tant features are early complete replacement of the lost blood in all patients, and emergency surgical operation in selected cases.

Employment of this method led to a halving of the mortality rate at Christchurch Hospital.

The results in a series of 93 admissions compare favourably with those reported in the literature.

We acknowledge with gratitude the help of Mr. J. T. Murray, hospital biochemist, who standardized and supervised the blood-volume estimations and made many important contributions to our work; and of Drs. A. F. Burry and A. V. Kurta, who assisted throughout the course of these investigations. The following surgeons and physicians were in charge of the patients included in the experimental series: M. H. Aiken, L. A. Bennett, W. H. Bremner, P. W. Cotter, W. M. Cotter, J. K. Davidson, H. E. H. Denham, D. McK. Dickson, M. K. Gray, J. F. Landreth, D. G. Radcliffe, and W. L. F. Utley. Without their help and co-operation this work could not have been undertaken.

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ARSENAMIDE TREATMENT OF FILARIASIS DUE TO *W. BANCROFTI* AND *A. PERSTANS*

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Arsenamide is a trivalent arsenical, and has the formula: $(\text{COOH} \cdot \text{CH}_2 \cdot \text{S})_2 = \text{As} \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{CO} \cdot \text{NH}_2$. It was first employed in the treatment of *Wuchereria bancrofti* infections by Thetford *et al.* (1948), when they reported the treatment of six cases. Since then the compound has been used by various other workers as summarized in the discussion below. This paper describes the results obtained in the arsenamide treatment of 37 cases of filariasis in Gambia, British West Africa, and the action of suramin in two trypanosomiasis patients whose blood contained *bancrofti* microfilariae.

Methods.—Four groups of cases were investigated: (1) Two cases of yaws were treated under close observation in the ward as a preliminary test for tolerance. (2) Eleven cases of filariasis were treated in the ward under similar close observation. (3) Twenty-one cases were treated in a village; among these there was one fatality due to acute hepatic necrosis. (4) Five cases were treated in the ward with low doses and special

precautions against toxic effects. For the present work the drug was supplied in 5-ml. ampoules of 2.5% buffered solution.

Group 1. Two Cases of Yaws

Case 1.—A man aged 46 complained of pain all over the body. He weighed 60 kg. He was given one intravenous injection of 5 ml. arsenamide, followed the next day by one injection of 7.5 ml. and then 10 ml. daily for 10 days (2 mg./kg. arsenamide, 3 mg./kg., and then 4 mg./kg.). He vomited after the fifth and sixth injections; occasionally a trace of albumin was found in the urine. During treatment he lost 3 kg. in weight, which he subsequently regained. His previous symptoms cleared up.

Case 2.—A man aged 25 had ulcers on the legs and on an arm. He weighed 66 kg. He was given the same injections as in Case 1 (1.9 mg./kg. arsenamide, 2.8 mg./kg., and then 3.8 mg./kg.). He did not vomit at all, but lost 2 kg. in weight, which was regained; occasionally a faint trace of albumin was found in the urine. The ulcers cleared up rapidly.

These cases suggested that 10 ml. of the solution (approximately 4 mg./kg.) daily would be tolerated. The dose level which was adopted for the trial against *W. bancrofti* was half this—namely, 5 ml. (about 2 mg./kg.) daily for 12 days.

Group 2. Cases of Filariasis Treated in Hospital

Eleven cases were treated in the research ward at Fajara. On admission the patients were examined clinically for any contraindication to treatment; and then two or three days were allowed to elapse so that the microfilaria cycle could settle after the change in habits. At 10 p.m. on the evening before the injections of the drug were to begin, two lots of 20 c.mm. blood were taken from the finger-tip and spread on a slide for enumeration of microfilariae in the usual way. Throughout the trial all the slides were examined and the microfilariae enumerated by one of us (J. A. McF.). All subsequent measured quantities of blood in the cases treated in the ward were taken within a few minutes of 10 p.m. Conditions were further standardized by all the injections being given in most cases within a few minutes of 10 a.m. The urines from these cases were examined daily for albumin, each patient was weighed daily, and a watch was kept for any signs of toxicity of the drug, particularly vomiting.

