CLINICAL EVALUATION OF ISONICOTINIC ACID HYDRAZIDE AS AN ADJUVANT IN THE TREATMENT OF LEPROMATOUS LEPROSY

WITH A NOTE ON THE DETRIMENTAL EFFECT OF ERYTHEMA NODOSUM LEPROSUM REACTIONS

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A clinical evaluation study of diasone, diaminodiphenyl sulfone (DDS) and dihydrostreptomycin (DHSM) separately, conducted in four institutions including Westfort, has been reported by Doull (2). The present evaluation study of the effects of isonicotinic acid hydrazide (isoniazid, INH) and of streptohydrazid on lepromatous leprosy, continued over a period of two years from September 1953 to September 1955, was modeled on that first study, and this report is modeled on the lines of Doull's report.

In evaluating the effect of any drug it seems desirable that its effect should be compared with that of an inert placebo. This is not permissible in a long-term study when human lives and well-being are at stake. However, the beneficial effects of the sulfones in leprosy are now sufficiently established so that new drugs may be compared with the sulfones, taking them as the base line in the search for more effective new medicaments.

MATERIALS AND METHODS

A total of 129 patients with lepromatous leprosy, varying as to age, sex, and degree of advancement, were divided into four groups (see below). One of them, serving as the control, received sulfones only; two received isoniazid plus the two medicaments that had proved most useful in the previous study referred to; the fourth, a small one, served for a "pilot study" of a compound drug. Specifically, the groups were:

Group A. Sulfone (control), 40 patients (26 males, 14 females).
Group B. Sulfone plus INH, 40 patients (26 males, 14 females).
Group C. INH, DHSM, and PAS, 39 patients (26 males, 13 females).
Group D. Streptohydrazid (pilot study), 10 patients (all males).

Dosage.—These drugs were given as below, no treatment being given on Sundays.

Sulfones: Diasone was used at first, then DDS. Diasone was started with one 330-mgm. tablet every second day for the first week, then one tablet daily for the second week, two tablets daily for the third week, and three tablets daily thereafter. After 18 months the supply of diasone was exhausted and DDS was substituted. One 100 mgm. tablet of that was given three times a week for the first month, then one tablet daily for the second month, thereafter the maximum dose of 200 mgm. daily.

Isoniazid: The dosage aimed at was 10 mgm. per kilo of body weight daily, but for staff reasons the dose given was 500 mgm. daily, six days a week.

Dihydrostreptomycin: Injections of 1 gm. twice weekly.

PAS: This was given in 0.5 gm. tablets in a daily oral dosage of 12 tablets for the first week, then 18 daily for another week, and 30 tablets daily thereafter.

Streptohydrazid: Each vial contained 1 gm. of streptomycin and 266 mgm. of INH combined in one molecule. One dose was injected twice weekly.

Assignment of patients to groups.—The assignment of patients to groups was done by the Leonard Wood Memorial, as shown in Table 1. It will be seen that groups A, B, and C are closely comparable with respect to age, weight, extent of the lepromatous lesions, and prior sulfone treatment.

Regarding Group D, since it had only 10 patients (males only) it would not be strictly comparable from the statistical point of view with the other groups in their entirety. Consequently, from among each of those groups 10 male patients were selected whose characteristics as listed in Table 1 would be comparable to these in Group D. To avoid complicating the table, the data of those subgroups are not included, but they are essentially similar to those of the male groups that are given.

TABLE 1.—*Distribution of the 129 patients (88 males and 41 females) in the experiment, by significant characteristics.*[a]

Characteristics	Sex and group						
	Males (88)				Females (41)		
	A (26)	B (26)	C (26)	D (10)	A (14)	B (14)	C (13)
Age (years)							
10-14	4	4	4	0	5	4	3
15-24	6	5	5	3	3	4	4
25-34	8	8	8	7	4	5	4
35 and over	8	9	9	0	2	1	2
Average[b]	26	28	27	28	23	23	24
Weight (pounds)							
Under 100	7	7	5	1	5	5	3
100-119	7	5	4	2	3	7	6
120-139	8	8	8	6	4	2	4
140 and over	4	6	9	1	2	0	0
Average[b]	113	116	125	122	106	106	110
Advancement of disease							
Slight (L1)	13	13	14	5	10	10	10
Moderate (L2)	13	11	10	4	4	4	2
Marked (L3)	0	2	2	1	0	0	1
Prior sulfone treatment							
None	3	4	2	1	0	1	1
$<$ 1 year	6	5	7	2	4	3	4
$>$ 1 year	17	17	17	7	10	10	8

a This distribution was made by the Leonard Wood Memorial by statistical methods. (Regarding the selection of 10-case groups of males from Groups A, B and C for comparison with Group D, see text.)

b Figures reduced to the nearest whole numbers, eliminating decimals.

