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TREATMENT OF TRICHURIASIS WITH DITHIAZANINE IN A HOSPITAL FOR MENTAL DEFECTIVES

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Since the publication of our preliminary report (Paine *et al.*, 1959) on the treatment of six patients known to be infected with trichuriasis, it has been possible to plan a controlled trial experiment with dithiazanine and arrange a full-scale treatment programme of all whipworm carriers at Coldharbour Hospital.

While the preliminary trial appeared to provide evidence of the efficacy of dithiazanine against human trichuriasis, the number of patients treated was small, and it was thought that the results might have been influenced by previous trials with other anthelmintics. Moreover, no control group of patients had been studied and there had been no long-term follow-up examinations to determine the possibility of relapse or reinfection.

Controlled Trial

Method

Twenty-four patients known to be infected with whipworm were chosen, 12 being selected for treatment with dithiazanine and 12 to serve as controls. Some attempt was made to match the individual patients for treatment and control in respect of their pre-treatment egg counts, and it was possible to allocate an approximately equal number with light and medium infections to each group. No claim is made, however, that a patient's whipworm load can be estimated from his faecal egg count.

The treatment group received dithiazanine orally, as "telmid" tablets, in the same dose as that used in the preliminary trial—that is, 200 mg. three times a day for five days, regardless of age and weight. The patients' weights in this trial ranged from 60 to 151 lb. (27 to 68.5 kg.). In view of the possible association between vomiting and failed treatment in the preliminary trial, the five-day course of dithiazanine was extended on this occasion by one additional 200-mg. dose of the drug for every dose interval when vomiting occurred. A tendency to constipation had been noted in the previous trial, and patients in both treatment and control groups therefore received two "senokot" tablets on each of the five treatment days, followed by two tablets three times weekly for the next two weeks.

Pre-treatment egg counts were carried out by the Stoll (1947) technique, since this method gives some indication of the severity of the whipworm infestation. Ten days after the completion of treatment, further faecal examinations were made by De Rivas's (1928) concentration technique, giving either positive or negative results only.

From the first day of treatment, a careful search was made for the adult whipworm, all faecal specimens being examined for 10 days, and, thereafter, one specimen weekly for three weeks. The worms were immediately placed in distilled water at room temperature, where they remained for 24 hours so that any motility might be noted.

All patients were observed for possible side-effects, and ward records were kept of the four-hourly temperatures, daily blood-pressures, and the incidence of vomiting and diarrhoea in each case. Pyrexia was taken to mean an axillary temperature of at least 99° F. (37.2° C.), and temperatures were recorded over a period of three weeks, commencing two days before treatment. Blood-pressures were taken for a 10-day period, also beginning two days before treatment. Vomiting was charted once for each dose interval in which it occurred, and diarrhoea when two loose motions occurred in one day.

Possible toxic effects from dithiazanine were investigated by means of haematological examinations, blood-urea levels, serum-protein estimations, and urine tests, before and after treatment; the post-treatment examinations being carried out between one and three weeks after the cessation of treatment. From two days before treatment, urine specimens from all patients were tested daily on the ward with "albustix" and "clinistix" for a period of three weeks, and any abnormal findings were sent for laboratory confirmation.

None of the patients selected had received anthelmintics during the two years preceding this trial.

Results

The results of the faecal egg counts are given in Table I. With one exception (Case 4), all the patients under treatment were rendered negative and all patients in the control group remained positive. Adult worms were recovered from all patients in the treatment group, but none from patients in the control group. The whipworms were discovered in faecal specimens between the third and sixth days of treatment, none being found thereafter. The worms were examined for motility, but all appeared to be non-viable. On the third day of treatment threadworms were seen in specimens from six patients in the treatment group.

Of the clinical findings shown in Table II, vomiting appears to be the only significant complication. This occurred in 7 of the 12 patients receiving dithiazanine but not at all in the controls. An analysis of the days

on which vomiting occurred shows that four of the seven patients vomited on the first day, four on the second day, two on the third day, one on the fourth day, two on the fifth day, and one on the sixth day of treatment. There was thus a tendency for patients to vomit more on the first and second treatment days, but one patient vomited a second time on the sixth day, and another on the fifth day only. Pyrexia did not occur except in Case 7 of the control group. This patient showed a transient rise of temperature before an epileptic convulsion. Diarrhoea was general, and this may be related to the routine administration of senokot tablets as described above; and the transient lowering of systolic and diastolic blood-pressures in a number of cases may also be attributed to the same symptom.