Results

Table I records the microfilariae counts of the 11 patients treated in the ward. Four to five days after the first injection the total number of *bancrofti* microfilariae had decreased by 22%; at nine days it had decreased by 86%; and at 12 days the total reduction was 98%. Subsequently, only occasional microfilariae were found in the blood of these patients. Finally, when the last blood samples were taken (at six months) all the patients were free from microfilariae except for one who still had two microfilariae per 40 c.mm., and one who still had one microfilariae per 40 c.mm. (at three months).

In eight of the patients *perstans* microfilariae were also present initially; 70–200 days after treatment their total numbers were reduced by 70%, and in four the blood became negative.

Toxic Features

Vomiting.—Three patients vomited occasionally. One other patient (Case 10) vomited a quarter to three hours after each injection; she was receiving the largest dose per kg. of body weight, and treatment was stopped.

Headache (4 cases).—This is difficult to assess, as it is a common complaint among Africans.

Signs of Death of Adult Worms or Allergic Reactions.—Two patients had pyrexia. One other patient developed enlarged tender glands in the axilla and one developed a tender epididymis.

Loss of Weight (1 case).—This was the patient (Case 10) who vomited considerably.

TABLE I.—Treatment of 11 Cases of Bancroftian Filariasis (Group 2) in Hospital by Arsenamide, 125 mg. Daily

Case No.	Age	Weight (kg.)	No. of Injections	Bancrofti Microfilariae per 40 c.mm. (<i>M. perstans</i> in parentheses)							
				Start	Day 4-5	9	12	26	40-60	70-100	200-250
1	28	55	12	67 (115)	48 (67)	9 (58)	4 (62)	4 (53)	0 (23)	0 (39)	—
2	50	55	12	40 (124)	26 (125)	6 (125)	5 (98)	1 (167)	0 (46)	0 (50)	—
3	30	65	12	399 (4)	461 (8)	72 (7)	7 (11)	1 (8)	4 (4)	1 (4)	—
4	40	58	12	73 (63)	63 (70)	10 (73)	0 (30)	0 (39)	0 (37)	—	0 (10)
5	17	42	12	302 (7)	336 (10)	31 (4)	0 (5)	0 (0)	0 (0)	0 (1)	0 (0)
6	40	62	10	459 (41)	—	24 (49)	0 (25)	—	1 (11)	0 (6)	0 (0)
7	18	61	12	580 (19)	454 (14)	107 (10)	24 (6)	—	4 (3)	0 (1)	0 (0)
8	16	49	12	808	518	75	3	—	1	1	0 (0)
9	50	48	12	231 (1)	107 (0)	76 (2)	9 (0)	—	0 (0)	2 (0)	2 (0)
10	50	41	9	117	22	—	0	—	0	0	—
11	25	54	12	103	75	—	1	—	0	—	—

The days are recorded after the first injection. Cases 5 and 10 were females, the rest males.

Damage to Liver (1 case).—In one patient (Case 6) the temperature rose, finally reaching 104° F. (40° C.) after the tenth injection; two days later he vomited repeatedly; and the next day he developed jaundice, with bile and albumin in the urine. He made a satisfactory recovery, and one month later was much improved. It was difficult to assess the cause of the jaundice, as it was possible that there was either previous liver damage or a coincidental infective hepatitis, both of which are fairly common in Gambia. Since the patients previously treated had showed no other toxic features the trial was continued; and subsequently five more cases were treated satisfactorily in the ward.

Albuminuria did not occur in any of the patients, apart from the one case noted above.

Group 3. Cases Treated in a Village

Twenty-one cases of filariasis were selected for treatment in a village which had been previously surveyed. Heavy infections were chosen. Each patient was examined clinically. The projected dose schedule was a daily injection of 5 ml. for 12 days. Since the lowest weight of any patient selected was 50 kg. no patient received a dose greater than 2.5 mg. of arsenamide per kg. daily. After the group had received 10 injections, however, treatment was discontinued because one of the patients died (see below). The injections were given between 6 and 7.30 p.m., after the villagers had returned from their work in the fields. They were given intravenously and slowly with the patients lying down. Urine specimens were examined for albumin before treatment, and 3, 6, 9, and 15 days after the first injection. All patients were weighed before and after the course of injections. On the evening before the injections were begun, measured quantities of blood were taken as described above, between the hours of 10 and 11 p.m. Any information on

toxic features volunteered by the villagers was recorded, and direct questions were asked only after the course was completed.