Examinations.—Physical and bacteriological examinations were made at two-month intervals, and weights and hemoglobin estimations were recorded. Urine examinations were made monthly. Red blood cell counts were made at three intervals during the first year. The patients receiving streptomycin had audiogram readings each quarter-year. Photographs in color and in black and white were taken at yearly intervals, or oftener when indicated. Lepromin tests were performed before and after the treatment period. Quantitative determinations of sulfone in the blood were made at irregular intervals.

Toxicity and suspension of treatment.—Group A: There were three deaths in this group, two due to chronic nephritis and one to acute nephritis following exfoliative dermatitis. Two patients absconded. One was taken out of the project because of secondary anemia following epistaxis, and one because he developed tuberculosis. Thus seven patients were lost from this group. Two others developed exfoliative dermatitis but continued treatment.

Group B: Only one patient was dropped from this group. Treatment had to be stopped because of exfoliative dermatitis. Two others were troubled by slight dermatitis, and one developed eczema.

Group C: Three patients were lost from this group. One was dropped because of exfoliative dermatitis. Complaints of abdominal pain and vomiting were usual, but only one patient stopped treatment for this reason. The third one was transferred to another institution. One female developed transient mental symptoms which cleared up when INH was temporarily withdrawn.

Group D: One patient was dropped when dermatitis was followed by acute lepromatous infiltration and he was regarded as becoming worse.

CLINICAL RESULTS

In reporting the first series trials Doull (2) stated:

> In planning the studies the difficulties of clinical appraisal were recognized. Descriptive accounts of individual cases have their place, but are insufficient for the purposes envisaged. Quantitative data are required of sufficient reliability to be used as indices of the condition of individual patients and of groups.
>
> Lacking any better method, the consultant was asked to give a numerical rating to the degree and extent of infiltration, nodulation and other lesions for various body sites, at each physical examination. If any lesion on the list was not present its absence was recorded. These ratings were added together for each type of lesion and used for comparison with results at later examinations. . . .
>
> At the conference in Japan. . . .it was agreed that no changes in nomenclature would be made during the study; i.e., a lesion called a nodule or a plaque at the beginning was so designated at the final examination, if still present.

In actual practice this system has not turned out to be of the statistical value that was hoped for. For example, plaques which were raised, red, infiltrated, and strongly positive for bacilli usually resolved completely or remained as hypopigmented, bacteriologically negative patches. The statistical significance of one plaque, therefore, was equal to that of a completely healed patch. Clinically this was an absurdity, but it could not be obviated as it was decided that all lesions had to be recorded as in their original form. Similar difficulties occurred when nodules resolved to blackened stigmata on the skin.

For future studies, it is suggested that it is not the presence of lesions that should be classified as 1+, 2+, or 3+, but their clinical significance, i. e., their degree of activity. These remarks apply to nodules or papules, plaques and macules. Infiltrations are in a slightly different category.

Subsidence of infiltration would bring it into a lower category and so could be reflected statistically. However, the flaw here is that a strongly positive infiltrated area can become bacteriologically negative, and yet the improvement need not be reflected by corresponding subsidence of infiltration. On the other hand, a strongly positive area may show no obvious infiltration. To my mind there is only one statistical yardstick in the evaluation of the effects of a drug, and that is its effect on the number of bacilli.

In the present work, the presence or absence of infiltration and nodules was recorded for five sites, viz., face, ears, trunk, buttocks and extremities. For macules and plaques four sites were recorded, the ears being excluded. The extent of the lesions were recorded as 0, 1+, 2+, or 3+. Table 2 shows the quantities of each type of four lesions evaluated in each group as they were constituted at the beginning and end of the experiment period. It shows that clinical improvement took place in each type of lesion in each group except the macules of Group D.

