do not believe that ENL, which is frequently caused by sulfone treatment of lepromatous leprosy, is beneficial to the course of the disease.

From Dr. C. B. Lara, Culion, Philippines.—As regards the importance of the erythema nodosum syndrome in the immunology of leprosy, anyone who has had decades of experience treating cases, especially in a leprosarium, can remember some patients who were definitely benefited by moderate or even severe reactions. Especially in those complicated by generalized suppuration of the lesions, the final outcome usually was a truly dramatic recovery. Less severe forms of reactions also seemed to have favored many other cases; but the majority of the patients who suffered moderate to severe reactions at Culion died within at most a few years from the beginning of intractable reactions. In those, leprosy indeed had seemed to subside considerably, that is, the skin lesions had flattened out, but most of these patients went down progressively from cachexia, tuberculosis, amyloid disease, secondary pyogenic infections, or nephritis. Very few patients died directly from lepra reactions within a month or two months during the attack of acute reaction. Occasional mild reactions did not seem to have a definite influence either for the better or for the worse. At Culion, at least, the majority of our paroled patients had not had definite (clinical) reactions during segregation.

After 35 years at Culion it is not possible for me to forecast in many reaction cases whether the patient will ultimately be benefited or not. Also, it is not yet possible effectively to control reactions; in many cases they recur despite all efforts. I would not deliberately provoke a reaction. Also, in the presence of a reaction, I would suspend active antileprosy treatment, which according to our experience tends to prolong or intensify the reactions.

All this is not meant to deny that some more suitable, better-directed and understood immunologic methods must be searched for and tried, with a view to activating and maintaining the reactive powers of the patients.

From Dr. E. Muir, London, England.—The important point is whether or not the reactions are under control. Severe, prolonged or frequently repeated reactions, if uncontrolled, may do a considerable amount of irreparable harm and should be avoided as much as possible. On the other hand milder reactions, especially when the patient is under sulfone treatment, can be of definite advantage, as the lesions become more vascular and the sulfones have more chance of penetrating. This is especially so when the reactions are not so severe that sulfone treatment has to be stopped temporarily, or when cortisone or similar treatment for reaction makes it possible to continue with the sulfone treatment uninterrupted. I have long believed that when a lepromatous case has improved to the point when bacilli can no longer be found by routine methods, the induction of mild reactions by iodides, while the sulfone treatment is still continued, considerably speeds up the elimination of residual disease. Ordinarily, however, this should not be attempted without careful supervision.

From Dr. Eduardo Rodriguez, Asuncion, Paraguay.—Patients with repeated reactions, erythema nodosum and erythema multiforme with iritis or idicocyclitis which caused blindness before the sulfone era, are no longer seen in the clinics. Patients who have had frequent and severe reactions suffer the inherent sequelae of the disease.

With the advent of the sulfone era there began a period of "involutions," or of conversions of clinical form. The effect seems to be the more beneficial if they are not very frequent or very prolonged. Actually, since their appearance has been "spontaneous" with the use of the sulfones, cases that need an indirect method to provoke such reactions must be few.

The fact that the change of clinical form (from lepromatous or borderline to tuberculoid or indeterminate) is preceded by reactions which are not severe or prolonged, is an indication of "involution" of the disease.

From Dr. Lauro de Souza Lima, São Paulo, Brazil.—It happens that I was the senior author with Dr. Schujman of the report published in 1936, based on a study we carried out at the Sanatorio Padre Bento here in São Paulo. However, that was more than twenty years ago.

If my answers to his questions were to be based on experience in that period, up to about 1947, they would be, in the order he put them: 1. Yes. 2. Yes. 3. (See below). 4. If "lepra reaction" means the erythema nodosum kind, yes.

I believe that what is actually bothering Dr. Schujman has ceased to exist because, with the sulfone treatment during these many years, such cases as he describes are no longer to be seen. Referring to his third question, from our present point of view I see no reason for inducing lepra reaction as an adjuvant means of therapy, since there is now available an effective medicament which itself alone can induce acute outbreaks of ENL.