Results

Table II records the microfilariae counts of these patients. In all the blood samples taken two weeks after the first injection, only a single *bancrofti* microfilaria was found. Sixteen of these patients had received 10 injections of arsenamide, but 2 had 9 injections, 1 had 8, and 1 had only 5. Seven months after treatment the blood of all the patients was free from *bancrofti* microfilariae. Two of these patients also contained appreciable numbers of *perstans* microfilariae in the blood; one patient became negative.

Toxic Features

Vomiting (7 cases, 33%).—One patient vomited after each injection, while the others vomited only occasionally.

Diarrhoea.—Four people complained of occasional loose stools during the course of injections. This feature is difficult to assess; it was not noted in the cases treated in the ward.

Dizziness occurred in two cases.

Generalized Pain.—One person complained of pains all over the body. This is a common complaint in Africans, and was probably associated with yaws.

Signs of Death of Adult Worms or Allergic Reactions.—One person developed a filarial abscess on the medial aspect of the thigh which subsequently broke down and discharged thick creamy pus; one developed a bilateral hydrocele; one had a transient enlargement of the scrotum; one had an enlargement of the epididymis. Several days after the injections had ceased one person developed weals on the skin associated with pruritus which cleared satisfactorily with mepyramine maleate.

Loss of Weight.—One person lost 3 kg. (associated with vomiting) and one lost 3.5 kg. (not associated with vomiting).

Signs of Liver Damage.—One man died from liver damage after receiving only three injections of the drug; this case is described in detail below. Another man developed jaundice four and a half weeks after the last injection; a fresh dry sterilized syringe and needle had been used for each injection, so this jaundice could not have been due to the passage of a virus.

Albuminuria did not occur in any case. The drug did not leak from a vein on any occasion.

The Fatal Case

The patient, a man aged 55, weighed 53 kg. He was given three daily injections of 5 ml. (2.4 mg./kg.). After the third injection he vomited and complained of vague retrosternal pains. The symptoms were mild and hardly seemed sufficient to contraindicate further treatment; but no more injections were given. Two days afterwards he felt well; but later that night developed pain in the back of the neck, staggered, and was unable to stand or sit up. This was reported next day, when the investigator returned to the village and found that the patient was comatose.

TABLE II.—Treatment of 21 Cases of Bancroftian Filariasis (Group 3) in a Village

Case No.	Age	Weight (kg.)	No. of Injections	Bancrofti Microfilariae per 40 c.mm. (<i>M. perstans</i> in parentheses)					
				Start	Weeks				
					2	5	12	17	30
14	35	65	10	228	0	1	0	0	0
16	38	56	10	52	0	0	0	0	0
17	40	70	10	65	0 (1)	0	0	0	0
18	37	67	10	185	0	0	0	0	—
19	21	31	10	132	0	0	0	0	0
20	60	62	10	141	0	0	0	0 (1)	0
21	45	68	10	284 (1)	0 (2)	—	—	—	—
22	50	61	10	35	0	—	0	0	0
23	40	31	10	116	0	0	0	0	—
24	35	61	10	166	0	0	0	0	0
25	35	50	10	141	0	0	0	0	0
26	25	64	10	21 (67)	0 (3)	0 (7)	0 (2)	0 (6)	0 (0)
27	28	65	10	263 (9)	1 (4)	1 (4)	0 (3)	0 (2)	0 (3)
31	50	67	10	59	0	0	0	0	0
32	35	52	10	652	0	0	0	0	0
28	36	58	10	1,337	0	0	0	0	0
29	55	50	9	64	0	0	0	0	0
30	18	63	9	132	0	0	0	—	—
13	36	61	8	230	0	0	0	0	0
15	35	50	5	834	0	0	0	0	0
12	55	53	3	19	Dead	—	—	—	—

The weeks are recorded after the first injection. Cases 13, 15, 19, 20, 23, 25, and 32 were females, the rest males. The dose was 125 mg. arsenamide per patient daily.

