Effects of the Administration of B663 [G 30 320, Lamprene, Clofazimine (Geigy)] on Three Groups of Lepromatous and Borderline Cases of Leprosy[1]

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It has been stated ([1, 6]) that the clinical response of lepromatous cases to B663 [Lamprene, clofazimine (Geigy)] is comparable to that of DDS; it is also generally accepted that this drug is quite useful in controlling *erythema nodosum leprosum* (ENL). However, we have not come across any report on the therapeutic performance of this drug among cases that had failed to respond to the sulfone drugs, particularly among relapsed cases.

MATERIALS AND METHODS

Three groups of patients were included in this study. **Group I,** the experimental group, consisted of 18 relapsed lepromatous cases with histoid lesions which previously had been rendered negative by DDS but after relapse no longer responded to this drug. They ranged in age from 30–59 years. **Group II** (15 patients, aged 10–59 years) and **Group III** (14 patients, aged 10–59 years) were control groups, both belonging to a drug trial conducted by one of us (J. G. T.) ([6]), and who were able to complete two years of treatment during the same period as **Group I.** Patients belonging to the latter control groups have had no previous active treatment, but during the trial **Group II** patients received B663 while those in **Group III** received DDS.

The same model protocol for drug trials undertaken by the Leonard Wood Memorial in Cebu was followed in a modified form in the present study. This required a preliminary general physical examination with chest x-rays of the lungs, supported by anatomical silhouettes that mapped the configuration, extent and distribution of the skin lesions, neurological charts, colored and black and white photographs, examination for motor loss and atrophy, contractures and absorption of the digits.

The laboratory examinations included urine, stool, complete blood examinations and kidney and liver function tests.

Biopsies were made in the preliminary period, after 48 weeks, and again at the end of the 96th week of treatment and were all obtained from the same lesion of each patient. However, in Group I some of the patients had small nodular histoid lesions which were removed entirely at biopsy. In such cases, similar nodules were selected beforehand, during the preliminary period, for the 48th and 96th week biopsies. When the nodules were larger, three punch biopsies from the same lesions could be made.

Bacteriological smears were secured from four required sites, namely, right and left ear lobes, right and left cheeks, and from two optional sites. This examination was done monthly in Group I and every two months in Groups II and III.

Methods of determining the Bacteriologic Index (BI). Three methods of determining the Bacteriologic Index were used. One was the Standard Bacteriologic Index employed at the Eversley Childs Sanitarium before the introduction of the Ridley Index ([2]), which was employed as the second method. In a third method, the average estimated number of bacilli per field was also used.

It is noted that in the Standard Bacteriologic Index, the range extends from a minimal reading of "very scanty" to a maximum of 4+ with "very numerous bacilli," compared to a range in the Ridley Index, starting from 1+, with "1 or more bacilli per 100 fields," to 6+, with "1,000 or more bacilli per field." When there were many low bacterial counts per field, as was the case toward the completion of the drug trial, the pluses obtained by using the Ridley Index were higher as compared to the Standard In-

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dex; 1+ in the standard scale was equivalent to 3+ in the Ridley Index.

In the third method of determining the BI, a decrease in the average bacterial count per field was registered from early stages of the trial. In other words, it is a sensitive method of detecting slight decreases in the bacillary count; perhaps this simple method of determining the BI may be found useful in short-term drug trials.

Administration of the drug. The dose for B663 was 200 mg/day, six days a week; that of DDS was 100 mg/day, also six days a week.

The total period of treatment in all the groups was 96 weeks. Many dropouts occurred before the end of the trial thereby reducing the number of cases in each group.

Composition of the groups. The usual preponderance of males over females in leprosy was present in the control Groups II (10/5) and III (12/2). The slight preponderance of females over the males in Group I (7/11) indicates the greater tendency for women to seek readmission to the sanitarium after relapse.

The relapsed cases (Group I) were, as might be expected, all past 30 years of age, while most of those in the previously untreated groups were below this age. There were too few cases to give meaningful comparisons as to the sex and age distribution in the three groups.

In drug evaluation studies, the type and advancement of the disease is taken into account in assigning patients to the experimental and control groups. This could not be done in the present instance as patients were admitted sequentially at irregular intervals and the requirement for prompt administration of active treatment prevented proper randomization into three equal groups.

The distribution as to the types of leprosy among those who completed the full two years is shown in Table 1. This distribution as to the type was unavoidably unbalanced. In the first place, there was only one case diagnosed clinically as borderline leprosy in the relapsed group, whereas this form of leprosy constituted, clinically, around one-fourth of the cases in Groups II and III. There were proportionately more L3 cases in Group I which were no longer responding to DDS before the drug trial.

All those in Group I (relapsed cases) exhibited histopathologically confirmed histoid lesions. The histopathological diagnosis of the patients' lesions were as follows:

LL (histoid lesion)	10
BL (histoid lesion)	5
LL and BL (histoid lesion) in same patient	2
Histoid lesion	1
Total	18

Fifteen histoid lesions were cutaneous and three were subcutaneous. Six of the previously untreated patients in Groups II and III also had histoid nodules. All were diagnosed pathologically as LL (histoid lesion); all the lesions were located on the surface of the skin.