TABLE 2.—*Quantitative evaluation of lesions in each group as constituted at the end of treatment, values before and after treatment.*

Group[a] (and cases)	Infiltrations		Macules		Plaques		Nodules	
	Before	After	Before	After	Before	After	Before	After
A (33)	159	85	22	11	28	8	13	9
B (39)	198	116	14	4	18	1	15	0
C (36)	154	82	30	15	10	2	6	2
D (9)	47	23	6	6	0	0	9	3

a Varying numbers of cases, from 1 to 7, were lost from the groups for reasons explained in the text.

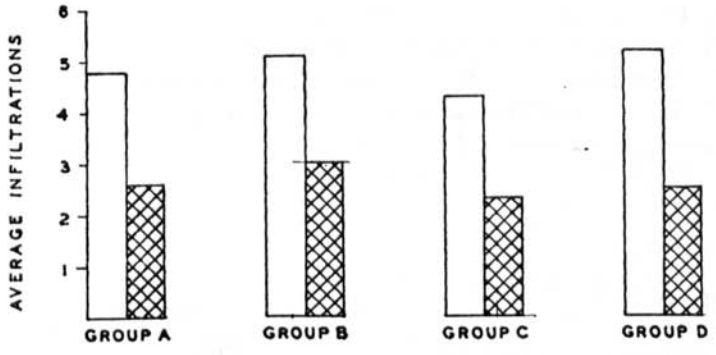
Since infiltrations were the commonest kind of lesion in all groups, and since their assessment gives the truest picture of any clinical change, the average figures for infiltrations of each group were assessed before and after treatment (see Text-fig. 1).

Group A improved from value 4.8 to 2.6, i. e., 46 per cent.
Group B improved from value 5.6 to 3.0, i. e., 41 per cent.
Group C improved from value 4.3 to 2.3, i. e., 47 per cent.
Group D improved from value 5.2 to 2.5, i. e., 51 per cent.

The degree of improvement was therefore almost equal with all of the four treatments.

BACTERIOLOGICAL RESULTS

In assessing the value of a drug it is helpful to know not only if a patient is bacteriologically positive or negative but also the degree of positivity. About technique, the following is again quoted from Doull.



TEXT-FIG. 1. Average degrees of the infiltrations in the four groups before treatment (hollow columns) and after treatment (cross-hatched columns).

Staining was by the conventional Ziehl-Neelsen method, using a standard lot of basic fuchsin, with acid alcohol (3% HCl in 95% C_2H_5OH) as decolorizer.

Findings were reported as follows: 4+, hundreds of bacilli to a field; 3+, 20-100 bacilli to a field; 2+, 10-20 bacilli to a field; 1+, fewer than 10 bacilli to a field; VS, very scanty bacilli, fewer than 10 to a slide; 0, no bacilli in 50 fields.

It is my experience that a recovering lepromatous case shows a slow but consistent drop in the bacteriological index. The index is obtained by adding together the degrees of positivity in all smears, a "very scanty" finding being counted as one-half. However, there are three ways in which errors can arise: (*a*) technique of the operator taking the smears, (*b*) errors in staining or decolorizing, and (*c*) judgment of the person examining the slides.

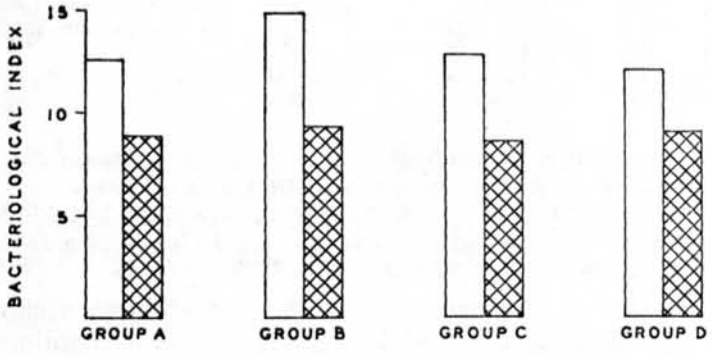
To minimize the possibility of error, the first three and the last three "bacteriological checks" are taken into account here. The first and the last checks consisted of 8 smears from 8 sites, *viz.*, ears, forehead, cheeks, and nasal cavity, right and left in each instance. The other checks consisted of four smears, from the ears and the nose.

