INTERNATIONAL JOURNAL OF LEPROSY

Volume 36, Number 4
Printed in U.S.A.

Chemotherapeutic Trials in Leprosy

6. Pilot Study of the Riminophenazine Derivative B.663 in Low Dosage (100 mgm. twice weekly) in the Treatment of Lepromatous Leprosy[1]

M. F. R. Waters[2]

The riminophenazine derivative B.663, first synthesized by Barry *et. al.* ([2]), was shown by Browne and Hogerzeil in 1962, ([5, 6]) to be effective in the treatment of lepromatous leprosy. This finding has been confirmed by a number of centers ([1, 8, 10, 12, 18]). In particular, at the Leprosy Research Unit, Sungei Buloh Leprosarium, considerable experience has been gained in the use of B.663 in the treatment of relapsed lepromatous leprosy due to the development of sulfone-resistant strains of *Mycobacterium leprae* ([10]). All such patients, when treated with B.663 in the dosage of 300 mgm. daily for six days each week, have shown satisfactory clinical, bacteriologic and histologic improvement. A pilot study of B.663, given in the same dosage for five months to previously untreated lepromatous patients ([12]), produced therapeutic results that were comparable to those obtained with standard sulfone therapy. However, this dose of B.663 invariably resulted in marked pigmentation of the skin, more obvious in lighter-skinned patients, many of whom complained strongly of the discoloration. In addition a small number of patients suffered from periodic mild diarrhea. It was therefore considered essential to study the effect of B.663 in much lower dosage, both on the rate of therapeutic response and on the degree of skin pigmentation developed. The dose of 100 mgm. twice weekly was chosen, and eight lepromatous patients were included in the pilot trial.

[1] Received for publication 14 May 1968.

[2] M. F. R. Waters, M.B., M.R.C.P., The Leprosy Research Unit, Sungei Buloh Leprosarium, Selangor, Malaysia and National Institute for Medical Research, Mill Hill, London, N.W. 7, England. *Requests for reprints* should be addressed to National Institute for Medical Research.

METHOD OF STUDY

The selection of patients, the investigations performed, and the methods of assessing progress were based on protocols previously developed at the Leprosy Research Unit, Sungei Buloh ([11, 12, 17]). Eight patients were selected from untreated patients admitted to the Leprosarium. The intake was restricted to those who were fully lepromatous, i.e., patients whose histology showed no features of borderline condition ([15]), whose morphologic index (MI) was 25 or more, and who gave no history of treatment with antileprosy drugs (Case 2 may have received one injection of dapsone before admission). In addition, random tests for urinary sulfone, using the method of Bratton and Marshall ([3]), were performed throughout the period of the trial, to ensure that patients were not surreptitiously taking dapsone (DDS) in addition to the prescribed B.663.

As analysis of previous trials ([17]) has shown that the rate of response to treatment is unaffected by either sex or race; therefore all patients 12 years old and over were considered for admission. By chance, all were males; racially they included Malays, Chinese, and one Gurkha. Before commencing treatment all patients received a full clinical examination, chest x-ray, urine analysis and blood count to exclude significant intercurrent organic disease. Worm infestation was treated before the start of B.663 therapy. One patient found to be suffering from iron deficiency anemia was treated with ferrous sulfate by mouth throughout the period of the trial.

Treatment consisted of B.663, 100 mgm. twice weekly for four and a half months. Patients were examined by an independent clinical assessor both before and at the end

of the duration of treatment. Similarly, two biopsies were made on each patient at 0 and at 4½ months for independent histologic assessment. Smears were made before the start of treatment and at one and a half months' intervals throughout the trail, and were scored independently for both the bacterial index (BI) and the MI. In addition an attempt was made to assess the rate of development and the depth of pigmentation resulting from B.663 therapy; however, it proved impracticable to arrange for the investigation to be carried out on a "blind" basis, and, as a compromise, the member of the scientific staff of the Leprosy Research Unit who was not in clinical charge of the trial patients examined each one briefly once a week to note the presence or absence of pigmentation.