CHEMOTHERAPEUTIC RESULTS

Clinical. The degree of clinical improvement produced by the respective drugs in the experimental as compared with the control groups is indicated in Figures 1-3.

The degree of clinical improvement as a whole appeared to be more marked in the control groups than among the relapsed cases in Group I, although the groups are too small to permit an adequate comparison of the results. On the other hand, all the latter had shown at least an appreciable degree of improvement in contrast with their previous lack of response to DDS treatment. In any case, the patients themselves were satisfied with the favorable results on their

TABLE 1. *Distribution of clinical types and disease severity.*

Treatment and severity of leprosy	Group I	Group II	Group III
Borderline	1	4	3
LL	4	2	0
LL	5	5	8
LL	8	4	3
Total	18	15	14

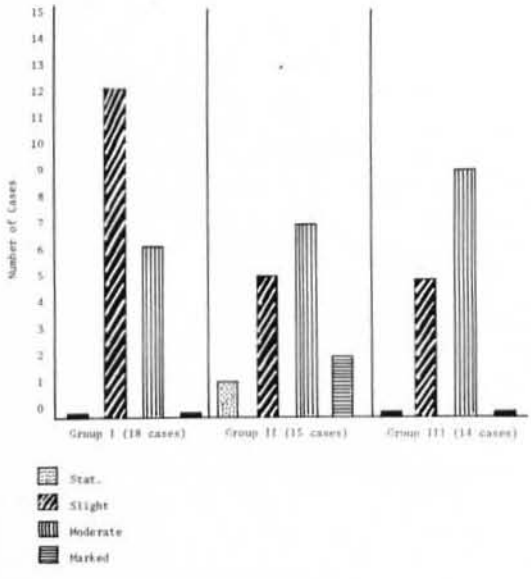

FIG. 1. Degree of improvement produced by B663.

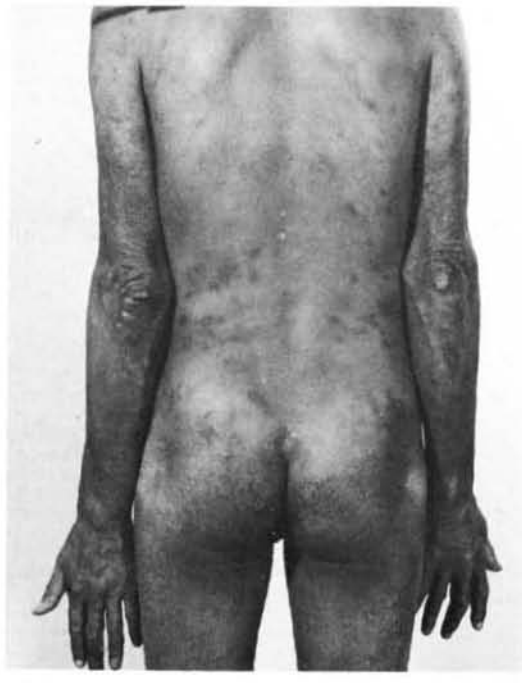

FIG. 3. Case I-15. Clinical and bacteriologic negativity after two years of treatment with B663. There is extensive ichthyotic skin over subsided lesions (a characteristic finding in many relapsed cases improved with Lamprene).

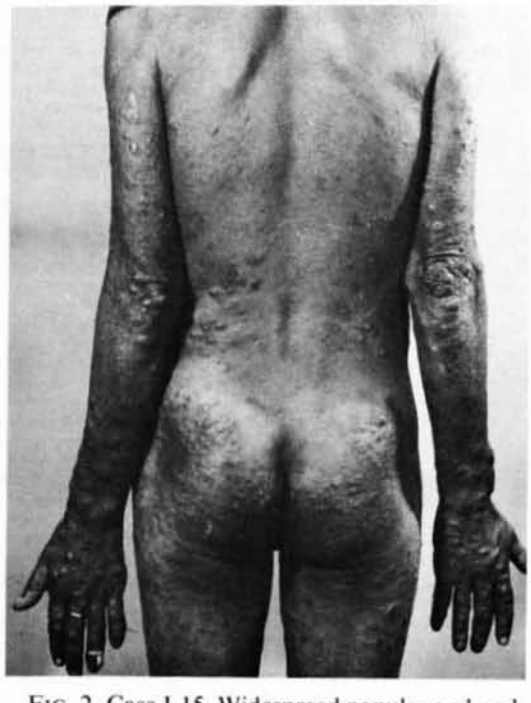

FIG. 2. Case I-15. Widespread papular and nodular lesions were present on the upper extremities, loins and buttocks.

skin lesions which gave them a more hopeful outlook for the future instead of their previous state of hopelessness and despair.

Effect of treatment with B663 and DDS on histoid lesions. B663 produced an intense grayish-black pigmentation in histoid lesions which obscured erythema, one of the evidences of clinical activity. The sites remained prominently pigmented for up to two years after discontinuation of the drug in many cases, and it was difficult to determine whether the pigmented lesions had already reached a residual stage unless they showed marked subsidence and wrinkling of the overlying skin. On the other hand, there was a moderate reduction in the size of even the larger nodules (Figs. 4-7).

The smaller nodular histoid lesions which were found on the three newly admitted patients in Group II which were later treated with DDS, and therefore not pigmented, became residual within one year after the start of the treatment.

