Lep. Rev. (1968) **39**, 2, 61-66

A Preliminary Report on the Use of B663 in the Treatment of Chinese Leprosy Patients with Chronic Reaction

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One of the gravest problems in the treatment of the patient with leprosy is the severe reactions which may occur while under therapy. This type of reaction resulting in permanent deformity, blindness, scars and disability is more prone to occur in the lepromatous patient.

A number of methods of treatment of reaction exist at the present time, none of which is completely satisfactory. Corticosteroids have often been resorted to, but though they may produce dramatic improvement in the acutely ill they increase the problems of therapy in the long term chronic reaction patient.

It has been apparent that some anti-leprosy drugs themselves can precipitate or accentuate the reaction and so it has become the practice to reduce the anti-leprosy drug in patients with a reaction. This presents a serious problem in patients with active disease.

During the past 10 years increasing attention has been given to a phenazine derivative known as G 30-320 GEIGY (B663) 3-(p-chloranilino)-10-(p-chlorphenyl)-2, 10-dihydro-2-(isopropylimino)-phenazine which was noted to have some effect against *M. tuberculosis* in laboratory animals. This action was not of importance in man but it now appears that B663 may be very effective against other Mycobacterial diseases, including leprosy.

In 1965 several articles suggested that B663 could prevent reactions and also suppress them when fully developed. The drug also had a beneficial therapeutic effect in eliminating the bacillus. However, the drug did tend to produce a pigmentation of the skin.

In November, 1966, a small supply of the drug was received and a patient was selected for trial.

Patient 1 (M.W. F/25)—Diagnosed as borderline leprosy in 1955, her lesions subsided rapidly and after about 2 years' therapy the treatment was discontinued. By 1961 she was an obviously lepromtous type patient with a B.I. of 5.2. On admission here she improved fairly rapidly for 9 months with a B.I. fall from 5.2 to 4.3 and then reaction started and continued relentlessly. B.I. fall was from 4.3 in June, 1963, to 3.8 in November, 1966, and most of 1966 she spent in bed with bouts of ulceration, iritis, neuritis, bone pain and high fever.
When B663 commenced, with 300 mgm. weekly, her B.I. was 3.8, M.I. 0%. Within 3 months the B.I. had fallen to 3.0 and she had only occasional ENL, no pain, no ulceration, no fever and no iritis. She was lightly pigmented but not obviously so. She returned to light work and later (after 6 months on B663) to full work. By the end of 6 months her B.I. was 2.5 and she was obviously pigmented but generally very well except for mild crops of ENL without pain or fever, occurring about once a month.

Requests were received from other patients who wished to have B663. Obviously the pigmentation was no real barrier to the patients with chronic reaction who wished to get better. The success with this patient, and the requests by other patients, prompted a trial on a larger scale.