CASE HISTORIES

Case 1. (No. 16104) Chinese male, age 23. This patient stated that some seven to eight years before admission he developed numbness and weakness of his right hand. Two years before being admitted to hospital he noticed thickening and redness of his face, and subsequently spots and lumps developed all over his body. On examination, there was widespread infiltration of the skin, with numerous lepromatous nodules and the fingers were particularly infiltrated and thickened. On the trunk and limbs proximally were several borderline annular lesions with anesthetic centers, whose edges were not clear cut but were tending to merge with the surrounding lepromatous infiltrate. The right hand showed radial, ulnar and median nerve weakness and associated muscle wasting; encircling the right arm was an ill-defined annular lesion, distal to which the arm was anesthetic. The clinical impression was that this patient had developed borderline (BB) or even borderline-tuberculoid leprosy (BT) eight years earlier, that his resistance had subsequently fallen, and that he had now progressed through borderline lepromatous (BL) to lepromatous leprosy (LL) ([15]). The lepromin test was negative, the Mitsuda reaction measuring only 2 mm. at three weeks. The admission smears gave an average BI of 5.0 and MI of 26. The histology showed active lepromatous leprosy (LL), the logarithmic biopsy index (LIB) ([13, 14]) being 5.4. Tuberculin tests ot 1 and 20 TU were negative, both at the start and on completion of the trial.

Case 2. (No. 16107) Malay male, age 45. He gave a three year history of numbness over the right forearm and wasting of the muscles of the right hand. Twenty days before admission he developed an ulcer on his right foot. On examination there was gross lepromatous leprosy of his face and limbs although the infiltrate was not quite confluent on his back. There was symmetric mild nerve enlargement save for the right superficial radial nerve, which was considerably thickened. The intrinsic muscles of the right hand were wasted, and marked glove and stocking anesthesia was present. Clinically the patient showed classic lepromatous leprosy, and histologically he was LL. The LIB was 3.65. Admission smears gave an average BI of 5.0 and MI of 27. The lepromin test was completely negative. The tuberculin tests to 1 and 20 TU were negative on admission, and on completion of the trial the patient was still negative to 1 TU but positive to 20 TU, reading 13 mm.

Case 3. (No. 16112) Chinese male, age 54. Three years before entering hospital he noticed that his left ankle was numb. Since that time, both ankles swelled intermittently, and for two years there had been slight numbness of his right ankle. Nine months before admission he developed red patches on his face, body, and limbs, which slowly became worse. On examination he was a thin anxious man. There were multiple erythematous flattened papules and small plaques over much of the body, coalescing over the face and upper limbs but more discrete on the trunk and less numerous on the lower limbs. A large flat plaque covered the left ankle and the lower half of the left leg. Appreciation of pinprick was diminished in this plaque and over both feet. Both superficial radial and both lateral popliteal nerves were slightly enlarged. The blood pressure was 158/100 and there was an apical systolic flow murmur, although the heart was not enlarged. Biopsy revealed active lepromatous (LL) leprosy

and confirmed the presence of a mild lepra reaction (leprosy exacerbation). The LIB was 5.4, the average BI 4.7 and the MI 26. The lepromin reaction measured 4 mm. at three days and 3 mm. at three weeks. The tuberculin test was negative to 1 TU but gave a reading of 14 mm. to 20 TU; after four and one half months' treatment there was an 18 mm. reaction to 1 TU.

Case 4. (No. 16113) Chinese male, age 12. This school boy noticed a red spot on the right side of his back about one and a half years before he was admitted. He then developed red spots on his thighs and legs and subsequently on his arms, face and nose. On examination there was widespread lepromatous infiltration with scattered nodules, present especially on the face, maculopapules and plaques. Faint infiltrated annular lesions were visible on the buttocks. There was slight symmetric nerve enlargement. Appreciation of pinprick was impaired over both forearms, the left more than the right, though not on the fingers; it was impaired also over both legs and the lower part of the thighs, although sensation was preserved in the region of the insteps. The fingers were slightly swollen, and the lymph nodes were palpable. The isthmus of the thyroid was just palpable. The pretreatment biopsies revealed active lepromatous (LL) leprosy, and the LIB was 5.1. The smears gave an average BI of 4.7 and an MI of 31. The lepromin test was negative, giving a reaction of 3 mm. at three days and 0 mm. at three weeks. The tuberculin test was negative to 1 TU but to 20 TU gave a reaction of 11 mm. at the beginning and 20 mm. at the end of the trial.