On admission to the ward he was still comatose but able to move his limbs. Reflexes were present and normal. Lumbar puncture showed: no increased pressure, Queckenstedt's test normal, Pandy's test positive, 60 lymphocytes per c.mm. No trypanosomes seen. Blood pressure, 230/120 mm. Hg. Urine contained no albumin or bile. There was some doubt whether or not he had a slight icteric tinge, but African observers considered that the colour of his conjunctivae was normal. Dimercaprol and penicillin were given, but he developed the signs of basal pneumonia and died four days later.

Post-mortem Findings.—The liver weighed 880 g. and was stained yellow, the kidneys 170 g. each, and the heart 284 g.; there was some atheroma of the heart and aorta. The urine contained no appreciable amounts of bile salts or pigments. **Histology.**—In the liver were numerous areas of recent focal damage from which most of the parenchymal cells had disappeared; there was considerable proliferation of fibroblasts, but no evidence of pre-existing cirrhosis. In the kidneys, the cells of the cortical nephrons showed the appearance of massive necrosis (part of this appearance could have been due to post-mortem autolysis); many of the medium and small arterioles showed medial fibrosis and irregular intimal thickening. It is concluded that death was due to widespread necrosis of the liver.

Group 4. Cases Treated with Low Doses in Hospital

The experience with the fourth group of patients indicated that although large doses of arsenamide were therapeutically effective they might also have dangerous toxic effects. Accordingly an investigation was made to discover whether a much lower dose, which would be small enough to be safe, might yet be sufficient to produce cure. For this purpose five patients were treated with strict precautions against toxic effects—namely, the dose was 0.3 mg./kg. daily (only one-eighth of that previously used), the patients were kept under careful supervision in hospital, and they were given 50 g. of dry skim-milk daily (protein-rich supplement) in addition to good hospital diet, so as to fortify the liver against the toxic effects of arsenic. No toxic effects were observed; and the therapeutic results are shown in Table III. Reduction of the microfilaria count was much

TABLE III.—Treatment of 5 Cases of Bancroftian Filariasis (Group 4) with 0.3 mg. Arsenamide per kg. Daily

Case No.	Age in Years	Weight (kg.)	No. of Injections	Bancrofti Microfilariae per 40 c.mm. (<i>M. perstans</i> in parentheses)			
				Start	Day 14	80	155
33	26	54	14	83	112	26	17
34	24	51	14	52	65	66	3
35	15	37	14	13	12	5	1
36	9	25	14	111	131	120	102
37	40	48	14	104 (58)	54 (21)	—	—

Case 35 was male, the rest females.

slower than it had been with large doses. Of the four patients who could be followed for five months the count was greatly reduced in two cases and probably the microfilariae will eventually disappear; in one case the count fell to a quarter of its original level, and in one case there has been no appreciable change. Thus the filaricidal effect of 0.3 mg./kg. daily, although considerable, is not completely satisfactory. From this small group of patients it might be deduced that 0.6 mg./kg. would be the minimum effective dose.

Treatment with Suramin

Suramin is very effective for the treatment of onchocerciasis, in which it kills the adult worm (Wanson, 1950). As regards its action on *W. bancrofti*, we have not found any reports which include an adequate follow-up of the patients for several months, to see whether the microfilariae disappeared. Such late disappearance would suggest that the adult worms had been killed or sterilized. Accordingly the

opportunity was taken of observing the action of suramin in two patients with trypanosomiasis whose blood also contained *bancrofti* microfilariae.

Case A.—A man aged 45, weight 60 kg., was given 1 g. of suramin intravenously on December 18, 21, and 23 and January 1 and 9 (total 5 g.). At 10 p.m. on December 18 his blood contained 7 microfilariae per 40 c.mm.; on March 7 (79 days after the first dose), 57; and on May 28, 62.

Case B.—A woman aged 35, weight 50 kg., received three intravenous doses of 1 g. of suramin between December 18 and January 4; and on January 9, 1 g. At 9.30 p.m. on January 9 her blood contained 23 microfilariae per 40 c.mm.; on March 7, 11; and on May 28, 10.