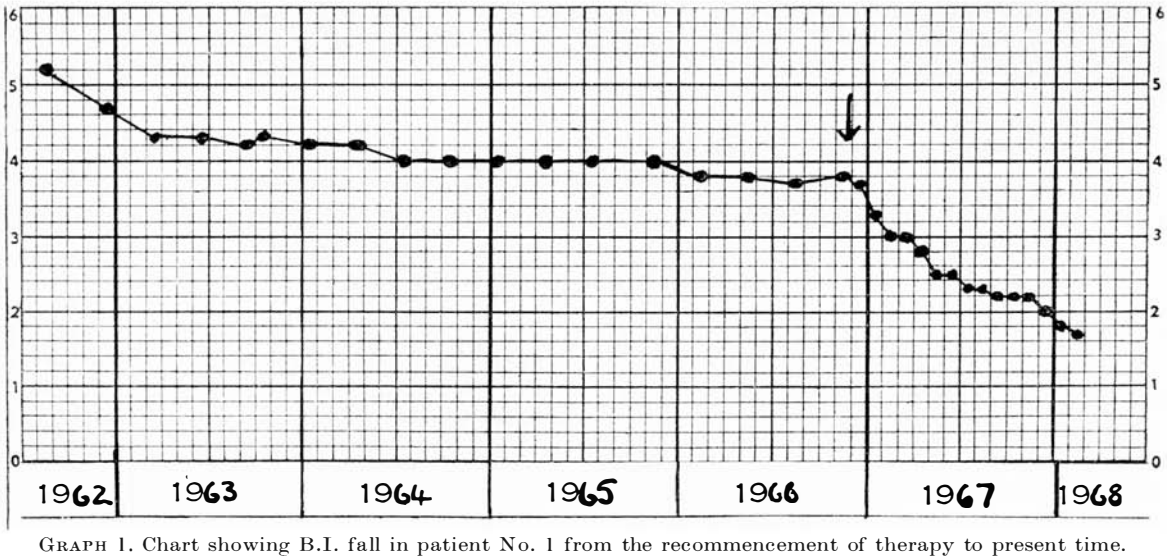
AIM OF THE TRIAL

It was decided that this suppressive effect should be further examined and also that, if possible, the minimum dosage that will control reaction should be ascertained. With this in mind, supplies of B663 were applied for and patients selected.

SELECTION OF PATIENTS

All patients under in-patient care were examined, taking into consideration:

(1) Reaction type, severity and frequency.
(2) Progress so far under treatment—especially rate of fall of B.I.
(3) Drugs used previously for leprosy therapy.



GRAPH 1. Chart showing B.I. fall in patient No. 1 from the recommencement of therapy to present time. Arrow indicates commencement of B663 at dose of 300 mgm. per week.

A total of 30 patients were selected as suitable. All had been under in-patient treatment for at least 2 years with reaction, so their previous responses and reaction pictures were well known. All had M.I. of 0% solid rods, except one patient who had recently relapsed.

They were all basically lepromatous though some had atypical features. None had a definite positive lepromin test.

Five had previously had treatment with good results and then ceased therapy against advice and relapsed, becoming highly positive.

Four were on prednisolone at the beginning of the trial.

Four patients had had leprosy for at least 20 years—the longest for 25 years with intermittent therapy.

Eight had pulmonary tuberculosis though all of these were now controlled; 3 were not receiving TB drugs any longer and the other 5 were still receiving INAH and PAS.

Ten patients had previous episodes of gastritis or frank gastric ulceration. One had had a gastrectomy for duodenal ulceration.

Two were diabetics, being controlled on Diabinase, in whom reaction was associated with diabetic instability.

PROCEDURE

All other anti-leprosy drugs were stopped when B663 was started. At about the time B663 was commenced colour photographs were taken, under controlled conditions, of each patient to record colour change.

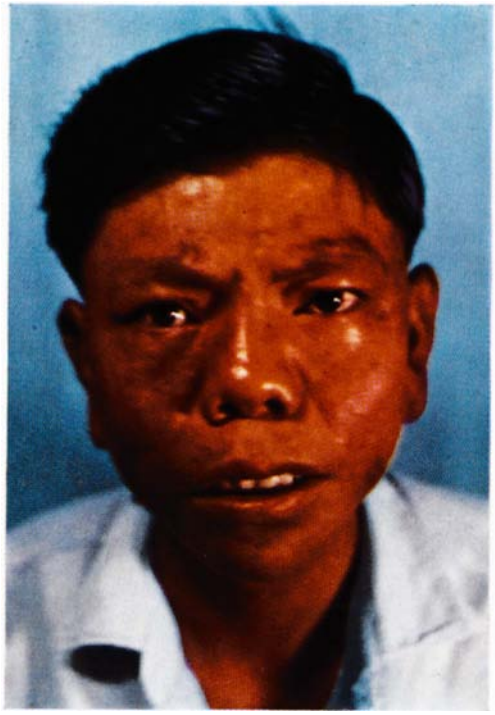
During the trial, skin smears were taken each month by the same experienced technician and a report given on Bacillary Index (Ridley reading) and Morphological Index. Haemoglobin and urine tests done each month; full blood counts, E.S.R. serum proteins, electrophoresis, and liver function tests were done each 3 months.

