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PRESENT STATUS OF SULFONE THERAPY AT THE PADRE BENTO SANATORIUM¹

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GENERAL STATEMENT

At the Second Pan-American Leprosy Conference, held in Rio de Janeiro in October 1946, we presented the first results with sulfone therapy at the Sanatorio Padre Bento, in Sao Paulo. For the present Congress our contribution is a summary of the facts observed in 1,287 patients who have been treated with these drugs since the beginning of the experiment, four years and five months ago. The results confirm those previously reported, and because of the time elapsed and the number of observations we may regard as definitely established some of the facts pertaining to sulfone therapy which were mentioned at Rio de Janeiro.

The first established fact is that the disease ceases to progress after the third to sixth month of treatment, regardless of the mode of administration of the drug, the type of the disease, or its degree of advancement. This statement holds true for all groups of patients whose clinical histories had shown, previous to the treatment, definite evidence of progression of the malady. For example, among the 847 lepromatous cases treated

¹Presented at the Fifth International Leprosy Congress, Havana, on April 5, 1948. For the basic translation from the Portuguese, appreciation is due Dr. Luis Rodriguez Plasencia, of Havana. The term "incharacteristic," employed by the author, has not been changed to "indeterminate," though that term was adopted by the Congress.—EDITOR.

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for from 12 to 36 months there has not been one recorded as having grown worse. The least favorable results were in those cases, 4.2 per cent of the whole, which have not shown any appreciable change in the clinical condition since treatment was begun.

The second fact is that regressive changes in the cutaneous lesions are not observed until after 3 to 6 months of treatment; and in this interval a small percentage of patients (12% to 15%) have shown slight to moderate, but temporary, aggravation of their lesions. On the other hand once improvement begins it is progressive, and no relapses occur. Improvement attains different degrees, from slight amelioration to total disappearance of lesions; and there is no possibility of establishing a relationship between the degree of improvement and the daily or total dosage or with the mode of administration. It may be possible to establish this relationship when the sulfone treatment is instituted under identical conditions of intensity in all cases.

The third fact which can no longer be disputed is the beneficial effect of the sulfones on the mucous membranes of the nose, mouth, pharynx and larynx. This effect is easily observed in advanced lepromatous cases with serious involvement, either dysphonia or aphonia, in which return to normal function attests the action of these drugs. Special mention is to be made of tracheotomized patients who, under sulfone treatment, have been able to discard their cannulas permanently. Finally, emphasis is to be laid on the influence of sulfone treatment on the serious eye involvement with acute attacks of iritis and iridocyclitis, i. e., ocular leprotic reaction, the repetition of which may lead to complete blindness. Since intensive treatment was instituted the incidence of this condition has been practically nil. It may also be said, tentatively, that even extensive infiltrations of the cornea in old lepromatous cases, proven by previous biopsies, have—according to the observations of Mendoza de Barros, previously ophthalmologist of the sanatorium—improved considerably and have become free from bacilli.

These facts suffice to show the usefulness and efficacy of this treatment. For a better understanding of its importance we will analyze the results in relation to the clinical type and with respect to the cutaneous, bacteriological and structural aspects.

CUTANEOUS ASPECT

RESULTS IN THE LEPROMATOUS TYPE

With respect to the lepromatous type, in which the activity of the sulfones is most clearly demonstrated, we will consider separately three different groups according to degree of advancement.

(1) The advanced group comprised 584 (64%) of our 847 cases. The results which have been obtained in this group are shown in Table 1. Complete disappearance of all specific lesions occurred in 46 cases (8%); there was marked improvement in another 143 cases (24%); lesser degrees of improvement were seen in 373 (64%); in only 22 cases (4%) did the condition remain unaltered. These results are indisputably extraordinary, considering the extent and duration of the disease in these cases.