Case 5. (No. 16121) Malay male, age 23. More than a year before he was admitted to the leprosarium, this patient noticed a red patch on the right side of his chest. Eight or nine months later he developed patches on his body, face and legs. Small nodules were present on both ears, whereas much of the skin of the face, body and limbs was covered with large coalescing lepromatous macules. In the upper half of the body these were mostly hyperpigmented, although some were erythematous. In the bathing-drawers area many were hypopigmented. There was fairly symmetric slight nerve enlargement. The right third toe was anesthetic. There was slight wasting of the thenar muscles, more on the right than on the left. The thyroid gland was palpable, as were the axillary and the right supratrochlear lymph nodes. The pretreatment biopsies revealed active lepromatous (LL) leprosy, and the LIB was 4.7. The smears gave an average BI of 4.3 and an MI of 29. The lepromin reaction measured 4 mm. at three days and 3 mm. at three weeks. The tuberculin test gave a reading of 13 mm. to 1 TU before treatment and 23 mm. after four and one half months.

Case 6. (No. 16123) Gurkha male, age 29. This patient stated that two and one half months before admission he developed a rash, first on his right arm, then on his legs and one month later behind his right ear. On examination he was severely pockmarked on his face and limbs. There were erythematous lepromatous plaques on his right forearm and behind the right ear. A moderate number of acute lepromatous plaques, some ulcerated, were present on the limbs and trunk. The conjunctivae were slightly reddened, and the supratrochlear, axillary and inguinal lymph nodes were moderately enlarged. The plaque on the right arm was anesthetic. The testes were slightly smaller and softer than normal, and his right ulnar, lateral popliteal, superficial radial, and left and right great auricular nerves were slightly enlarged. Biopsies of the right forearm and left thigh revealed active lepromatous (LL) leprosy, with a biopsy index of 4.9. Smears gave an average MI of 40 and a BI of 4.7. The lepromin test gave a reaction of 4 mm. at three days and 0 mm. at four weeks. The tuberculin reaction (1 TU) measured 4 mm.; at the end of the trial the reaction was negative to 1 TU, and measured 10 mm. to 20 TU.

Case 7. (No. 16124) Malay male, age 14. Six months before admission, this school boy noticed a red patch on his left elbow, and then another on his left leg. Four months later red lumps appeared on his thighs and right forearm. On examination, coalescing lepromatous macules covered most of the trunk. Scattered nodules were

present on all four limbs, chiefly on the extensor surfaces. In addition there were a few small plaques with punched-out centers suggestive of old borderline lesions that had subsequently become infiltrated and lepromatous. There was fairly symmetric moderate nerve enlargement. The centers of these lesions were anesthetic. Pinprick sensation was also impaired over patchy areas of the limbs wherever the skin was more markedly infiltrated. Biopsies of the right forearm and left elbow revealed regressing lepromatous (LL) leprosy, and the LIB was 4.4. Skin smears gave an average BI of 4.8 and an MI of 33. The lepromin test gave a reading of 4 mm. at three days and 0 mm. at three weeks. The tuberculin test was negative both on entry and at completion of the trial.