In these two cases there was no evidence that suramin was able to kill or sterilize the adult worms of *W. bancrofti*. Wanson (1950) states that it does not kill the adults of *W. bancrofti*, *Loa loa*, *Acanthocheilonema perstans*, or *A. streptocerca*, although no evidence is given for this statement. In our laboratory at the National Institute for Medical Research, in London, suramin had no lethal action on *Litomosoides carinii*. Clearly the chemotherapeutic reactions of filarial worms differ according to the different species.

Discussion

The action of a chemotherapeutic drug must be considered from two aspects, that of the parasite and that of the host—that is, therapeutic action and toxicity.

Therapeutic Action

Arsenamide in high doses (2 mg./kg. daily) causes disappearance of the microfilariae of *W. bancrofti* from the blood within two weeks. Since this period is much less than their normal life span, their disappearance must be directly due to a lethal action of the drug. Such an action has been demonstrated *in vitro* in concentrations of approximately one in a million (Hawking, 1950). (The gradual disappearance of the microfilariae after small doses (0.3 mg./kg.) was presumably due to failure of replenishment after death of the adult worms.)

Since the disappearance of microfilariae caused by arsenamide is permanent (more than seven months, at least) there is evidence that death or permanent sterilization of the adult female worms has been brought about: on general grounds, and by analogy with the experimental findings with *Litomosoides* in cotton rats, it is almost certain that the adult worms have been killed. This effect is produced by doses of about 1 to 2.5 mg./kg., usually given daily for 15 days. Thus Thetford *et al.* (1948) and Otto *et al.* (1952, 1953) gave 1 mg./kg. for 15 days. In the present series the number of injections varied from 5 to 12 (9 patients received 12 injections, 17 received 10, 3 received 9, 1 received 8, and 1 received 5). Since the daily amount given was not calculated on a weight basis, the actual dose varied from 1.8 to 2.5 mg./kg., according to the weight of the patient. All the courses of injection were effective in removing microfilariae from the blood. With much smaller doses (0.3 mg./kg.) the antifilarial effect, although considerable, is not complete. Perhaps the minimum curative dose is about 0.6 mg./kg.

Arsenamide also causes considerable reduction in the number of *M. perstans* microfilariae in the blood. It is possible that arsenamide kills many of the adult worms of *A. perstans*, although a long period of observation might be necessary to obtain evidence of this, since these microfilariae may live over two and a half years in the absence of the adult worm (Gönnert, 1942). As this parasite is non-pathogenic, however, such action is of academic interest only.

Toxic Action

As described above, intensive treatment with arsenamide may produce various minor toxic effects—for instance, vomiting, dizziness, headache, loss of weight, and (possibly) diarrhoea. Localized inflammation or allergic reactions due to the death of adult worms may also develop during treatment. All these, however, are overshadowed by the

tendency of arsenamide to cause damage to the liver, which may proceed (as in the case described above) to fatal necrosis. In the present series of 35 patients treated with doses of 1.8 to 2.5 mg./kg. a day one patient developed pyrexia after the tenth dose, and jaundice appeared three days later; one man developed jaundice about four and a half weeks after the last of 10 injections (the relation of this to the treatment is not clear); and one man suffered fatal necrosis of the liver three days after receiving three doses of 2.4 mg./kg., total 7.2 mg./kg. Ampoules from this batch of material were returned to the manufacturers. Chemical examination revealed no alteration of composition, and biological assay showed no increase of toxicity. Therefore the toxic effect on the liver must be due to the unchanged compound, probably to the arsenic part of the molecule; there is no reason for believing that the benzamide part of the molecule has any significant toxic action.