TABLE 1.—*Results in 584 advanced lepromatous cases.*

Route of administration	Results					
	Lesions cleared	Much improved	Improved	Unchanged	Worse	Total
Oral	14	35	29	1	0	79
Intravenous	12	31	53	10	0	106
Combined	20	77	291	11	0	399
TOTAL	46	143	373	22	0	584

In connection with this high index of improvement, which includes 96 per cent of the patients, there is one important aspect which should be emphasized, this is the stabilization, in about 7 per cent of the total, of the ascending curve of improvement. The patients looked better, or much better, as compared with their condition before treatment but improvement ceased and they remained stationary after 18 or 20 months of treatment.

It is also to be said of this group as a whole that, along with the progressive recession of the specific lesions, there appeared more or less severe eruptions of erythema nodosum type, more rarely of erythema multiforme type, with a total frequency as high as 50 per cent. A large proportion of these patients had never had acute eruptions before. It seems that sulfone therapy increases the frequency of this type of eruption in advanced lepromatous leprosy. In our opinion this is a favorable indication.

(2) In the 158 moderately advanced cases the results were even more satisfactory, as is shown in Table 2. There was a higher percentage of cases (84, or 53%) in which the lesions cleared up, and also a larger proportion (54 cases, 34%) showing marked improvement; only 6 (4%) showed no change in their condition.

TABLE 2.—Results in 158 moderately advanced lepromatous cases.

Route of administration	Results					
	Lesions cleared	Much improved	Im-proved	Un-changed	Worse	Total
Oral	19	18	6	2	0	45
Intravenous	30	10	8	1	0	49
Combined	35	26	0	3	0	64
TOTAL	84	54	14	6	0	158

(3) In the 99 incipient cases, which are the most important of all from the point of view of prophylaxis, the results of sulfone therapy were extraordinary.

It is to be said that we do not give to the term "incipient" the quantitative meaning in which it is generally employed in our classifications, indicated by the numerical index L_1 ; we use it in its qualitative sense as suggested by the pathology and the clinical features of this form of the disease. In our opinion the lepromatous form establishes itself, in the general run of cases, by two successive and distinct stages: (a) In the first phase the cutaneous manifestations have the banal aspect of the "incharacteristic" lesions of the Pan-American classification—the simple macular ones of the Cairo classification—but the structure is prelepromatous or frankly lepromatous, with numerous bacilli. (b) In the second phase, on these elements or on other areas of the integument there are superimposed initial elements proper to the lepromatous form; that is to say, small spots or areas of a yellowish or ferruginous color which gradually attain the typical aspect of annular, flat lesions with a well-defined inner circle and a diffuse, imprecise outer edge which indicates progressive involvement of the neighboring skin.

There are 105 cases registered in our files as incipient lepromatous according to this concept, but 6 of them have been

treated for only six months. The results in the 99 which have been treated for 12 to 20 months are given in Table 3. There is shown a high proportion of clinical cures or marked improvement (67% and 14%, respectively), demonstrating the advantage of early treatment. That is perhaps the most important possibility which we have, provided the results are permanent, of changing the prophylactic aspect of the leprosy problem.

TABLE 3.—*Results in 99 incipient lepromatous cases.*

Route of administration	Results					Total
	Lesions cleared	Much improved	Im-proved	Un-changed	Worse	
Oral	25	7	13	0	0	45
Intravenous	12	1	1	0	0	14
Combined	29	6	5	0	0	40
TOTAL	66	14	19	0	0	99

There is in this group an interesting and paradoxical aspect which must be emphasized. That is the appearance, in a certain number of the cases which have cleared up, of an erythema nodosum condition represented by two, three or four reddish, transient elements constituting a rather discrete eruption, in instances recurrent. We have no definite interpretation for this eruption appearing after the total disappearance of the specific lesions, and usually with no germs in the perivascular infiltrations or in the walls of the vessels themselves as shown in the histological slides.