Effect of treatment on the Bacteriologic Indices. Comparison of the results as analyzed by the three methods of obtaining the

TABLE 2. *Results of bacteriological examination of skin smears.*

Percent decrease in BI after treatment	Bacterial Indices								
	Standard BI			Ridley Index			Average no. of bacilli per field		
	Group I	Group II	Group III	Group I	Group II	Group III	Group I	Group II	Group III
0-25 (stat)	1	1	4	2	2	5			
26-50 (slight)	2	1	1	3	4	7	2	1	2
51-75 (moderate)	5	4	5	3	5	2	1		2
76-99 (marked)	6	8	4	6	3		5	4	5
99-100 (neg)	4	1		4	1		10	10	5
Total	18	15	14	18	15	14	18	15	14

BI already described are shown in Table 2.

In Table 2, the percent decrease was obtained by averaging the pluses of the eight sites from each patient (four sites in the control group) before treatment, and subtracting from it the average pluses obtained from the same sites after treatment. The percentage of reduction in the bacillary density was then determined.

When the decrease of the BI was less than 25% from the pretreatment figures, the improvement in the bacterial load was considered minimal and the disease status stationary. When the reduction was 50% or more, the improvement in the BI was judged to be moderate or marked, and when the reduction came close to 100%, the case was considered to have become "negative" or "nearly negative." It will be noted in Table 2 that, based on the Standard BI, while 17 of 18 cases (94.4%) in Group I and 14 of 15 cases in Group II (93.3%), showed bacteriologic improvement after two years of treatment with B663, only 10 of 14 cases (71.4%)

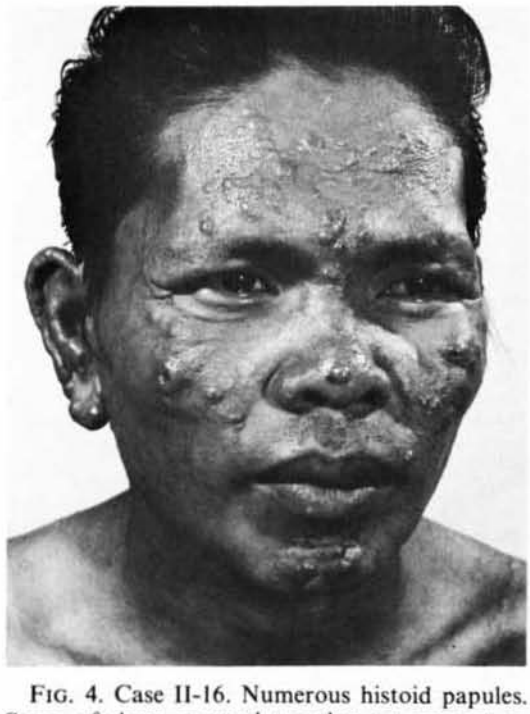

FIG. 4. Case II-16. Numerous histoid papules. Some of them grouped together are present on the face: one on the right malar region shows the typical central erosion characteristic of some of the larger histoid cutaneous nodules. Leprotic infiltration on face and right ear is evident.

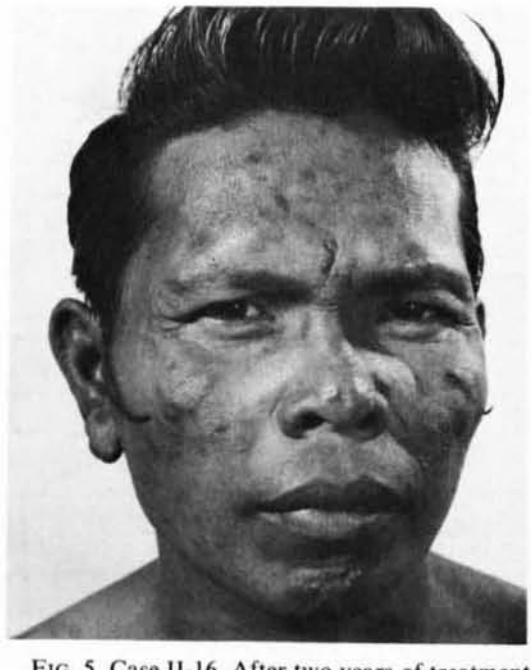

FIG. 5. Case II-16. After two years of treatment with B663. Many of the papules have disappeared and leprotic infiltration was much improved, but the bacteriologic improvement was only slight.

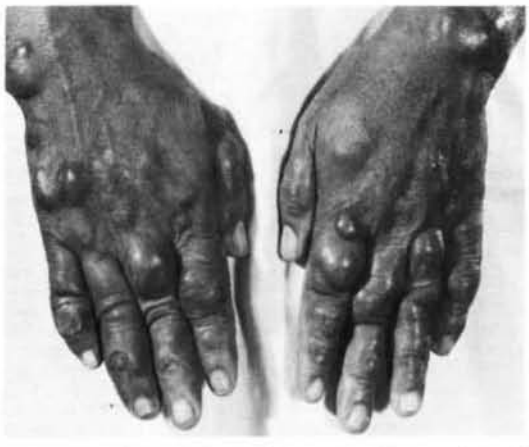

FIG. 6. Case I-16. Characteristic location of histoid nodules on wrists and at the dorsum of hands and fingers.