Most patients commenced therapy with 300 mgm. B663 per week. The more severely reacting patients, including some on Prednisolone, commenced on 600 mgm. B663 per week.

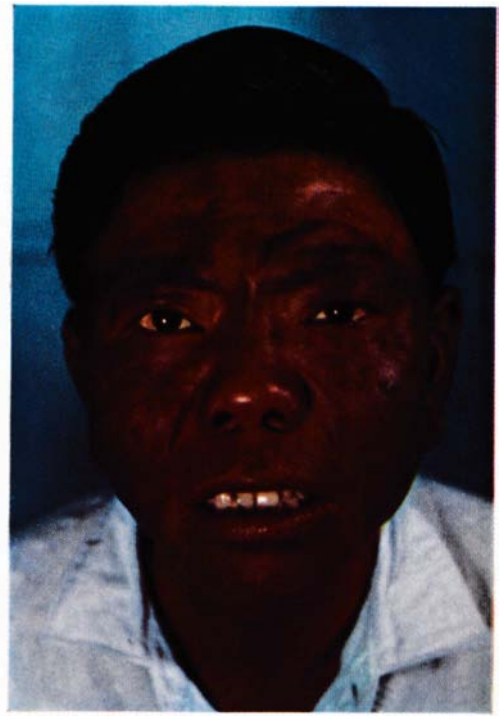
No change was made in other drugs given for preventing or reducing reaction. A careful check was kept on all patients in the trial and if reaction continued the dosage of B663 was increased until the level was found where reaction was no longer present, and then the other anti-reaction drugs were reduced and once the patient had been reaction free for one month at least the B663 was gradually reduced.

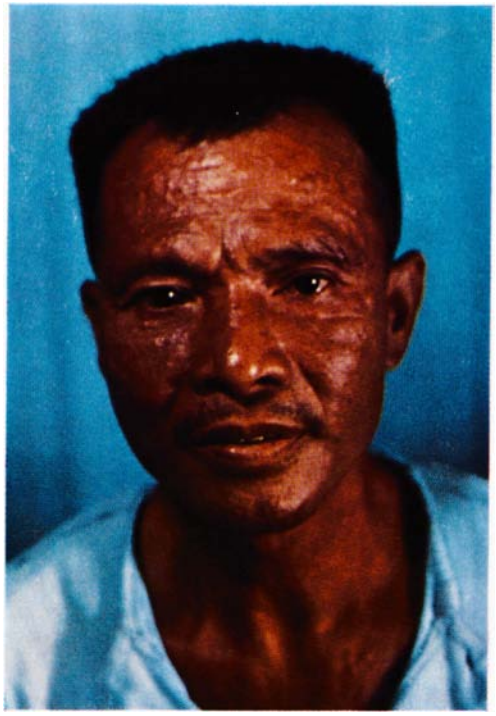
It was found that most patients became reaction free on 600-900 mgm. per week, a few requiring 1,200 mgm. per week, while a number of patients did very well on 300 mgm. per week.

Patient 11
Pre-B663 therapy.



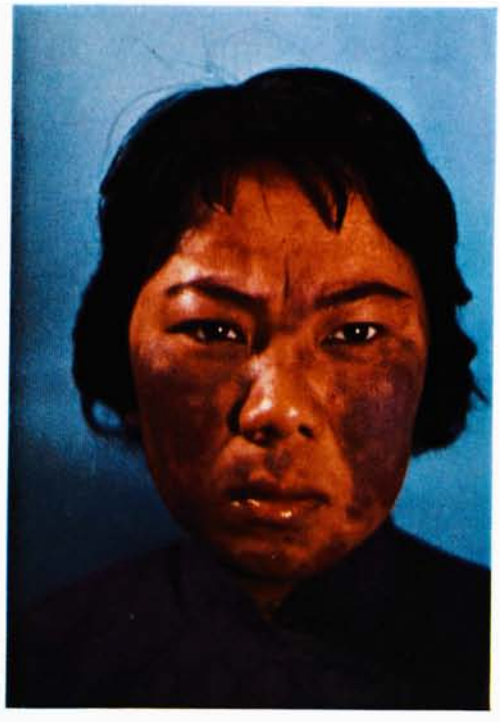
Patient 11
After 6 months B663 therapy, showing very dark pigmentation.