TABLE I.—*Results of Treating Trichuriasis with Dithiazanine, Showing the Egg Carrier State Before and After Treatment and the Number of Adult Worms Recovered. Comparative Findings are Given for Untreated Controls*

Case No.	Pre-treatment Egg Counts. Average per Gramme of Faeces. Stoll Technique	Post-treatment Examination of Faeces for Trichuris Eggs. De Rivas's Concentration Technique	No. of Adult Trichuris in Stools	Threadworms Present in Stools
		Treatment Group		
1	100	—	46	—
2	200	—	6	Present
3	600	—	11	—
4	900	Present	12	Present
5	3,200	—	10	—
6	3,600	—	18	Present
7	4,900	—	7	—
8	5,200	—	23	Present
9	5,400	—	131	,,
10	6,800	—	121	—
11	7,400	—	35	Present
12	9,200	—	92	—
		Control Group		
1	<100	Present	—	—
2	100	,,	—	—
3	500	,,	—	—
4	500	,,	—	—
5	700	,,	—	—
6	1,400	,,	—	—
7	1,400	,,	—	—
8	1,400	,,	—	—
9	1,500	,,	—	—
10	2,000	,,	—	—
11	4,700	,,	—	—
12	5,800	,,	—	—

TABLE II.—*Clinical Side-effects of Treating Trichuriasis With Dithiazanine, Showing the Incidence of Pyrexia, Fall of Blood-pressure, Vomiting, and Diarrhoea in Treatment and Control Groups*

Case No.	No. of Days When Pyrexia Occurred	Treatment Days When Systolic and Diastolic Blood-pressures Fell by 10 mm.	No. of Dose-intervals When Vomiting Occurred	No. of Days When Diarrhoea Occurred
		Treatment Group		
1	—	—	2	5
2	—	—	1	1
3	—	2nd	6	6
4	—	5th	—	1
5	—	—	1	4
6	—	2nd, 4th, 9th	1	2
7	—	—	—	1
8	—	1st, 6th	—	4
9	—	2nd	—	3
10	—	6th	12	1
11	—	—	—	2
12	—	2nd, 4th	2	2
		Control Group		
1	—	2nd, 8th	—	4
2	—	1st	—	2
3	—	—	—	1
4	—	6th	—	2
5	—	9th	—	5
6	—	—	—	3
7	1	—	—	1
8	—	6th	—	1
9	—	—	—	3
10	—	1st	—	1
11	—	—	—	2
12	—	—	—	4

The results of the laboratory examinations, shown in Tables III and IV, provide no evidence of toxicity. The

TABLE III.—*Results of Haematological Examinations Before and After Treating Trichuriasis With Dithiazanine. Findings are Given for Treatment and Control Groups*

Case No.	Pre-treatment Examinations: Hb (%)	Total White Cells	Description	Post-treatment Examinations: Hb (%)	Total White Cells	Description
			Treatment Group			
1	87	4,900	Normal	99	8,500	Normal
2	90	9,600	6% eosinophils. Otherwise normal	108	9,000	,,
3	81	7,600	Normal	91	6,000	,,
4	84	8,200	,,	92	7,000	,,
5	73	7,000	,,	100	6,400	,,
6	84	5,000	,,	94	4,600	,,
7	84	9,700	10% eosinophils. Otherwise normal	81	7,600	7% eosinophils. Otherwise normal
8	92	6,800	Normal	110	5,600	Normal
9	81	8,200	,,	78	6,800	,,
10	78	10,000	6% eosinophils. R.B.C.s hypochromic and microcytic	81	8,400	,,
11	87	7,100	Normal	103	11,000	,,
12	87	8,600	,,	85	9,000	,,
			Control Group			
1	95	10,600	Normal	89	8,600	Normal
2	84	7,400	,,	114	9,900	,,
3	78	5,200	R.B.C.s hypochromic. Differential white cells normal	87	6,800	,,
4	80	9,700	Normal	87	10,400	,,
5	90	6,100	,,	86	8,400	,,
6	64	6,400	R.B.C.s microcytic. Differential white cells normal	92	10,200	,,
7	76	9,000	Normal	83	7,200	,,
8	87	8,200	,,	91	6,000	,,
9	78	7,600	7% eosinophils. Otherwise normal	77	6,600	,,
10	95	5,600	Normal	95	8,200	,,
11	95	5,400	,,	73	7,000	,,
12	87	8,300	No film	84	11,600	,,