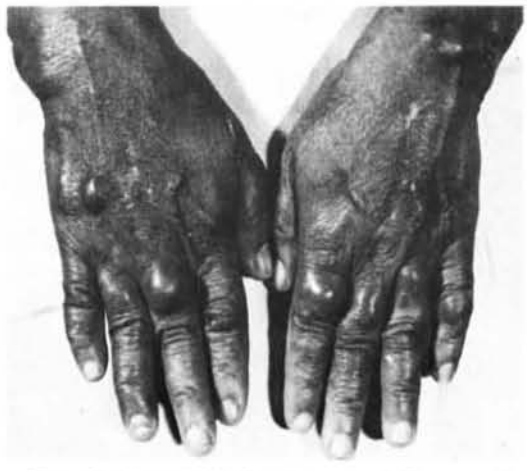

FIG. 7. Case I-16. One year and five months after completion of a two year treatment with B663. During this period no specific treatment was received by the patient. The three unchanged shiny nodules were very hard and fibrotic.

in Group III treated with DDS showed similar improvement. Although the differences in the improvement of the bacterial load of cases in the three groups, as shown in Table 2, are not significant since they were based on too few cases, there were indications of a probable slight improvement in bacterial counts among those receiving B663, especially the relapsed cases, compared to those under DDS treatment.

Other clinical findings in connection with treatment of B663. The black pigmentation produced by Lamprene is a positive clinical fact that cannot be overlooked or minimized in connection with the use of this drug in the treatment of leprosy. For this reason, its manifestations and the psychological effects of its occurrence in individual patients as well as on other observations have been studied with some care.

The degree of pigmentation as it affects the lepromatous compared to the borderline cases is given in Table 3. Among 28 lepromatous and 5 borderline cases receiving standard doses of B663, only one slight lepromatous and one borderline case did not develop any pigmentation. In about one-third of the cases it was light, but was moderate to severe among the rest. The degree of pigmentation was judged independently by two observers. A certain individual predisposition towards pigmentation was noted among the patients receiving the drug.

These figures show that in a general way, the more advanced the disease, the deeper the pigmentation of the skin lesions. There were too few cases of the borderline type to fully confirm the general impression of one of us (J.N.R.) that the borderline lesions (BL) as a rule stain less deeply than the lepromatous infiltrations and nodules, although there were a few of the former who stained even more deeply than the lepromatous ones.

Anyone who has seen the face of a moderately pigmented case receiving B663 will realize that the patient will thereafter encounter much difficulty in his social relationships; as a matter of fact, the dark coloration emphasizes the patient's condition even more effectively than the lesions of the disease.

We are aware of a drug trial using smaller doses of B663 which diminished the pigmentation to some extent in some cases but still seriously marked the others in an unpredictable manner.

These experiences demonstrate that because of the pigmentation, this drug cannot be recommended for mass treatment.

The reddish pigmentation became noticeable among most of our lepromatous patients on the "normal looking" portions of the skin by the end of the first month. It is possible that this redness really covered the entire body surface but the black pigmentation obscured it at the site of the lesions.

The red coloration appeared in the skin of a healthy breast-fed infant two days after the mother first received B663.

TABLE 3. *Relationship between the black pigmentation and the type and severity of leprosy among patients receiving B663 (Groups I and II).*[a]

Degree black pigmentation	Borderline		LL		LL		LL		Total	%
	Group I	Group II	Group I	Group II	Group I	Group II	Group I	Group II		
No. pig.	1		1						2	6.0
Slight		1	3		1	1	2	3	11	33.0
Moderate		1		2	1	2	2	1	9	27.0
Marked		2			3	2	4		11	33.0
Total[b]	1 (3.0)	4 (12.1)	4 (12.1)	2 (6.1)	5 (15.2)	5 (15.2)	8 (24.2)	4 (12.1)	33	100.0
No. of cases	18	15	18	15	18	15	18	15	—	—

[a] Group III was not included because the patients were treated with DDS.
[b] Figures in parentheses represent percentile.

Effects of B663 treatment on reactions. *Erythema nodosum leprosum* (ENL). Four of the relapsed cases in Group I who were receiving DDS had severe ENL reactions before being admitted to the drug trial. During two years' treatment with B663, the severity of the attacks was ameliorated in three and suppressed in one case. After discontinuation of the drug and return to DDS treatment, the ENL attacks returned to their former severity except in one patient who remained free of reaction during one year of follow-up.

In Group II, also consisting of patients who received B663, no ENL appeared, while among those receiving DDS in Group III, five patients developed ENL.

The reversal reaction. One of us (J.N.R.) undertook a special study of this form of reaction as it occurred in some of the patients in Group I. The term *reversal reaction* was coined by Wade (7) in 1955 to designate a phenomenon occurring among cases classified as lepromatous treated with sulfone drugs and considered by him as a reaction towards a more resistant form or stage of leprosy. Rodriguez (3) had reported earlier that this form of reaction, formerly called pseudo-exacerbation by Souza Lima and Rath de Souza (5), also occurred in borderline leprosy.

Reversal reaction occurred in six relapsed cases in Group I out of 27 such cases receiving B663 at the time, giving a rate of about 20%, which is considerably higher than the more usual rate of around 5% found by one of us (J.N.R.) in other trials with active drugs, including rifampin.