Despite these highly favorable results of sulfone therapy in the lepromatous form as regards the skin lesions, it is to be said that in the peripheral nervous system the results have been nil or insignificant. Contrary to our hope that the usual sequelae of nerve involvement would recede, they have been seen to appear in full force during the treatment. This probably indicates previous involvement of the nerves and inability of the sulfone therapy to stop and cause recession of the lepromatous processes in that location. This fact is evident in our advanced and moderate cases, and makes us realize the importance of treating cases of this type at an early stage, when there are no discernible consequences of nerve involvement. By prolonged observation of these cases we can determine the ability

or inability of the sulfones to impede the appearance of such changes.

RESULTS IN THE TUBERCULOID TYPE

It is universally admitted that the tuberculoid form is benign and of good prognosis, and it is an indisputable fact that in a high percentage of cases spontaneous cure occurs within a relatively short time. This concept makes difficult an evaluation of the results of the treatment in cases of this type, for it is among them that occur so many miraculous cures.

There are, however, two reservations which apply to the idea of benignity of the tuberculoid form. These are: (1) The increasing recognition of some proportions of cases, predominantly of the reactional variety (major of the Cairo classification), either classical or of the intermediate or borderline variety, which undergo transformation to the lepromatous type; (2) The cases of the torpid figured variety (minor of the Cairo classification) of eight, ten or more years of duration, the lesions of which remain stationary or, as a result of repeated occurrences of tuberculoid lepra reaction, spread and involve enormous areas of the skin, and in which—a more serious development—the tuberculoid process invades the nerves and gives rise to marked mutilations.

We selected 25 cases of this latter variety interned in the sanatorium, with cutaneous manifestations of from five to ten years continuous progression and subject to repeated outbreaks of tuberculoid lepra reaction. After instituting intensive sulfone therapy we observed no more of these reactions; and, after from 12 to 20 months of treatment, there was either disappearance of all the cutaneous lesions or return to the original uncharacteristic appearance. These effects can only be attributed to the medication. In these cases, as in those of the lepromatous type, we could see no influence whatever on the nerve lesions; the treatment failed to impede the appearance or the progression of neural manifestations.

Though demonstrative, our material is not quantitatively sufficient to permit a definite judgment regarding the action of the sulfones in the tuberculoid type. For this reason we utilized the patients at the Lapa Dispensary, in Sao Paulo city, where the treatment work is also under our direction. There we found, recorded as paroled or under observation, 200 tuberculoid cases of every variety which had been treated with chaulmoogra for 10 years or more, and whose clinical histories repeat what has been said about the cases in the Padre Bento Sana-

torium. When the sulfone treatment was instituted—by mouth, as is necessary with dispensary cases—results identical with those observed in the segregated patients were obtained. Progressive regression of the skin lesions occurred, which in the majority was not complete after twelve months of treatment. Here, as before, there was no influence on the nerve lesions.

It is evident that in order to ascertain the ability of the sulfone therapy to prevent the involvement of the nerves in tuberculoid leprosy, we must employ it in early cases.

RESULTS IN THE INCHARACTERISTIC FORM (SIMPLE MACULAR)

In this group it is very difficult to evaluate the results of sulfone therapy, and from the cutaneous point of view the matter is complex. For one thing, it is known that about 40 per cent of the cases regress spontaneously; and, for another thing, it is the form from which, by transformation after an average of 4 to 5 years, almost all of the cases of the polar forms originate. In less time than that it would be quite premature to make any statement about the results of sulfone treatment in patients of this kind.

In the meantime, admitting the activity of the sulfones in the established forms, lepromatous and tuberculoid, the answer to the problem of prophylaxis in endemic countries may depend to a great extent on the results of sulfone therapy of these incharacteristic forms. Though a high percentage of them are not contagious, many of them will in the future be the sources of contagion. The institution of intensive sulfone therapy in the dispensaries, in order to keep under treatment all the initial cases of leprosy while still in the non-infectious phase, is the course to be followed. It is obvious that only after at least three years of that practice can we judge the results and its prophylactic value, considering that the classical treatment with chaulmoogra oil has completely failed in this and other particulars.