Case 8. (No. 16126) Chinese male, age 31. Two years before admission this patient developed a left foot drop and the left leg and foot became numb. Eighteen months later he noticed redness and swelling of his fingers and toes. On examination there was infiltration of his face and ears, and his fingers and toes were swollen. Scattered nodules were present, especially at the elbows, knees and heels, and over the left toes. The skin of the left calf was dry and scaly and behind the left knee the edge of an old borderline annular lesion was just visible. There was moderate nerve enlargement, especially of the left superficial radial and the left lateral popliteal nerves. The left foot drop was complete, and there was anesthesia in the left leg and foot from below the knee. The extensor muscles of the left leg were wasted and there was also slight wasting of the intrinsic muscles of the left hand. There was patchy impairment of sensation in the right leg and the right forearm. The conjunctivae were mildly injected, the testes were smaller and softer than normal, and lymph nodes were moderately enlarged. Clinically the patient was considered to have deteriorated from borderline to lepromatous leprosy. Histologically he was graded as active lepromatous (LL) leprosy and his LIB was 5.6. His skin smears gave an average BI of 4.5 and an MI of 29. The lepromin test was negative both at three days and at three weeks. The tuberculin test was negative to 1 TU; but gave a reading of 12 mm. to 20 TU; at the end of trial there was a 4 mm. response to 1 TU.

RESULTS

Clinical. During the four-and-one-half months-trial period, all eight patients were satisfied with their progress. None developed erythema nodosum leprosum (ENL), although Case 2 suffered from mild ulnar neuritis at four months. Case 3 was admitted with a definite lepra reaction (leprosy exacerbation), which only very slowly subsided, and his lesions were still erythematous at his final assessment.

The independent assessor rated the improvement as "moderate" in three patients (Cases 3, 4 and 8), "between slight and moderate" in three patients (Cases 5, 6 and 7), as "slight" in one patient (Case 2), and as "no change" in one (Case 1). However, the latter patient felt better and at three months reported that he could breathe more easily through his previously blocked nose. Moreover he (together with Case 8) was retained in the leprosarium for reconstructive surgery; B.663 was continued at the same dosage, and at one year the independent assessor considered that his improvement was "moderate."

No evidence was obtained from the random urinary sulfone tests that any patient was taking dapsone in addition to the B.663. On the other hand the skin color of all eight patients was consistent with their taking B.663, although the depth and distribution of the color change varied considerably. Thus Case 3 showed only slight B.663 discoloration after four and a half months, whereas in the other seven it was far more definite. Patients with diffuse infiltration tended to develop the typical red brown color; patients with nodular leprosy usually in addition developed hypermelanosis of the localized lesions. The discoloration was first detected about six weeks after the beginning of treatment, and insidiously but steadily deepened over the ensuing three months. The final depth of pigmentation (of either variety) was often little realized, either by the doctor in clinical charge of patients or by the medi-

TABLE 1. *Bacteriologic and histologic response of eight patients treated for 4½ months with B.663 (100 mgm. twice weekly).*

	Bacterial index (BI)		Logarithmic biopsy index (LIB)	
Case No.	At start	After 4½ months' treatment	At start	After 4½ months' treatment
1	5.0	4.8	5.4	5.15
2	5.0	4.8	3.65	3.6
3	4.7	4.7	5.4	4.7
4	4.7	5.0	5.1	4.6
5	4.3	4.2	4.7	4.95
6	4.7	4.7	4.9	5.5
7	4.8	4.7	4.0	4.95
8	4.5	4.7	5.6	5.5
Average	4.7	4.7	4.84	4.87

cal research worker who reviewed them weekly. Thus the latter considered that after four and a half months, the lesions of Case 8 were hardly darker than at the start of the trial; review of his photograph revealed that considerable color change had occurred and the patient himself complained of it at four months. The development of pigmentation as a result of B.663 therapy posed serious problems for the independent assessor, which will be discussed in a later section.

No other ill effects of B.663 were detected. Regular white blood counts remained normal throughout the trial period; Case 5 developed a ureteral calculus, which was not passed for several months, but regular urine examinations of the other seven patients were normal. No patient complained of diarrhea.

Bacteriologic. As only lepromatous patients were admitted to the trial it is not surprising that no significant fall occurred in the BI over four and a half months. Details of the results are given in Table 1.

The MI showed in every case the dramatic fall associated with effective treatment ([18]). Indeed this was already apparent at only one and a half months in five patients; by three months all eight cases showed a significant fall, and by four and a half months the MI had invariably reached the "baseline" of 0 to 2. These results confirm that even at the low dosage of 100 mgm. twice weekly, B.663 was a fully active antileprosy drug capable of killing leprosy bacilli. Details of the results are given in Table 2, and the fall of the MI is shown in Figure 1.