TABLE 3.—*Average bacteriological indices before and after treatment, for* (a) *the four groups in total, and* (b) *the groups divided with respect to the occurrence of erythema nodosum leprosum (ENL), with percentages of reduction.*

Group (and cases)	Total (117 cases)			Without ENL (58 cases)			With ENL (59 cases)		
	Before	After	Decrease	Before	After	Decrease	Before	After	Decrease
A (33)	12.6	8.8	30.0%	11.1	5.7	48.7%	13.8	11.3	18.1%
B (39)	14.9	9.5	36.2%	12.3	7.8	36.6%	16.4	11.7	28.6%
C (36)	12.8	8.7	32.0%	6.0	3.0	50.0%	13.5	10.8	20.0%
D (9)	12.0	9.0	25.0%	18.7	11.7	37.4%	9.0	8.0	11.1%

The first section of Table 3 shows the average bacteriological indices of the groups at the beginning and toward the end of the treatment period (see also Text-fig. 2). Because smears were examined on alternate months, each index represents the average result of three records over a six-months period in the first and last parts of the two years of treat-

ment. These indices reveal that the four groups, although not selected on the basis of the original bacteriological condition, were closely balanced in this respect at the beginning, and that in total the diminution of bacilli was fairly similar under all four treatments. The percentages of decrease range from 36.2 (Group B) down to 25.0 (Group D), with an average of 32.3 per cent.



TEXT-FIG. 2. Average bacteriological indices of the four groups before treatment (hollow columns) and after treatment (cross-hatched columns).

It is our practice before recommending the probational discharge of a patient to insist on at least one full year's history of continuously negative smears. It may be of interest to note the cases recommended for discharge in each group of this study.

Group A.—Seven patients of this group have been discharged as arrested. Five had received at least 4-1/2 years of sulfone treatment, which is the average time required for a moderately-advanced lepromatous case. One early lepromatous case required only 32 months treatment. One other case converted from lepromin negative to positive; this was a reacting tuberculoid case, and required nearly 4 years treatment.

Group B.—Nine patients of this group were discharged. Seven had received at least 6 years treatment with sulfones. One borderline case was treated for 3 years and 3 months. One reacting tuberculoid case became negative and was discharged after 14 months of observation.

Group C.—Of the fifteen patients of this group discharged, eleven had had 5 or more years of treatment. Two were wrongly classified as lepromatous; one was borderline and the other tuberculoid. Two early lepromatous cases required 41 and 28 months treatment respectively.

Group D.—No case in this group became arrested.

Arrest of the disease depends upon (*a*) the stage of the disease, as early cases respond most quickly and (*b*) the duration of the treatment. It will be noted that wrong classifications appear inevitable, and are shown up only by subsequent developments. Such cases should perhaps be withdrawn from the study, but they are left in as they occur in all the groups, and will probably occur in all groups selected for future studies.

ERYTHEMA NODOSUM LEPROSUM

The condition of erythema nodosum leprosum (ENL) deserves close study, because it is so little understood and its significance is so debatable. Pepler *et al.* (4) have shown that the pathology is not that of true erythema nodosum but of panniculitis, and they have suggested that it should be called "panniculitis nodosa leprosa." The committee on classification of the Madrid congress (3) stated that it is usually of good prognostic significance. This is in accord with the opinion of Wolcott (6), and Wade (5) has indicated that this view is widely held. Recently I myself wrote (1): "Muir has found that cases exhibiting erythema nodosum show a greater diminution of bacilli than non-reacting cases. With this, we are in complete agreement, and, where possible, we avoid treating this manifestation." Kooij, however (personal communication), has found in a controlled study that the period before the achievement of arrest was 53 months where ENL had not occurred, whereas in the cases which had experienced ENL the period was 72 months.

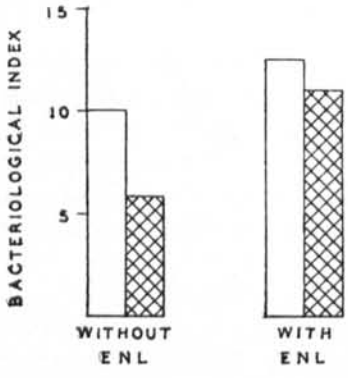
This type of reaction is the commonest one seen in cases under sulfone treatment. In this study, what were considered toxicity effects were: 5 cases of exfoliative dermatitis, 3 of drug dermatitis, 3 of eczema probably due to the drugs, 2 of severe gastritis due to PAS, and 1 of mental breakdown probably due to INH. There were 59 cases which showed ENL, and 58 which did not.