PATHOLOGIC RESULTS

The diagnoses appearing in the Tissue Reports made by one of us (R.M.A.) on biopsies submitted to the Pathology Laboratory from the three groups appear in Tables 4, 5 and 6. These tables present the clinical evaluation according to the Cairo classification in an attempt to indicate extent of involvement. The histologic evaluation is per Ridley and, as indicated, in these charts and elsewhere in this paper, may vary dependent on biopsy site selection. This procedure, in spite of its potential for controversy, was useful in demonstrating the apparent relationship between extent of involvement and

TABLE 4. *Histopathologic diagnosis in Group I.*

Case	Clin. dx	Histology[a]			Case	Clin. dx	Histology[a]		
		Pretreat.	48th wk	96th wk			Pretreat.	48th wk	96th wk
1	LL	1. LL* 2. LL* 3. LL* 4. LL* 5. LL*	LL	LL	10	LL	1. LL* 2. LL* 3. LL* 4. LL* 5. ENL	Histoid	LL, resolving
2	LL	1. LL 2. LL* 3. LL	LL, resolving	LL, resolving	11	L_2N_2	1. BL*	LL	LL, resolving
3	LL	1. LL* 2. ENL 3. ENL	LL	LL, resolving	12	L_1N_3	1. BL* 2. BL*	Hyalinization fibrosis	Chronic inflam. dermat.
4	LL	1. LL* 2. LL*	LL	LL, resolving	13	LL	1. BL* 2. BL* 3. BL*	LL	LL
5	L_1N_3	1. Chronic granuloma 2. LL*	Cellulitis	Histoid atypical	14	LL	1. Histoid (early) 2. LL 3. BL	Histoid	LL, resolving
6	LL	1. LL* 2. LL*	BL	LL, resolving	15	LL	1. LL** 2. LL*	LL	LL, hyalinization
7	LL	1. BL* 2. BL*	LL	BL, resolving	16	LL	1. Histoid 2. Histoid 3. BL* 4. BL*	BL	LL
8	LL	1. LL*	LL, resolving	LL, resolving	17	BB	1. Histoid 2. Histoid	No biopsy	LL
9	LL	1. LL* 2. LL	LL	LL, resolving	18	L_3N	1. Histoid 2. Histoid atypical 3. BL 4. BL	LL	LL

[a]Single asterisk (*) indicates histoid morphology and double asterisks (**) atypical histoid.

TABLE 5. *Histopathologic diagnosis in Group II.*

Group II. Previously untreated, received B663									
Case	Clin. dx	Histology[a]			Case	Clin. dx	Histology[a]		
		Pretreat.	48th wk	96th wk			Pretreat.	48th wk	96th wk
1	BB	BB	I	Refused	9	BB	LL* BL	LL	LL
2	L_3N	LL	BB	LL	10	LL	LL	I	I
3	BB	BL	I	I	11	LL	LL	LL	LL, resolving
4	L_1N_2	LL	LL	LL	12	L_3N_2	BL	LL	LL
5	L_2N_3	BL	LL	LL	13	L_1N_2	LL	LL	LL, resolving
6	BL_3	LL	LL	LL	14	BB	BL	BL	I
7	LL	LL* LL	LL	LL	15	LL	BL	LL	LL
8	LL	LL* LL	LL	LL					

[a] Single asterisk (*) indicates histoid morphology.

TABLE 6. *Histopathologic diagnosis in Group III.*[a]

Group III. Previously untreated, received DDS									
Case	Clin. dx	Histology[b]			Case	Clin. dx	Histology[b]		
		Pretreat.	48th wk	96th wk			Pretreat.	48th wk	96th wk
1	LL	LL* BL	BL	LL	8	LL	LL	LL	BL
2	BL_3	BL	LL	LL	9	LL	BL	I	Scar
3	L_2L_3	LL*	LL	LL	10	BB	BL	LL	BL
4	LL	BL	LL	LL	11	LL	LL	LL	LL
5	LL	LL* LL*	LL	LL	12	LL	LL	LL	LL
6	LL	LL	LL	LL	13	BB	BL	LL	I
7	L_2N_3	LL*	LL	LL	14	LL	I	BT	I

[a] Sequential biopsies taken from the same lesion.
[b] Single asterisk (*) indicates histoid morphology.

the change in histopathology with duration of therapy.

Biopsies from ten patients taken during the pretreatment period were diagnosed histologically as LL (histoid lesion), five as BL (also a histoid lesion), two cases had both LL and BL histoid lesions and one case was simply diagnosed as "histoid."

Of the ten cases diagnosed as LL in the preliminary period, eight were found to have become "LL (resolving)" after two years of treatment with B663. In another case, the tissues had undergone hyalinization; two had unchanged histopathologic appearances and one (taken from a subcutaneous nodule) was diagnosed as "atypical histoid."

The criteria followed by the pathologist in the histologic diagnoses of "residual lepromatous" lesions were as follows: 1) there was a remarkable decrease in the size and

extent of the leproma, and 2) marked decrease in the bacterial load.

Of five patients with initially diagnosed BL lesions, one showed a resolving BL structure after two years of treatment with B663, one case showed only changes of chronic inflammatory dermatitis, and in the last three, the histologic structure had changed to LL. This same unexpected pathologic result occurred also in the control Groups II and III.