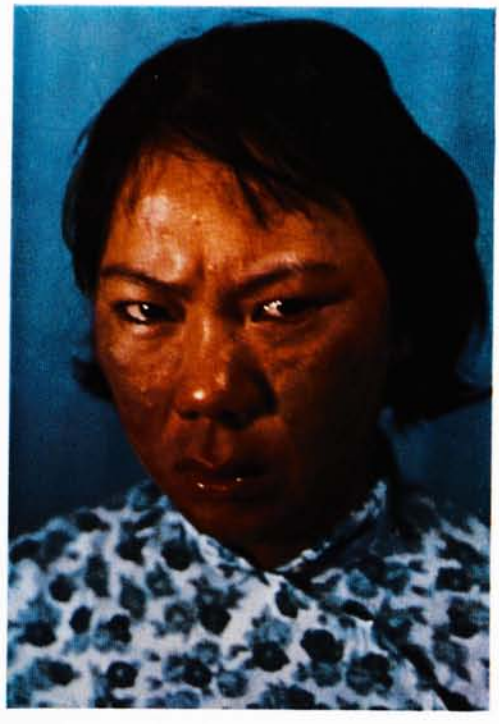


Patient 13
Pre-B663 therapy, showing nodules on face.

Patient 13
After 6 months B663 therapy, showing marked clearing of the skin, and light to medium pigmentation.



Patient
Pre-B663 therapy.



Patient 15
After 6 months on B663, showing marked variation in pigmentation of the skin.

GROUPS

The 30 patients selected fit into 5 main groups.

A. Four patients on prednisolone.

B. Sixteen patients with generalised chronic reaction (excluding mainly neuritis)—skin lesions, ENL and generalised reaction, iritis, bone pain and fever. Some of these were also receiving drugs for treatment of tuberculosis.

C. Seven patients whose reaction was mainly neuritis—chronic pain and tenderness, with or without paralysis.

D. Two patients with diabetes as a pre-precipitating cause of reaction—placed in separate group because of interlink of reaction and uncontrolled diabetes.

E. One case of relapse—new lesions, rising skin smear with return of normal morphology.

RESULTS AFTER 6 MONTHS OF B663 THERAPY

Group A

Four patients on prednisolone, 3 female and one male. Average weight 99 lbs. Three out of 4 patients were easily weaned off prednisolone within 4 months once adequate B663 was given to control reaction.

All 4 patients are obviously much better clinically and in all there has been some improvement in B.I. but this has not been marked.

Patient 1 (F/30)—On prednisolone 10 weeks only but had previously had several courses—B.I. fall 3.3 to 3.2, clinically better, ulcers healed and less pain when on B663, 1,200 mgm. per week.

Patient 2 (F/46)—On prednisolone from September, 1966, requiring 15 mgm. daily to control reaction and prevent ulceration. Received 900 mgm. B663 weekly as maximum. Now off prednisolone for 2 months and reaction free—B.I. fall 2.0 to 1.7.

Patient 3 (M/35)—Many courses of prednisolone over last 10 years—was on 5-10 mgm. daily from November, 1965, to October, 1967. Received 900 mgm. B663 weekly and now off prednisolone and reaction free—B.I. fall 2.2 to 1.7.

Patient 4 (F/35)—Long history of irregular therapy and courses of corticosteriods. On prednisolone from June, 1966, till now—up to 20 mgm. daily at times. Severe reaction on October, 1967, was complicated by infected ulcers and B663 increased to 1,200 mgm. weekly in November, 1967. Mild reaction continued till December. Prednisolone is now reduced to 5 mgm. daily and no reaction. B.I. fall 2.8 to 2.5 in 6 months is above average for this patient, whose physical condition is much better than it has been for the last 18 months.