At present we have had 15 cases of this form under treatment for 8 to 20 months at Padre Bento. As yet we have not recorded any instance of transformation to the lepromatous type. The lesions of 8 of these patients have been completely cleared up, and 3 have converted to the tuberculoid form. Another communication on this matter is in preparation.

In the Lapa Dispensary there are registered about 130 cases with incharacteristic lesions which have received sulfone treatment for 8 months. This time is short, but it may be said that

here, also, no case has become lepromatous. On the contrary, some patients have shown partial repigmentation of the achromic lesions.

BACTERIOLOGICAL FINDINGS

The bacteriological findings are not less significant than those pertaining to the cutaneous manifestations. The most prominent fact, and one that justifies our hope and confidence in sulfone therapy, is the reduction of the index of positivity of nasal smears in lepromatous cases to a mere 2 per cent. Knowing how uncertain are the results of this examination when the ordinary methods are employed, we took the precaution of obtaining the material by scarification of the nasal mucous membrane. Of 879 smears made by this method from treated lepromatous cases, 102 (12%) were positive, all of them from advanced or generalized cases, of which one would expect perhaps 100 per cent to have been positive before the beginning of the treatment.

Less favorable are the findings in material from the skin, whether smears or histologic sections. Those of smears will be ignored, for they depend so greatly upon the manner of collecting the material. With regard to the histologic sections, our findings are as follows:

(1) Modification of the morphology of the bacillus, observed after the first months of treatment in all cases. Much later, and in a small percentage, there is alteration of the tinctorial properties, and progressive diminution in the numbers of typical rod forms until they are completely absent.

(2) Gradual disappearance of the germs, with or without modification of their morphology, in the perivascular lepromatous infiltrations and the walls of the vessels. This is seen first in the papillary body, and then in the whole extent of the corium. This may, perhaps, explain the cessation of the evolution of the process and the nonappearance of relapses of the cutaneous manifestations.

From these findings it seems evident that there is no correspondence between the results of the treatment from the cutaneous and the bacteriological points of view. On the one hand there is marked regression to the point of complete disappearance of the specific cutaneous lesions, and on the other hand persistence of the germs, at times in relatively large numbers even though with modified morphology. This was evident in 64 biopsy specimens of residual lepromas; only 10

per cent were negative, while in 90 per cent there were found acid-resistant germs in variable quantities, though in 65 per cent they were morphologically altered.

Particularly interesting and illustrative are the findings in 150 sections of skin from the sites of old lesions in incipient and moderately advanced lepromatous patients, which had become normal in appearance. The results were as follows: (a) in 50 per cent they were absolutely negative; (b) in 45 per cent small numbers of morphologically modified germs were to be found, almost entirely located in the nerves and muscles; (c) in the remaining 5 per cent, besides modified germs, rare bacillary forms were observed, also located in nerves and muscles.

HISTOLOGICAL FINDINGS

The improvement of the cutaneous condition is observed objectively with ease by the decrease of infiltration, the lesions gradually returning to the level of the surrounding skin though often—especially in advanced cases—leaving the areas wrinkled and atrophic; and by return of previously pigmented lesions to the normal color, and also repigmentation of dyschromic areas. These clinical changes can be verified by the histological examination.

To ascertain this fact, biopsies were made of all varieties of lesions, especially of the lepromatous form, before the beginning of the treatment and periodically afterwards in order to secure specimens corresponding to the different stages of the clinical regression up to cicatrization, and including areas of normal appearance from which lesions had disappeared. In this large series of biopsies, numbering 1,500, we can demonstrate schematically two orders of facts.

First in frequency is the progressive degradation of the lepromatous structure, from the first stage of regression described by Rath de Souza and Lecheren Alayon, with all the gamut of aspects of transition to a final stage in which we can find only a simple chronic inflammatory condition without any character of specificity, with more or less sclerosis of the connective tissue according to the degree of the regressive process.