TABLE IV.—*Results of Blood Urea, Serum Protein, and Urine Examinations Before and After Treating Trichuriasis With Dithiazanine. Findings are Given for Treatment and Control Groups*

Case No.	Pre-treatment Examinations: Blood Urea (mg./100 ml.)	Serum Protein (g./100 ml.)	Urine	Post-treatment Examinations: Blood Urea (mg./100 ml.)	Serum Protein (g./100 ml.)	Urine
			Treatment Group			
1	30	5·4	—	49	6·7	—
2	44	6·1	Trace albumin and sugar	48	6·5	Trace albumin
3	31	6·8	—	48	6·4	—
4	51	6·8	—	52	7·0	—
5	33	6·0	—	37	6·5	—
6	45	6·8	—	37	6·5	—
7	31	7·0	—	37	6·8	—
8	21	6·1	—	43	6·7	—
9	51	6·7	—	46	7·0	—
10	40	6·7	Trace albumin and sugar	37	6·5	Trace albumin
11	36	7·2	—	45	7·2	—
12	24	5·5	Trace albumin	32	6·5	Trace albumin
			Control Group			
1	41	7·2	—	42	7·2	—
2	51	7·2	—	52	6·8	—
3	48	5·4	—	46	6·1	—
4	48	6·5	—	35	6·5	Albumin, epithelial cells, scanty R.B.C.s
5	36	6·1	Trace albumin	40	6·3	Trace albumin, occasional polymorph
6	32	6·8	—	38	6·5	—
7	32	7·3	—	36	6·7	—
8	25	7·2	—	40	6·7	—
9	52	6·5	—	43	6·5	—
10	30	7·2	—	36	6·8	—
11	35	7·4	—	40	7·2	—
12	31	6·8	—	48	6·3	—

figures for haemoglobin and total white cells (Table III) and for blood urea and serum protein (Table IV) were within normal limits before and after treatment. Abnormalities in the urine (Table IV) occurred in certain patients from the treatment group, but also in some of the controls, and, in any event, these proved to be transient changes possibly associated with an intercurrent infection in the ward.

Conclusions

The controlled trial experiment confirms the impression gained from our preliminary trial that dithiazanine iodide, given as an oral dose of 200 mg. three times daily for five days, is an effective anthelmintic against human trichuriasis. Not only is the faecal egg count reduced to zero in a high proportion of cases, but it seems that adult worms also are eliminated by the sixth day of treatment.

The use of a laxative concurrently with dithiazanine in this trial did not significantly alter the rate of egg clearance observed in the preliminary trial (11 of 12 patients cleared of eggs as against five of six in the preliminary trial). Since the combined use of dithiazanine and a laxative failed to achieve total egg clearance, other methods of treatment should be considered.

In agreement with the findings of Swartzwelder *et al.* (1957), no worms recovered from treated patients showed motility after immersion in distilled water; but, since further experiments with nutrient media were not carried out, no evidence was obtained as to viability.

Apart from the occurrence of vomiting in more than half of the patients treated, the trial shows an apparent absence of clinical side-effects in mental defectives (see below). A tendency for vomiting to occur during the first two days of treatment is noted.

From the results of haematological examinations, blood-urea levels, serum-protein estimations, and urine tests, dithiazanine appears to be non-toxic in the dosage used in this trial.

Mass Treatment Programme

At the close of the controlled trial experiment it was decided to extend the treatment programme to cover all possible whipworm carriers in the hospital. While trichuris eggs are sometimes found in faecal specimens from the general population, and while a hospital population may be open to reinfection from outside sources, it seemed reasonable to plan a full-scale treatment programme with dithiazanine if concurrent disinfection of the hospital buildings and grounds were arranged. Any risk of subsequent reinfection from outside sources would be covered by routine egg counts from new admissions and other possible contacts.