Group B

This group comprised 16 patients. These were: 4 females aged 28-40 years and weight average 96 lbs., and 12 males with ages 21-53 years and weight average 114 lbs.

The group is divided into sub-groups according to the amount of B663 needed to control the reaction.

(*a*) Those patients requiring 300 mgm. B663 per week:—There were 3 patients (2/F, 1/M) who required only 300 mgm. of B663 per week. The B.I. fall was excellent in each patient, 3.7 to 3.0, 2.7 to 1.7 and 1.5 to 0.5. None of these patients became deeply pigmented. One who had previously tended to have ulcers and pain constantly rapidly improved and has not had ulceration or pain for the past 5 months.

(*b*) Those patients requiring 600 mgm. B663 per week:—There were 9 patients in this group (3/F, 6/M). The B.I. fall also very good, averaging 0.9 over 6 months, with a maximum fall of 3.3 to 1.5 in the 6 months. In some of this group the pigmentation was very obvious though in others it did not appear to be unnatural.

(*c*) Those patients requiring 900 mgm. B663 per week:—There were 3 patients in this group, each of whom had severe lepromatous leprosy of long standing. All showed good clinical improvement and decreasing reaction and pain once the higher dosage was reached. The B.I. fall was 2.5 to 2.3, 3.0 to 2.0 and 3.7 to 2.8. The third patient had previously shown a B.I. fall of only 4.8 to 3.7 in 27 months while constantly suffering reactions, pain, iritis and neuritis. He is now reaction free.

(*d*) One patient who required 1,200 mgm. B663 per week:—
A patient who had stopped his therapy in 1960, when he was previously progressing well. After 18 months without treatment he returned because of reaction and a high B.I. He spent the next 5 years in and out of reaction, with fever, pain, ulceration and neuritis—frequently very depressed and uncooperative. Since starting B663 his general condition has been improving and since he took 1,200 mgm. weekly he has been reaction and pain free and has become co-operative and cheerful: in short a changed personality.

This group included a number of patients receiving therapy for pulmonary tuberculosis who are still taking INAH and PAS. There is no obvious difference in their response to that of the others in the trial.

TABLE 1 **Progress of Patients in Group B**

Patient No.	Sex/Age	Minimum Duration of Leprosy years	Duration of Regular Therapy years	Duration of Reaction years	Maximum Dose of B663 mgm.	At Commencement Weight lbs.	At Commencement B.I.	B.I. at 3 months	At 6 months Weight lbs.	At 6 months B.I.
6	M/50	13	3	3	300	105	2.7	2.0	123	1.7
7	F/35	23	5	5	300	92	1.5	1.0	102	0.5
8	F/60	16	3	3	300	88	3.7	3.2	98	3.0
9	F/43	5	3.25	3.5	600	105	2.7	2.2	112	1.8
10	M/21	7	4	4	600	108	3.3	2.3	122	1.5
11	M/27	8.5	4	3	600	109	2.0	1.8	118	1.5
12	M/35	6	4.25	5	600	106	3.5	3.2	107	2.8
13	M/49	7	5	5.5	600	125	1.5	1.2	132	0.8
14	M/44	6	5	5	600	1 11	2.5	2.0	124	1.3
15	F/28	9	3.25	3.5	600	95	3.5	3.0	106	2.5
16	F/55	5	4	5	600	108	1.2	0.8	107	0.5
17	F/49	6	4	3.5	600	130 (oedema)	4.0	3.8	111	3.5
18	M/53	30	2.25	4	900	130	3.7	3.0	154	2.8
19	M/31	12	5	4	900	118	2.5	2.3	120	2.3
20	M/38	13	11	5	900	120	3.0	2.3	126	2.0
21	M/38	10	4	4	1,200	88	3.0	2.7	98	2.2