After 48 weeks of treatment, all biopsied histoid lesions at the preliminary examination (not including Case 5 whose biopsied lesion indicated cellulitis), except Nos. 10 and 14, had lost their histoid architecture, by the end of the two years of treatment with B663, only a deep-seated nodule located on the forearm of Case 5 was diagnosed atypical histoid histologically.

In four other relapsed cases who were dropped from the present study for various reasons and had subcutaneous histoid nodules, the histoid structure persisted even after about two years of treatment with B663.

In 8 of 15 patients who completed the two year treatment in this group, the biopsied lesions in the preliminary period were diagnosed as LL. Of these, the same lesions were found to be "resolving" at the end of the drug trial in only two cases; five others finished with the diagnosis (LL) as at the preliminary biopsy, and in one, the initial LL lesion had become indeterminate. Therefore, only three of eight cases in the group showed marked improvement histologically when compared to Group I.

Of the five cases with biopsied lesions histopathologically diagnosed as BL during the preliminary period, two became indeterminate while three became LL histopathologically after treatment with B663 and had apparently become worse by this criterion.

Referring to Case 1, with a preliminary diagnosis of BB, the patient refused biopsy at the end of the two year treatment, although he had become indeterminate at the end of one year.

The histopathologic findings for Group III are given in Table 6. The important difference between Group III and the preceding two groups was that the patients in it received DDS instead of B663. Of 14 patients belonging to this group, the initial histopathologic diagnosis of the biopsy lesions in nine was LL, in four the pretreatment biopsy was reported as BL, and in one the biopsied lesion was indeterminate.

In no case were any of the original lesions reported histopathologically as resolving among the patients in this group at the end of the study. However, this does not necessarily mean that no improvement occurred among those found to still be LL at the last biopsy. Indeed, all of them showed varying degrees of improvement when judged by increased replacement of leprotic cellular infiltrate by normal appearing tissue after two years' treatment with DDS, but the histopathologic improvement was not as marked as among those receiving B663.

Again, in three instances, the initial BL lesions were transformed to LL at the end of the trial.

LEPROMIN TEST RESULTS

Among the patients in the experimental group (Group I), consisting of relapsed cases with histoid lesions, two batches of lepromin were used, namely, a standard lepromin prepared from ordinary lepromatous lesions and a similarly prepared lepromin from histoid nodules which showed numerous *M. leprae* in smears. The two preparations were adjusted according to bacillary content to produce the same strength of lepromin.

The rationale of using a histoid lepromin was based on the original observation of Wade ([8]), confirmed by Rodriguez ([4]), that the *M. leprae* in acid-fast stained sections of histoid lesions appear to be longer and larger than those in ordinary lepromatous lesions. It was hoped in the present study that some differences in the responses of their respective lepromins might be proven to exist.

There were no significant differences in the response to the two lepromins with reference to the 48 hour or the 21 day readings during the pretreatment period and again in regard to these readings after 96 weeks of treatment in this group.

Summarizing the results of the Mitsuda test, only one (Case 12) showed a positive reaction to the standard and histoid lepromin, producing a 5 × 5 mm nodule at the pretreatment period which was reduced to 4 × 4 mm after two years of treatment with B663. This patient was clinically considered to be

a burnt-out case (L1N3).[3] In the experience of one of us (J.N.R.), many previously lepromatous which become burnt-out cases give positive Mitsuda reactions.

As for the Fernandez reaction, none of these relapsed cases, including a BL case, was able to mount a definitely positive reaction if the measure of positivity is held at a minimum diameter of 10 mm of the palpable red area of reaction. However, in six lepromatous patients (Cases 2, 4, 6, 7, 10 and 12), the red areas came close to a positive reaction measuring about 7 mm to 8 mm at the pretreatment tests. The only borderline case (No. 17) was completely negative with respect to the Fernandez reaction at both the pretreatment and posttreatment tests. Moreover, rather contrary to expectations, all the red areas of responses to the Fernandez were reduced in area after two years of treatment with B663, some to complete negativity, in spite of the fact that these cases had improved clinically, bacteriologically and histopathologically.

Only two cases (Nos. 1, 14), both borderline, gave positive Mitsuda and Fernandez tests; the former remained positive at the posttreatment period, while in both cases the Fernandez became "doubtful."

After treatment, Cases 11 and 13 developed histopathologically resolving lesions, but this favorable result was not reflected by the results of the Fernandez and Mitsuda tests since both became completely negative at the end of the drug trial.

The biopsied lesions of Cases 3, 5, 12 and 15 were BL histopathologically, yet the Fernandez reaction was completely negative in two of them and "doubtful" in the other two. Similar findings were obtained among the lepromatous cases.

With reference to the Fernandez test, four were completely negative at the preliminary period and the rest gave only "doubtful" results. The largest area of erythematous response, measuring 6 × 6 mm, appeared in Case 2, clinically diagnosed as BL3 whose biopsied lesion was BL histopathologically at the preliminary period. This reaction was reduced to 4 × 4 after one year with DDS. The two year result was not read, but the histopathologically diagnosed BL lesions at the pretreatment period became LL after two years of DDS treatment.

Case 5, diagnosed as LL (histoid lesion), had negative Fernandez reaction at the start, but became 4 × 4 after 48 weeks of treatment, as may be expected, but was reduced to a small red area (2 × 3 mm) after the 96th week.