Preparation for Mass Treatment

Of the 154 patients resident, only 81 were known to be whipworm carriers; but it was decided to treat all patients simultaneously, so that any who might have been whipworm carriers despite a negative faecal egg count should also be freed from the infestation. The hospital staff had not been examined previously for whipworm, but shortly before the mass treatment of patients was due to begin selected members of the staff, known to have been in contact with infected patients, were asked to submit specimens of faeces. From the first 12 members of the staff examined, one was found to be whipworm-positive; and two more positive results were reported from a further group of specimens. All staff working at the hospital were then asked to take part in a mass treatment programme, and each of the small minority who declined sent three specimens for testing; all were shown to be whipworm-negative. Three staff dogs were tested for whipworm, but were all reported negative. Though it is known that the human and canine forms of whipworm are distinct species, the dogs were examined to extend the search for possible carriers.

The destruction and removal of trichuris ova from the hospital estate and buildings presented a major problem. As moisture is favourable to embryonation, the various methods of disinfection which depend on antiseptic solutions were regarded as unsuitable. Samples of soil from the hospital estate had failed to show the presence of trichuris ova, but it was decided to burn with flame guns all hospital roadways and areas of grass that had been liable to contamination by patients. The wards, and the hospital buildings where whipworm carriers had been accommodated, were to be cleaned systematically with vacuum cleaners, and any ward floors and other surfaces that had been wax-polished would be cleaned with turpentine 24 hours beforehand. All the patients' furniture, bedding, clothes, books, and small equipment would be cleaned by vacuum, and selected items would be sterilized by autoclave also. The disposable paper containers and filters from the vacuum cleaners would be destroyed daily in the hospital incinerator.

Four empty wards, considered free from trichuris ova, would be made ready to accommodate the patients while their regular wards were being cleaned.

Method

Several days before the mass treatment was due to begin, all staff had been issued with a five-day course of dithiazanine tablets, to be taken as from the first treatment day. Staff on leave during the mass treatment were advised to complete the course before returning to duty.

Also before treatment, vacuum-cleaning had been started in a small annexe of single rooms to be made available for a group of patients specially selected for kitchen duties during the treatment programme.

On the first treatment day all patients were confined to their wards to receive a five-day course of dithiazanine tablets. The same dosage was used as in the control trial, and, on this occasion also, treatment was continued by one additional 200-mg. dose of dithiazanine for every dose interval when vomiting occurred. Records of vomiting and observations regarding general health were kept in the ward, but in view of the results of our controlled trial experiment other possible side-effects were not specially considered. Two weeks after cessation of treatment every patient's urine was tested with albustix and clinistix and any abnormalities were sent for laboratory confirmation (see below).

On the fifth day of treatment arrangements were made to transport all the patients to temporary accommodation. The selected kitchen workers were taken to the small annexe already described, and the remaining patients removed to the empty wards prepared for them. The flaming of the hospital roadways was carried out in sections to provide, at an early stage, "clean" routes between the regular wards, the kitchen unit, and the temporary accommodation. Kitchen dustbins were also flamed at this time.

Before leaving his regular ward each patient was bathed. He was then wrapped in a clean blanket and conveyed by wheel-chair to his temporary abode. On being received into this unit he was provided with a cleaned and vacuumed set of clothes by the nurses awaiting his arrival. Nursing staff entering the temporary wards left their shoes on the threshold and used a second pair for duty in the "clean" area.

All the patients continued in this temporary accommodation until their regular wards had been cleaned throughout, but after a 10-day absence the last patient was returned. By this time the main part of the hospital roadways had been flamed, and there was direct access to the wards and other departments. Many patients therefore returned to their usual occupations, and normal arrangements for holidays were resumed. Vacuum-cleaning of the occupational and recreational departments continued until three weeks after the patients had returned to their regular wards, and, on account of heavy rainfall, it was six weeks later before the contaminated areas of grass had been burnt with flame guns.

Post-treatment faecal examinations were made by De Rivas's (1928) concentration technique, with which even scanty ova will return a positive result. Specimens were sent to the laboratory from all patients and staff, including the small minority who had not accepted treatment; and, since more than 200 examinations were required, about 20 specimens were dispatched each week over a 10-weeks period. Any patient or staff returned positive received a further five-day course of dithiazanine tablets, and this was followed by the examination of further specimens of faeces. About three months after the mass-treatment programme had begun the situation was reviewed, and the immediate results of treatment were assessed. Six months after the mass treatment a second survey of faecal specimens was begun in order to obtain the long-term results of treatment. Intermediate examinations were made also in certain cases where relapse from treatment had occurred previously.