Histologic. Improvement during treatment was assessed by the logarithmic biopsy index (LIB) ([13, 14]) and by the histologic appearance of activity. For fully lepromatous (LL or LI) patients, the LIB is of little value for periods under six months, and individual results require at least two six-monthly periods of observation for accurate interpretation. Five patients showed a fall in their LIB over the four and a half months trial period; in three (Cases 5, 6 and 7) the final LIB was higher than the pretreatment figures. The results are recorded in Table 1.

In six patients the pretreatment histology revealed active leprosy; in two (Cases 7 and 8) the appearances were of regressing disease. After four and a half months, the histology of Case 2 was graded as "regressing," that of Case 1 as "almost quiescent, and that of the remaining six patients as "quiescent." Thus in all eight cases the disease became less active histologically.

DISCUSSION

Hitherto the lowest dose of B.663 reported in the literature has been 100 mgm. daily for six days each week ([10]). Even on this dose marked pigmentation has oc-

TABLE 2. *The effect of treatment with B.663 (100 mgm. twice weekly) on the morphologic index (MI) in eight previously untreated lepromatous patients.*

Case No.	The morphologic index (MI) after different periods of treatment			
	At start	1½ months	3 months	4½ months
1	26	30	8	1
2	27	17	1	0
3	26	6	3	0
4	31	6	1	0
5	29	9	5	0
6	40	13	6	1
7	33	8	8	0
8	29	19	6	2
Average	30.1	13.5	4.8	0.5