TABLE 2 **Progress of Patients in Group C**

Patient No.	Sex/Age	Minimum Duration of Leprosy years	Duration of Regular Therapy years	Duration of Reaction years	Maximum Dose of B663 mgm.	At Commencement Weight lbs.	At Commencement B.I.	B.I. at 3 months	At 6 months Weight lbs.	At 6 months B.I.
22	M/41	11	2.5	4	600	114	2.5	2.0	126	1.5
23	M/41	25	5	5	600	109	2.3	2.0	116	1.7
24	M/33	12	6	6	600	106 (oedema)	2.3	1.8	104	1.7
25	F/36	8	6.5	6	900	96	1.5	1.0	110	0.5
26	M/40	4	3.5	4	900	105	2.0	1.8	103	1.7
27	M/26	9	3	5	900	102	3.5	3.2	104	3.0
28	M/37	15	3	3	1,200	108	4.2	3.5	106	3.0

Group C

Mainly neuritis.

This group comprised 7 patients (6 male and one female) in whom the main form of reaction was neuritis and in whom the B.I. fall was slow.

(*a*) Those patients requiring 600 mgm. B663 per week:— There were 3 patients in this group and their B.I. fall was better than usual—average fall 0.7 in 6 months.

(*b*) Those patients requiring 900 mgm. B663 per week:— There were 3 in this group and the B.I. fall averaged 0.6 in the 6 months. All became free of neuritis.

(*c*) One patient who required 1,200 mgm. B663 per week:—
This dose was not given in the first 3 months, and it is difficult to assess if he really needed to receive such a high dose as he has an unstable personality. His B.I. fall has been dramatic, from 4.2 to 3.0 in 6 months, whereas previously the fall was from 4.5 in 1964 to 4.2 in 1967.

In all these patients there has been no increase in obvious muscle weakness or loss since commencement with B663. One of these patients with a bad history of irregular therapy required 900 mgm. to control neuritis. He stopped his own B663 therapy in December for 2 weeks and neuritis returned. It required a further 4 weeks to eliminate pain again and a few weeks later, when pain returned, it was discovered he was only taking 100 mgm. daily instead of 200 mgm. as ordered. Since resuming the higher dose pain has again disappeared.

Group D

Two diabetics, both men.

Mr. G, aged 65, weight 166 lbs.

Mr. K., aged 46, weight 106 lbs.

Mr. G. had received intermittent therapy for over 20 years. On admission even small doses of routine drugs aggravated reaction, except Vadrine. B.I. fall from 5.0 to 4.3 over 3 years with M.I. fall of 25% to 0%. On B663 the B.I. fall was from 4.3 to 3.8. The patient's diabetes is stable, and he is obviously better and says so; he has had no real reaction since he commenced B663 and urine has remained sugar free. However, nodulation of his hands has returned over the last 3 months since Streptomycin was stopped.

Mr. K. has diabetes (controlled by Diabinase), pulmonary tuberculosis and a gastric ulcer and has also had chronic reaction with ulceration and iritis since 1965. B.I. has fallen 3.3 to 3.0 on B663 at 600 mgm. weekly but the patient generally feels very well and no problems with diabetes or gastric ulcer.

Group E

Male patient aged 35.

He commenced therapy in 1962 but was always reactive and had early attacks of neuritis and acute paralysis. Smear came down gradually between 1962 and 1967 and then became stationary at B.I. 1.8 in spite of continued drug therapy. In July, 1967, new lesions appeared with an increase in B.I. from 1.8 to 4.0 and return of over 10% normal form bacilli. 900 mgm. B663 weekly resulted first in a M.I. fall from 10% to 0% in 12 weeks and then a B.I. fall from 4.0 to 3.7. Clinically he is well, with no return of neuritis or reaction.

SIDE EFFECTS

Apart from the skin pigmentation no undesirable complication has occurred. Only one patient complained of gastric discomfort, but this eased when he took B663 with his meals instead of 'on an empty stomach'.

No appreciable difference in response has been noticed in patients under treatment for tuberculosis or other intercurrent disease.

Some patients complained of marking of their clothes. Reddening of the urine was not constant and only occurred in patients on high dosage, but some women stated that while washing their hair the water became red.