Reference has already been made to any side-effects observed in the patients during mass treatment. Members of the staff who had received dithiazanine were asked to describe their reactions. Their symptoms were then listed under vomiting, diarrhoea, constipation, malaise, headache, and "no complaints," and the main trends noted. It was appreciated, however, that there had been no control group amongst the staff, and that only tentative conclusions were possible.

Results—Patients

Three months after mass treatment started it was possible to make the first survey of results. 82 patients were known to have been positive at some time before mass treatment (18 of these had been treated with dithiazanine at a previous trial). Of the 64 whipworm carriers who had not received previous treatment, 54 (84%) became negative after one five-day course of dithiazanine. By including the patients treated at previous trials (since they had therefore received two courses of dithiazanine), it was found that 76 (93%) of the 82 whipworm carriers had become negative after two courses of treatment. Similarly, 81 (99%) of 82 became negative after three courses of treatment, the remaining patient requiring four courses before he became negative. At the time of the three-monthly review, therefore, all patients had become negative for whipworm as judged by the results of faecal examinations.

Nine months after mass treatment, when the results of the second survey were known, the long-term findings were assessed. Of the 82 patients originally positive for whipworm, nine had shown trichuris ova in faecal specimens examined since the three-monthly review. This represented a relapse of 11% from the immediate results of mass treatment. Further courses of dithiazanine tablets were given to the nine patients until they were all returned negative; four patients requiring one repeat course, four patients two, and one patient three repeat courses of treatment. The time interval between a patient's last negative specimen and his next positive specimen was noted in all relapsed cases, as this interval may be used in distinguishing between relapse from treatment and reinfection, by reference to the life-cycle of the whipworm. Since embryonation for three weeks outside the host and maturation for three months within the host are both needed to complete the egg-laying cycle, a "negative-to-positive" interval of less than 16 weeks would almost exclude the possibility of reinfection. Even when a fully embryonated egg enters the host immediately before treatment, a negative-to-positive interval of less than 13 weeks will still exclude reinfection. Some of the patients relapsed more than once, and there were in all 14 "negative-to-positive" intervals, eight of which were less and six more than 13 weeks. In considering these time intervals, however, allowance should be made for the delay arising from the long-term review of cases. All patients were reported negative for whipworm at the nine-monthly review, and further specimens two months later, from the relapsed cases, still gave negative results.

No attempt was made to count the adult worms in faecal specimens during the mass treatment, though many were observed.

Of the 154 patients receiving dithiazanine in the mass-treatment programme, 61 (40%) vomited. When the occasions of vomiting were analysed according to the treatment day, it was found that 40 occurred on the first day, 25 on the second, 25 on the third, 11 on the fourth, 27 on the fifth, 4 on the sixth, and 1 on the seventh day of treatment. As in the controlled trial experiment, there was a general tendency for patients to vomit in the early stages of treatment, but in a certain number of cases the reverse applied. No patient showed any other significant side-effects, and there was no diarrhoea.

When tested after mass treatment, 15 patients not included in the control trial showed traces of albumin and other minor abnormalities in the urine, but on further testing these changes proved to be transient and apparently unrelated to the administration of dithiazanine tablets.

None of the 82 patients originally found to be positive for whipworm had shown symptoms or signs attributable to the infestation, and after this treatment programme there was no obvious evidence of improved health in any of the patients receiving dithiazanine; but mental defectives do not readily complain of minor subjective symptoms.

Results—Staff

After the pre-treatment examination of specimens, two whipworm carriers were found who had been in contact with infected patients and one carrier who attended to the hospital drains. All three had been employed at the hospital for several years. Soon after the completion

of mass treatment, however, a new member of the staff was appointed who was found to be whipworm-positive. In this case there had been no previous connexion with the hospital, and the individual concerned lived several miles away in a small village. None of the staff responded to the first course of dithiazanine tablets, but one responded to the second course, another to the third course, and the third became whipworm-negative after four courses of treatment. The fourth member of the staff was given eight courses of dithiazanine tablets without effect, and as he was a regular consumer of alcohol (mainly cider), complete abstention was advised for one week, to be followed by a ninth course of treatment. This resulted in a series of negative faecal specimens without further relapse. The member of the staff who had required four courses of treatment returned a positive specimen at the nine-monthly review, but in this case one additional course of dithiazanine was followed by negative specimens.