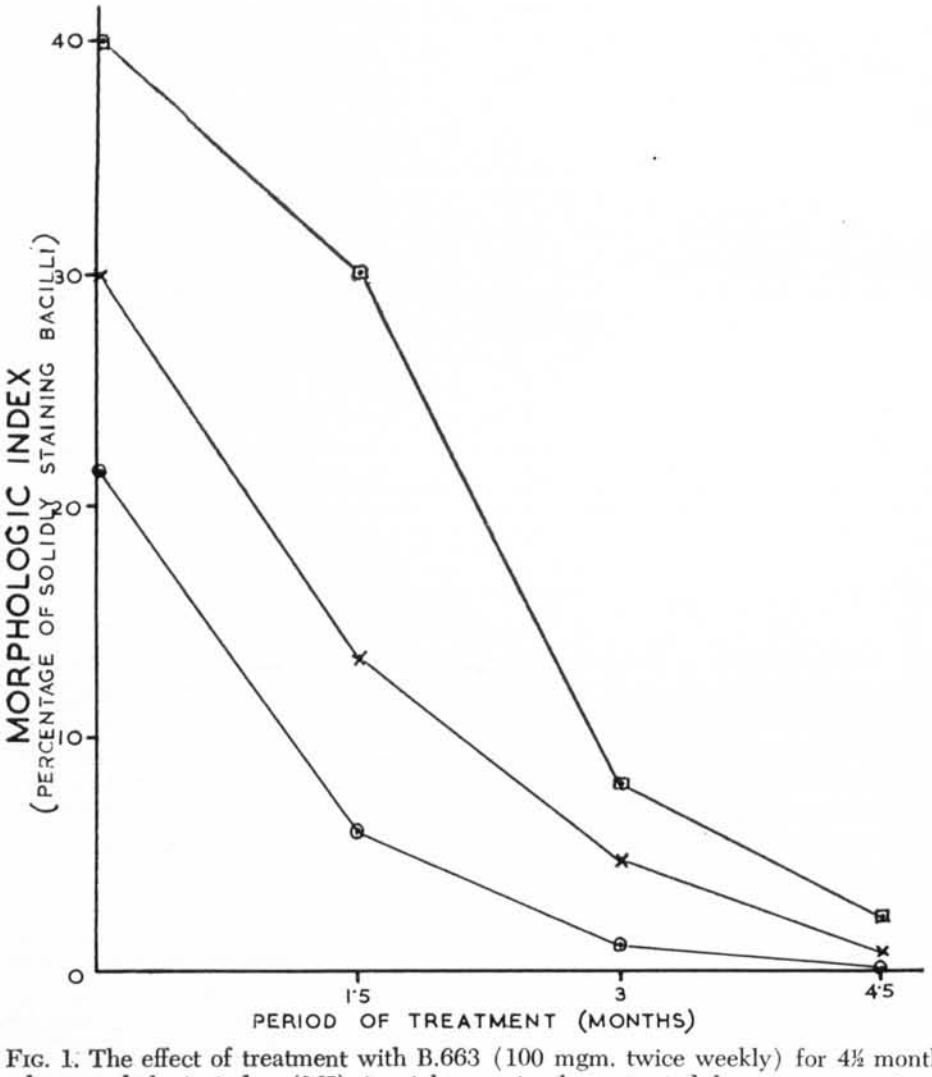

FIG. 1. The effect of treatment with B.663 (100 mgm. twice weekly) for 4½ months on the morphologic index (MI) in eight previously untreated lepromatous patients. Average MI (all 8 cases X——X; Maximum MI □——□; Minimum MI O——O)

curred in paler-skinned patients. For this reason and because of the occasional occurrence of diarrhea it was essential to investigate the therapeutic activity of still smaller doses of B.663. However, until the minimum inhibitary concentration (MIC) has been titrated in the mouse foot pad, and extrapolated to man, any further reduction in the dosage of B.663 in man must be decided empirically. For this reason the dose of 100 mgm. twice weekly was chosen, and the results here presented confirm that the drug is fully active at this level. The rate of clinical improvement was comparable to that obtained with DDS or with B.663 in higher dosage, and the rate of fall of the MI was equally rapid ([11, 12, 17]).

On the dose schedule of 100 mgm. twice weekly, no toxic effects of B.663 were detected. In particular no patient suffered from diarrhea. However, all patients developed pigmentation to a lesser or greater degree. This was usually first detected six weeks after the start of treatment, compared with one to four weeks with larger dosage ([12]). The depth of pigmentation attained by four and a half months was also definitely less than with 300 mgm. B.663 daily. Patients noticed and complained of the pigmentation, but were less troubled by it than patients receiving the higher dosage. Indeed one patient (Case 8) with foot drop was prepared at the conclusion of the trial to be discharged home and to work for three months still on B.663 before returning for a tendon transplant operation. On his return to the leprosarium his depth of skin pigmentation was unchanged and no sulfone was detected in his urine, confirmatory evidence that he continued on B.663 and that he was satisfied enough with his treatment not to take additional drugs. Although B.663, 300 mgm. daily, causes red discoloration of the urine ([10]), this was less obvious on the dose of 100 mgm. twice weekly, especially when the urine was dilute. Therefore the color of the urine on the lower dose gave less definite evidence that the drug was being taken regularly as prescribed.

Quite fortuitously, no dark-skinned patients were included in the present trial. However one dark-skinned Malay patient and one Southern Indian (Dravidian) who were excluded from the trial, the first because his MI was below 25 and the second because he was histologically BL, were each given B.663, 100 mgm. twice weekly for four and a half months. At the end of this time neither patient complained of pigmentary change and in fact little or none could be detected. In view of the various claims for the anti-inflammatory activity of B.663 ([1, 4, 7, 18]) it is also of interest to record that the latter patient developed a marked lepra reaction (leprosy exacerbation) while on B.663. The fact that none of the eight lepromatous patients included in the pilot trial developed ENL is of little significance. At Sungei Buloh ENL is rare before the MI has reached a baseline of 0-2, i.e., until afer three to six months' treatment ([17]); and in a recent trial of low dosage DDS ([11]) no ENL occurred in six patients over a similar four and a half months trial period. Furthermore there is no evidence from this small series of patients that B.663 depresses delayed hypersensitivity of the tuberculin type; indeed, in five of eight patients the tuberculin test was stronger at the completion of the trial than before treatment.