DISCUSSION

All patients selected had set patterns of neuritis and generalised reaction which had persisted for at least 2 years prior to the commencement of this study, and which had not responded to routine methods of therapy. In 6 months on B663 the progress of these patients has been extraordinary. Some of them rapidly became reaction free and remained so. A few developed reaction in the first few weeks and some continued with mild reaction until the dosage was raised and an adequate dosage was given. Only one patient had had a bad reaction and this reaction was less severe than previous reactions that she had experienced.

The E.S.R. for many of the patients showed a dramatic fall, e.g., 94 mm. to 30 mm., 108 mm. to 20 mm., and 120 mm. to 33 mm., but in some patients the E.S.R. did not change significantly.

Initially many patients showed abnormal Albumin-Globulin ratios and changes in the proportions of serum proteins, but this ratio tended to correct itself and the serum proteins resumed their normal proportions.

Most patients showed increase in appetite and increase in body weight.

As the change from anti-leprosy drug to B663 was the only common factor, it would appear that B663 is, in fact, effective in reducing and controlling reaction and at the same time it appears to encourage a more rapid rate of clearance of the acid-fast debris as shown by the increased rate of fall of the B.I. in so many patients. It has previously been shown that the B.I. fall in Chinese lepromatous patients can be expected to average 1.0 per annum in the B.I. range 6.0 to 1.0. Hence a fall of greater than 0.5 in the 6 months under review exceeds the estimated average.

Subjectively the patients are much improved, they seem happier, more cheerful and more inclined to activity. This is mirrored particularly by the better attendance at physiotherapy and general co-operation.

DOSAGE LEVEL

It was found that 9 patients required 900 mgm. weekly, 13 patients required 600 mgm. weekly and 3 patients required only 300 mgm. weekly to control reaction. There were only 4 patients who required 1,200 mgm. weekly and of these 4 there were 2 who had received prednisolone for a long time. The one patient who received 1,800 mgm. weekly was a very chronic patient of heavy weight and on an mgm./lb. basis his dosage correlates well with the others. Hence it would appear that the average Chinese patient

of about 90-120 lbs. weight can be controlled on 600-900 mgm. weekly depending on the severity of the reaction. It has also been noted that once reaction is controlled it is sometimes possible to reduce the dosage level of B663, though if the dose is reduced very quickly reaction will reappear, but can again be controlled by increasing the dosage of B663 again.

CONCLUSIONS

Chronic lepra reaction in typical and atypical lepromatous leprosy in Chinese patients can be controlled by the use of B663.

Patients previously on corticosteroids can be weaned off them while on B663.

The patients' general physical condition improves, they look better, eat better, sleep better and even say they are better.

The dosage appears to be between 600 and 900 mgm. per week in patients of average weight (90-120 lbs.) to control reaction, but that once reaction is controlled the dosage may be reduced and the patient will continue to progress well.

The Bacillary Index falls rapidly suggesting that B663 assists in the clearance of the acid-fast debris, but the rate of fall differs in different patients.

There is a correlation between the weekly dosage of B663 and the severity of the skin discolouration. Ths patients on low dosage showed less discolouration and patients who had showed deep pigmentation showed some fading of the pigmentation when the dosage was reduced. It has been reported (Ahrens) that the pigmentation, considered one of the main disadvantages, is reversible and so is not a contra-indication to the use of this drug. Certainly skin discolouration is not a disadvantage in an institution, or to patients who know of the complications and disappointments of other therapeutic drugs and who wish to recover their health as soon as possible.

There certainly seems to be a place for the regular use of B663 in the treatment of chronic reaction patients and investigations and trials should be continued to clarify the situation and the optimum dosage.

SUMMARY

A study of the effects of B663 in a group of 30 Chinese leprosy patients with chronic reaction has been commenced. Over a period of 6 months it appears that B663 is of definite value in this type of patient and that skin discolouration is not a major problem.

ACKNOWLEDGEMENTS

Special thanks go to Messrs. J. R. Geigy S.A. for generous supplies of B663 and for much helpful advice, and to Dr. S. G. Browne who assisted with the selection of patients and other details. Also to the patients and staff who have co-operated in this trial.

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