Second—though not in importance, for we think it more important—is the condition observed in a large series of cases which, for lack of a better term, we have called “pseudo-exacerbation” and which we consider beyond doubt the most demon-

strative proof of the activity of the sulfones.¹ It is seen in lepromatous cases, some of long standing, which early in the course of treatment present eruptions of new lesions which are superimposed on or coexist with the original ones.

The most interesting feature of this condition is the histological structure of the lesions. In the cases presenting this apparent aggravation, biopsy specimens taken during the phase of exacerbation show predominantly epithelioid cells disposed in the manner of nodular structures, with or without giant cells, resembling in some the picture which we are accustomed to seeing in reactional tuberculoid leprosy.

The substitution of the tuberculoid for the lepromatous structure evidences a radical transformation of the reacting capacity of the organism, in these cases caused without the slightest doubt by the sulfones. This effect seems to us demonstrative of an activity of these drugs, apart from their bacteriostatic effect, presumably of the nature of capacity for stimulating the reticulo-endothelial system.

DISCUSSION

The results of sulfone treatment of which an over-all picture has been presented, never before recorded with other drugs, were obtained without any accident of importance, attesting to perfect tolerance for this medication in all forms of the disease and at all ages. The dosage should be raised to the maximum whenever there is no contraindication. Visceral involvement is no contraindication; on the contrary it is much benefited by this therapy.

Practically speaking, there are no appreciable differences between the results obtained with the oral and the intravenous routes of administration, when they are used exclusively. Our experience indicates that there is an evident superiority in the combination of the two routes, concomitantly or in alternating series.² Nevertheless, there are cases in which intravenous injections are definitely preferred. These are: (a) all acute cases, especially those with the so-called leprotic ocular re-

¹This condition was mentioned at the Second Pan-American Conference in Rio de Janeiro, in 1946, and is the subject of a separate paper. [This other paper referred to will appear in the JOURNAL, in the next issue.—EDITOR.]

²The sulfone drugs employed in our experiments were: orally, diasone (Abbott) and a similar product made by the Instituto Butantan of Sao Paulo, and diamidin (Parke, Davis); intravenously, promin. In a single patient, promizole was used for a time but stopped for lack of the drug.

actions, in which intensification of the intravenous sulfone therapy is decisive and quickly arrests the process; (b) cases of acute eruptions of erythema nodosum or multiforme type, without marked fever; and (c) most important, certain cases of erythema nodosum provoked by the oral administration of the sulfones, which have the special character of being accompanied by ostealgias, arthralgias and intense neuritis; these cases subside when the intravenous administration is substituted for the oral.

In our intensive employment of sulfone therapy for more than four years we have not observed any accident of major importance. The incidents and accidents which would suggest discontinuing the employment of these drugs were predominantly of temporary nature provided, of course, the treatment was correctly oriented. In this connection three kinds of phenomena were observed: (1) Phenomena of toxicity due to the medicament, especially anemia, without any serious consequences when the proper measures to correct them are taken. (2) Phenomena of intolerance on the part of the patient, such as nausea, vomiting, intestinal disturbances, which might be serious should the treatment be unwisely continued; also certain forms of dermatitis, among them one of special aspect, tricophytoid, and all of them without any real importance. (3) Specific phenomena due to leprosy itself, represented by acute eruptions of erythema nodosum or erythema multiforme, which when not accompanied by marked fever do not indicate a suspension of treatment; and the condition called "pseudoexacerbation" of the disease for which increase of the daily dosage is indicated.

SUMMARY.

Terminating our summary exposition of the results of sulfone therapy at the Sanatorio Padre Bento, we can state in conclusion that:

(1) Sulfone therapy is not yet the ideal treatment we have been wishing for the treatment of leprosy, but in view of the results so far obtained in a large number of cases over a long period of time it constitutes a really active and useful treatment, the only one in the history of leprosy.

(2) It is highly desirable that its benefits be extended to all segregated patients, and to the dispensaries for treatment of early cases, even to those which are noninfectious, as a possibility—at the moment—of approaching with success the problem of the prophylaxis of leprosy.