One important result of the pigmentation produced by B.663 was that the independent assessor soon realized which drug was being used in the pilot trial. Clinical assessments could therefore no longer be carried out blind. However, although there was a greater scatter in the individual assessments of clinical improvement in this trial, the average clinical improvement for the eight patients is very similar to that recorded in the immediately preceding trial of six patients receiving DDS in low dosage ([11]). But the pigmentation, and especially the hypermelanotic pigmentation occurring in localized lesions, made the latter stand out far more clearly than at the beginning of treatment. The impression given to the independent assessor was that the lesions had increased in size (which he had at first rationalized on the ground that the patients were putting on weight under the good conditions of the leprosarium) but that they nevertheless looked less active. Therefore in carrying out his assessments the

independent assessor concentrated especially on the signs of activity in lesions, viz., their degree of erythema and edema, and the succulence and smoothness of the surface. In this way bias from observing the pigmentary changes of B.663 was kept to a minimum, but because of the skin discoloration it would appear impossible to carry out a blind or double blind trial of B.663. This point should be borne in mind in any trial design ([17]), especially as a formal controlled clinical trial of B.663 compared with standard DDS therapy now appears to be highly desirable.

SUMMARY

Using a trial design previously evolved at Sungei Buloh Leprosarium, a pilot trial was performed of B.663, in the dosage of 100 mgm. twice weekly, in eight patients with previously untreated lepromatous leprosy. The therapeutic results, as measured by clinical, bacteriologic and histologic assessment, and especially by the rate of fall of the morphologic index, were similar to those obtained with sulfone therapy or with B.663 in the dosage of 300 mgm. daily.

Although B.663 pigmentation was produced in all eight patients, it developed more slowly and was less intense than with standard dosage. Difficulties resulting from skin discoloration in assessing the clinical progress of patients on B.663 are discussed.

RESUMEN

Empleando un esquema de ensayo previamente desarrollado en Sungei Buloh Leprosarium, una prueba experimental con B.663 se llevó a efecto empleando una dosis de 100 mgm. dos veces por semana, en ocho enfermos con lepra lepromatosa, no tratados previamente. Los resultados terapeúticos según una evaluación clínica, bacteriológica e histológica y particularmente por la medida de la caída del índice morfológico, fueron similares a aquellos obtenidos con terapia sulfónica o con B.663 en dosis de 300 mgm. diarios.

Aunque la pigmentación del B.663 se produjo en los ocho pacientes, ella se desarrolló mas lentamente y fué menos intensa que con la dosis standard. Las dificultades que resultan de la decoloración de la piel en la evaluación de la mejoría clínica de los enfermos que reciben B.663 se discuten.

RÉSUMÉ

On a eu recours à un plan d'essais thérapeutiques déjà mis à l'épreuve au Sungei Buloh Leprosarium, pour mener un essai pilote de traitement par le B.663, à la dose de 100 mgm. deux fois par semaine, chez huit malades atteints de lèpre lépromateuse et non traités antérieurement. Les résultats thérapeutiques, tels qu'ils ont pu être mesurés par des évaluations cliniques, bactériologiques et histologiques, et plus particulièrement par la rapidité de la chute de l'index morphologique, se sont révélés semblables à ceux qui avaient été obtenus à la suite de la thérapeutique sulfonée, ou à la suite d'un traitement par le B.663 à la dose de 300 mgm. par jour.

Quoique la pigmentation propre au traitement par le B.663 ait été relevée chez chacun des huit malades, elle s'est développée plus lentement et était moins intense qu'à la suite d'un traitement par les doses standard. On discute des difficultés qu'entraîne la décoloration de la peau pour évaluer l'amélioration clinique des malades soumis au traitement par le B.663.