Another patient (Case 3) with completely Fernandez negative reaction at the start of treatment, had a 48 hour reading of 2 × 2 mm after one year and 3 × 4 mm after two years of treatment with DDS.

Three other cases (Nos. 6, 7, 14) had negative Mitsuda and Fernandez reactions from beginning to end. The third one (Case 14), clinically diagnosed as lepromatous due to infiltrations present on the ear lobes, face and other parts of the body, had a localized macule on the buttocks, which was histopathologically diagnosed as indeterminate at the preliminary examination. Biopsy of the same lesion after two years of treatment with DDS showed it to be TT.

DRUG RESISTANCE TEST RESULTS

Drug resistance tests in the foot pads of mice were performed on two patients by Dr. Eduardo de la Cruz of the Leonard Wood Memorial Laboratory at the Eversley Childs Sanitarium, Cebu, because of their irregular treatment and relapse record. These two patients who had relapsed after prolonged DDS treatment and were tested for drug resistance in the mouse foot pads at the pretreatment period were found to have bacilli sensitive to 0.001% of the drug in their diet. One of them who received fairly adequate DDS treatment for a period of over a year had shown a rapid deterioration of the disease during this period. The question is raised as to whether there may be other factors responsible for lack of the response of the patient to DDS treatment besides drug resistance of *M. leprae* to DDS.

DISCUSSION

In the present drug evaluation study, it has been found that a pathologic assessment of the improvement following B663 treatment gave more significant results than either the clinical or the bacteriologic criteria employed. Furthermore, the histopath-

[3]The apparent incongruity of mixing the Cairo Congress classification symbols with those of the Ridley-Jopling designations was recognized but specifically requested by the authors; so also in Tables 4, 5 & 6. —Editor

ologic findings have pinpointed certain aspects of such studies that have not been reported on previously. These indicate the advantage of instituting a "histopathologic control" of drug evaluation studies.

The practice of "multiple biopsies" employed by one of us (J.N.R.), which was followed in the experimental group (Group I), is considered a necessary procedure in order to arrive at an exact and more advantageous type-diagnosis of cases under special study. It consists of taking two or more biopsies from lesions which clinically characterize different types of leprosy found on the same patient, or for the uninitiated, from clinically disparate lesions, instead of only one lesion selected for the pretreatment biopsy. After long experience with this method, it was found, among other things, that most BL cases were found to show histopathologically confirmed LL lesions elsewhere in the body, in addition to the usually more striking borderline skin manifestations. The type-diagnosis is based on the histopathologic findings of the predominant lesions.

Similarly, it was found by Wade *et al* [9, 10], in 1939–1940, that when biopsies were taken from patients at the lepromatous end of the borderline spectrum, multiple biopsies done especially on reacting cases may show pathologic findings corresponding to TT, BT, BB and even BL of the Ridley-Jopling classification; two or more of them coexisting in the same patient, if the lesions to be biopsied are carefully selected beforehand.

Referring to the nine cases with histopathologically confirmed BL lesions that transformed to an LL architecture after two years of treatment with either B663 or DDS, such change may be interpreted as the effect of these active drugs of converting the immunopathology of BL cases from one of at least partial granuloma formation to complete suppression of the ability of these patients to mount such response. Moreover, in spite of this presumed loss of resistance, these patients showed clinical, bacteriologic and histopathologic improvement.

In this connection, however, it should be recalled that this reversion had taken place in only one lesion from each patient and it does not necessarily reflect any changes which may have taken place in the other lesions present.

The real explanation for this phenomenon is not apparent from the results of the present study. However, it is the experience in the Philippines that many histopathologically confirmed BL lesions are in reality in a state of reaction as judged clinically by their sudden onset and rapid spread. Close clinical examination shows that such lesions are frequently associated with ordinary slightly reactive LL lesions which are not as conspicuous as the reacting ones and, as a result, are not usually selected for biopsy. The histological reversion of a lesion from BL to LL structure may, therefore, simply indicate the subsidence of a reactional state permitting the original basic lepromatous histopathology of the lesion to become apparent. This reversion can occur spontaneously with the subsidence of the reaction. Hence, this phenomenon does not necessarily reflect a true immunopathologic change.

Furthermore, cutaneous histoid lesions which lose their histopathologic structure after treatment are probably "reactive lesions." The histopathology of subcutaneous histoid nodules does not change and are, therefore, to be considered as fixed lepromata.

SUMMARY

The black pigmentation alone produced by B663 precludes its use for mass treatment of leprosy, not to mention its high cost, but it is definitely the drug of choice in cases that fail to respond to adequate doses of DDS, particularly among relapsed cases who have progressed on to an advanced stage when they consider themselves as hopeless cases beyond all relief.

Among such cases under B663 treatment, even the treatment-resistant cutaneous and subcutaneous nodules, except the fibrotic stone-hard ones, are reduced in size and many disappear completely. When such nodules, appearing around the joints of the upper and lower extremities which characterize the advanced stages of the lepromatous type in the Philippines and other countries, were biopsied, many of them showed histoid architecture histopathologically.

For reasons not established in this study, relapsed cases where histoid lepromas have failed to respond to DDS, were proven by sequential histopathologic examinations to respond more favorably to B663 than the

previously untreated cases administered with the same drug and with DDS.