Of the 56 staff who received dithiazanine tablets, 19 (34%) complained of vomiting, and in four cases this was severe enough to cause absence from work. 27 (49%) complained of diarrhoea and 21 (40%) had definite malaise. Less frequent were complaints of constipation (six cases) and headache (five cases). 27 members of the staff (49%) experienced a sense of general apathy which they associated with taking the tablets. 12 of the staff (23%) claimed that they were unaffected by the treatment.

Discussion

Swartzwelder *et al.* (1957) have demonstrated that satisfactory results are to be obtained from treating human trichuriasis with dithiazanine, and in our preliminary report (Paine *et al.*, 1959) we confirm these findings. Our controlled trial experiment and mass-treatment programme have been designed to discover whether patients with positive trichuris egg counts can be finally cleared from the infestation, and whether a partially closed community, such as a hospital for mental defectives, can be freed from whipworm by the use of dithiazanine.

The results described above provide evidence that about 80% of whipworm carriers show negative faecal specimens after one five-day course of treatment with dithiazanine. Failed cases may receive further treatment without apparent risk of toxicity. Our results have shown also that, while three courses of treatment produced negative faecal specimens in 99% of cases, a further review after six months may demonstrate return positives in 11% ; which will again respond, however, to further treatment with dithiazanine. The number of courses of treatment originally required to render a patient whipworm-negative has little influence on his tendency to relapse, since three of our relapsed cases first became negative after a single course of treatment and six after several treatments.

Relapse from treatment may be distinguished from reinfection by the negative-to-positive interval, which will exceed 13 weeks (or 16 weeks in most cases) if reinfection has occurred. These intervals are explained by the embryonation and maturation periods of the whipworm. On this basis the nine " return positives " at our long-term review were probably cases of relapse from treatment. Relapse would seem to imply that the whipworm has been protected in the body from the full effects of dithiazanine, and our case which failed to respond to treatment until alcohol was withheld suggests that this substance may enable the worm to withstand the effects of the dye.

Dithiazanine has been associated with vomiting in all our treatment trials, this occurring in 40% of patients and 34% of staff in the mass-treatment programme. Since there has been a general tendency for vomiting to occur early in treatment, some improvement might be expected if a smaller dose of dithiazanine were given during the first two days. In a proportion of cases, however, vomiting was increased on the fifth day of treatment, both in the controlled trial and in the mass-treatment of patients. Whether the response to treatment would be affected by a smaller initial dosage of dithiazanine is open to question, and, in this connexion, one should consider the risk of producing dithiazanine-resistant whipworms by undertreatment. We would prefer that vomiting should be minimized by the prophylactic use of one of the anti-emetic drugs now available.

It is of interest that the whipworm carriers at Coldharbour Hospital included one member of the staff who was found to be whipworm-positive without having had any previous connexion with the hospital or a history of travel abroad. One of us (T. V. C.), who has worked in this area for 20 years, has found that symptomless trichuriasis is endemic but comparatively uncommon.

No conclusions can be drawn regarding the effectiveness of the general measures to remove trichuris ova from the hospital buildings and grounds, since it was not possible to treat a control group without these precautions. To have provided such a control would have invalidated the treatment programme for the whole hospital, and, while we are without proof that these general measures were successful, there is no evidence that any case of reinfection occurred.

Summary

The treatment of trichuriasis with dithiazanine was studied in a hospital for mental defectives by means of a controlled trial with 24 patients, and this was followed by a mass-treatment programme which included 154 patients and 56 members of the staff. 80% of positive cases became whipworm-negative after one five-day course of dithiazanine, and after three such courses 99% showed negative faecal specimens.

Transient vomiting is the only side-effect of the treatment, and dithiazanine is without any demonstrable toxic effects.

The hospital was free from the infestation many months after the beginning of treatment.

We thank the nursing, artisan, and technical staff, who, by their unremitting efforts and co-operation, contributed so largely to the success of this treatment programme. We are grateful to Eli Lilly and Co. Ltd. for supplying " telmid " tablets and for a generous grant from their American Research Fund.

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