Acknowledgments. The Leprosy Research Unit is administered jointly by the Malaysian Ministry of Health and the British Medical Research Council. Thanks are due to the staff and patients of the Sungei Buloh Leprosarium without whose assistance this work could not have been carried out. I am particularly grateful to Dr. K. M. Reddy for acting as independent clinical assessor, Dr. D. S. Ridley of the Hospital for Tropical Diseases, London, who carried out all the histologic assessments, Dr. J. M. H. Pearson for weekly assessments of pigmentation, Dr. R. J. W. Rees for assistance in planning the trial and subsequent discussions, and Dr. P. D. Fowler of Geigy (Manchester), for the supply of B.663.

REFERENCES

1. Atkinson, A. J., Jr., Sheagren, J. N., Barba Rubio, J, and Knight, V. Evaluation of B.663 in human leprosy. Internat. J. Leprosy **35** (1967) 119-127.
2. Barry, V. C., Belton, J. G., Conalty, M. L., Denneny, J. M., Edward, D. W., O'Sullivan, J. F., Twomey, D. and Winder, F. A new series of phenazines (rimino-compounds) with high antituberculosis activity. Nature (London) **179** (1957) 1013-1015.
3. Bratton, A. C. and Marshall, E. K. A new coupling component for sulfanilamide determination. J. Biol. Chem. **128** (1939) 537-550.

4. Browne, S. G. "B.663." Possible anti-inflammatory action in lepromatous leprosy. Leprosy Rev. **36** (1965) 9-11.
5. Browne, S. G. and Hogerzeil, L. M. B.663 in the treatment of leprosy. Preliminary report of a pilot trial. Leprosy Rev. **33** (1962) 6-10.
6. Browne, S. G. and Hogerzeil, L. M. B.663 in the treatment of leprosy. Supplementary report of the pilot trial. Leprosy Rev. **33** (1962) 182-184.
7. Hastings, R. C. and Trautman, J. R. B.663 in lepromatous leprosy. Effect in erythema nodosum leprosum. Leprosy Rev. **39** (1968) 3-7.
8. Hastings, R. C. and Trautman, J. R. (1968) Unpublished data.
9. Pettit, J. H. S. The treatment of erythema nodosum leprosum with B.663. A controlled study. Internat. J. Leprosy **35** (1967) 11-16.
10. Pettit, J. H. S. and Rees, R. J. W. Studies on sulfone resistance in leprosy. 2. Treatment with a riminophenazine derivative (B.663). Internat. J. Leprosy **34** (1966) 391-397.
11. Pettit, J. H. S. and Rees, R. J. W. Chemotherapeutic trials in leprosy. 4. Dapsone (DDS) in low dosage in the treatment of lepromatous leprosy. A demonstration pilot study. Internat. J. Leprosy **35** (1967) 140-148.
12. Pettit, J. H. S., Rees, R. J. W. and Ridley, D. S. Chemotherapeutic trials in leprosy. 3. Pilot trial of a riminophenazine derivative B.663 in the treatment of lepromatous leprosy. Internat. J. Leprosy **35** (1967) 25-33.
13. Ridley, D. S. A logarithmic index of bacilli in biopsies. 2. Evaluation. Internat. J. Leprosy **35** (1967) 187-193.
14. Ridley, D. S. and Hilson, G. R. F. A logarithmic index of bacilli in biopsies. 1. Method. Internat. J. Leprosy **35** (1967) 184-186.
15. Ridley, D. S. and Jopling, W. H. Classification of leprosy according to immunity. A five-group system. Internat. J. Leprosy **34** (1966) 255-273.
16. Waters, M. F. R. Leprosy in Malaysia and South East Asia. Internat. J. Leprosy **35** (1967) 198-201. (*Editorial*)
17. Waters, M. F. R., Rees, R. J. W. and Sutherland, I. Chemotherapeutic trials in leprosy. 5. A study of methods used in clinical trials in lepromatous leprosy. Internat. J. Leprosy **35** (1967) 311-335.
18. Williams, T. W. Jr., Mott, P. D., Wertlake, P. T., Barba Rubio, J., Adler, R. C., Hill, G. J. II, Perez Suarez, G. and Knight, V. Leprosy research at the National Institutes of Health. Experience with B.663 in the treatment of leprosy. Internat. J. Leprosy **33** (1965) 767-775. (Part 2)