No positive correlation was established between the clinical, histopathologic and bacteriologic findings and the result of the Fernandez (48 hour reading) and the Mitsuda tests (21 days) in the borderline and lepromatous cases before and after two years of treatment with B663 and DDS. No differences were observed with regard to the responses to the Fernandez reaction between the borderline and lepromatous cases, before and after two years of treatment with B663 and DDS.

For research purposes, a more accurate type-diagnosis of the cases may be arrived at by adopting the practice of "multiple biopsies" at the preliminary period. Likewise, in drug evaluation studies, "pathologic control" based on sequential biopsies starting from the preliminary period, is essential.

There is evidence to show that there may be other causes for the lack of response in lepromatous cases to the treatment with DDS besides drug resistance developed by *M. leprae*.

RESUMEN

La pigmentación roja que produce el B663 dificulta su utilización para el tratamiento masivo de la lepra, sin mencionar su elevado costo, pero es definitivamente la droga de elección en los casos que no responden a dosis adecuadas de DDS, especialmente en casos de recaída que han llegado a un estado avanzado y que se consideran a si mismos como casos sin esperanzas, lejos de cualquier posibilidad de mejoría.

En estos casos bajo tratamiento con B663, aún los nódulos cutáneos y subcutáneos resistentes a tratamiento, a excepción de los fibróticos que son duros como piedra, se reducen de tamaño y muchos desaparecen completamente. Cuando se toma biopsia de estos nódulos, que aparecen alrededor de las articulaciones de las extremidades superiores e inferiores y que son característicos de las etapas avanzadas de la forma lepromatosa en las Filipinas y otras partes del mundo, muchos de ellos muestran una arquitectura histológica histoide.

Por razones no establecidas en este estudio, los casos de recaída cuyos lepromas no respondieron a DDS, se comprobó que respondían más favorablemente al B663 que los casos no tratados previamente con la misma droga y con DDS, por medio de exámenes histológicos secuenciales.

No se estableció una relación clara entre los hallazgos clínicos, histológicos y bacteriológicos y el resultado de las pruebas de Fernandez (lectura de 48 horas) y la prueba de Mitsuda (lectura de 21 días) en los casos dimorfos y lepromatosos antes y después de dos años de tratamiento con B663 y DDS.

En trabajos de investigación, se puede llegar a un diagnóstico-tipo más exacto adoptando la costumbre de "biopsias múltiples" en el período preliminar. Asimismo, en estudios para evaluación de drogas, el "control patológico" basado en biopsias secuenciales a partir del período preliminar es esencial.

Hay evidencia que demuestra que pueden haber otras causas para la falta de respuesta de los casos lepromatosos al tratamiento con DDS, además de la resistencia desarrollada por el *M. leprae* hacia la droga.

RÉSUMÉ

La pigmentation noire produite par le B663 supprime, à elle seule, toute possibilité de l'emploi de ce produit pour le traitement de masse de la lèpre. Et ceci compte non tenu en outre de son coût élevé. Néanmoins, le B663 constitue à coup sûr le médicament de choix pour les cas qui ne répondent pas à des doses appropriées de DDS, et particulièrement les récidives qui ont progressé à un degré tellement avancé de la maladie, que ceux qui en souffrent se considèrent eux-mêmes comme des cas sans espoir pour lesquels il n'est plus possible de rien tenter.

Chez des cas de ce genre, mis en traitement par le B663, même les nodules cutanés et sous-cutanés résistant au traitement sont réduits en dimension, à l'exception des nodules fibrotiques à centre induré. Les nodules peuvent même disparaître entièrement.

Lorsqu'ils apparaissent autour des articulations des extrémités inférieures ou supérieures (ce qui caractérise les stades avancés de la lèpre lépromateuse aux Philippines et dans d'autres pays), la biopsie de tels nodules montre, chez nombre d'entre eux, une image histologique de type histoïde.

Des examens histologiques en série ont montré que les cas de récidive dont les lépromes histoïdes n'avaient pas répondu au traitement par la DDS, réagissaient plus favorablement au B663, que les cas traités pour la première fois par ce produit, ou que les cas traités par la DDS.

Aucune corrélation positive n'a pu être établie entre les observations cliniques, histologiques et bactériologiques d'une part, et d'autre part avec les résultats des épreuves de Fernandez (lecture à 48 heures) et de Mitsuda (lecture à 21 jours), dans les cas lépromateux ou borderline, avant et après deux années de traitement par le B663 et par la DDS. Aucune différence n'a été constatée en ce qui concerne les réponses à la réaction de Fernandez chez les cas borderline, comparés aux cas lépromateux, avant et après deux années de traitement par le B663 et par la DDS.

Pour des raisons de recherche, il a semblé nécessaire d'établir un diagnostic de type plus précis, en adoptant la pratique des biopsies multiples lors de la période préliminaire. De même, lors des études portant sur l'évaluation des médicaments, on considère comme essentiel un contrôle pathologique basé sur les biopsies pratiquées, dès le début de l'étude.

Certaines données suggèrent qu'il peut y avoir d'autres causes à l'absence de réponse des cas lépromateux au traitement par la DDS, outre la résistance aux médicaments développée par *M. leprae*.

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