This reaction was seen occasionally before the use of the sulfones, but it has increased tenfold since their use began. It has varying degrees of severity, from evanescent pea-sized erythematous nodules to large plaques where they have coalesced, resembling a boil. They may or may not be painful. They may break down and suppurate. The reaction is not an allergy to sulfones, since it occurs exclusively in lepromatous cases. It is seen almost exclusively in such cases in which bacilli can be demonstrated; I know of only one case in this project, and one other case, in which ENL occurred but bacilli could not be found.

The bacteriological indices have been worked out for the cases divided into two classes, those which had not had ENL and those which had it, and these are shown (by treatment groups) in the second and third parts of Table 3. In total, combining the 58 cases without ENL, their bacteriological index was 10.0 before treatment and 5.8 after treatment (42% reduction). In the ENL-positive group of 59 cases, the figures were 12.5 and 11, respectively (12% reduction). This comparison is shown graphically in Text-fig. 3. Here we see clear evidence that ENL is detrimental to the patient and that the reaction should be controlled. The possible value of the corticosteroids in this connection should be considered.

SUMMARY AND CONCLUSION

A controlled study carried out over a period of two years of the effects of sulfones alone, of isoniazid plus sulfone, of isoniazid plus dihydro-



TEXT-FIG. 3. Comparing the bacteriological indices of the 58 cases of the combined groups in which there was no ENL and the 59 cases which had ENL, before treatment (hollow columns) and after treatment (cross-hatched columns).

streptomycin plus PAS, and a pilot study of streptohydrazid, is reported. Flaws in the method of statistical evaluation are pointed out. The significance of erythema nodosum leprosum is investigated, and the necessity of controlling the reaction is stressed.

ACKNOWLEDGMENTS

This study was instigated and controlled by the Leonard Wood Memorial and was carried out in parallel in South Africa and the Philippines, except that it was continued for two years here instead of being terminated at the end of one year. Thanks are due the Leonard Wood Memorial for the invitation to take part in the investigation and for supplies of drugs, photographic equipment, etc. Thanks are also due to the Secretary for Health, Department of Health, Union of South Africa for permission to submit this article.

RESUMEN

Preséntase aquí la reseña de un estudio de dos años de la isoniacida como coadyuvante de los regímenes terapéuticos que, en una investigación concertada bajo los auspicios de la Fundación Conmemorativa Leonard Wood, se mostraron antes ser los más eficaces, a saber, las sulfonas solas y la dihidroestreptomicina con PAS. Un grupo testigo del mismo tamaño (40 casos al empezar) recibió solamente las sulfonas: diasona en los primeros 18 meses y luego DDS. Un cuarto grupo ("piloto" de 10 casos) recibió un compuesto que contenía tanto estreptomicina como isoniacida eb la molécula.

Se hacen comentarios acerca del método usado en el estudio anterior para justipreciar la mejoría clínica. Se sugiere que la actividad de las lesiones es más importante que su mera presencia, pero que el índice bacteriológico es la única pauta de valor estadístico.

Muéstrase (Tabla 2) que hubo mejoría clínica en casi todas las formas de lesiones en todos los cuatro grupos en tratamiento. Tomando las infiltraciones como la forma más común de lesión y la que aporta el cuadro más exacto de la modificación clínica, se observó (Texto, Fig. 1) que el grado de mejoría era casi idéntico en todos los grupos. Los índices bacteriológicos (Table 3 y Texto, Fig. 2) también revelaron grados muy semejantes de mejoría en los cuatro grupos.

Se ha creído generalmente que no es nociva la reacción del tipo del eritema nudoso leproso (ENL). El análisis de los datos de estos casos (Tabla 3 y Texto, Fig. 3) demuestra que la reducción del índice bacteriológico entre los 58 casos que no acusaron dicha reacción fué mucho más destacada (42 por ciento) que entre los 59 que la acusaron (12 por ciento). Dedúcese que esta reacción es perjudicially debe cohibirse, tal vez con el uso de cortisona.

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