There had been considerable previous experience with this compound, and many patients had tolerated much greater total dosages without ill effects. Thus Murgatroyd (1937) administered it (under the name K324) to eight patients with sleeping sickness in the Gambia in doses as high as 35 mg./kg.; doses greater than 2.5 mg. produced vomiting, abdominal pain, or diarrhoea, and in one case there was severe jaundice. Thetford *et al.* (1948) and Otto *et al.* (1952) treated 18 cases of filariasis with doses of 1 mg./kg. daily intravenously for 15 days and observed only minor toxic reactions. Similarly, Otto *et al.* (1953) treated a further 15 cases with the same dose schedule. The main toxic features observed were diarrhoea and nausea; one case had severe lymphadenitis. Hawking (1950) treated four patients with daily injections of 100 or 150 mg. for seven days—that is, 1.7 to 2.5 mg./kg. The larger doses were followed by vomiting and diarrhoea, but there was no suggestion of liver damage. In East Africa 36 cases have been treated with doses of 1 mg./kg. daily for about 14 days; one case of jaundice occurred (Filariasis Research Annual Report, 1952). We have also heard privately of two cases of non-fatal severe hepatitis with jaundice which occurred in the West Indies after treatment with arsenamide. No evidence of special toxic action on the liver of rabbits, dogs, or monkeys was seen by Otto and Maren (1950), or by Drudge (1952), who gave dogs 2.2 mg. of arsenamide per kg. intravenously daily for 15 days.

Apparently the death described above was another example of the tendency of arsenic compounds to cause extensive necrosis of the liver in a very small proportion of the cases treated with it. Such subjects must be predisposed to this damage by accessory factors, but the nature of such factors and the causation of widespread liver necrosis in man are still largely unknown. The possible accessory factors include:

(a) *A Virus Infection, Latent or Incipient.*—Hepatitis, presumably infective, certainly occurs in Gambia, since several Europeans developed it recently. In the present investigation a clean sterile syringe and needle were used for each injection, so there was no possibility of passage of infection by this means; moreover, the incubation period was much too short for viral hepatitis to develop from the patients' injections.

(b) *Lack of Essential Nutrients, Especially Tocopherol and Cysteine.*—This food deficiency causes hepatic necrosis in rats (Himsworth, 1950). Many Africans are certainly malnourished, but there is no evidence that the state of nutrition of the present patient was worse than that of others in the same village who were treated. However, in any further trials with arsenical compounds it would be advisable to take the precaution of fortifying the liver against such toxic action by giving a protein-rich supplement—for example, 50 g. dried milk daily in addition to the usual food.

It is concluded that arsenamide, in daily doses of 1 mg. or more per kg. for 10 to 14 days, is an effective drug for the sterilization of bancroftian infection in patients, and that its use is not devoid of risk. Since filariasis is not a fatal disease, it is accordingly not justifiable to use arsenamide for general treatment. In any further investigation of this drug careful precautions should be taken to avoid damage

to the liver: the dose should be kept low, preferably below 0.6 mg./kg.; the patients should be treated in hospital under strict medical supervision; and the protein content of the patient's diet should be increased—for example, 50 g. of skim-milk powder daily in addition to a good general diet—in order to fortify the liver, the protein supplement being given for three days before, during, and three days after treatment.

Summary

Thirty-two cases of filariasis due to *W. bancrofti* were treated with arsenamide (*p*-bis-(carboxymethyl-mercapto)-arsino-benzamide). The dose was 125 mg. (1.8–2.5 mg./kg.) daily by intravenous injection, usually for 10–12 doses.

This treatment removed most of the microfilariae of *W. bancrofti* from the blood within two weeks after the first dose, and all but two of the patients were free from microfilariae six months later. It is concluded that the treatment killed or sterilized the adult worms; it also killed many of the microfilariae (and the rest disappeared in the absence of adult worms to replenish their numbers). The treatment also caused a significant reduction in the number of *A. perstans* microfilariae present, indicating a filaricidal action on this worm also.

The drug undoubtedly has a toxic effect upon the liver. In two cases the treatment was followed by jaundice, three days and four weeks respectively after the last injection; and one patient developed fatal necrosis of the liver after having received only three injections. Other minor toxic effects included vomiting, dizziness, headache, and loss of weight. A few patients showed localized inflammation or allergic reactions, apparently around worms which had been killed.

Five more patients were treated with much lower doses (0.3 mg./kg.) daily for 14 days under strict medical supervision, and with a protein-rich supplement to fortify the liver. No toxic effects were observed. Among the four patients who were followed for five months the microfilaria count was reduced almost to zero in two, it fell to a quarter in one, and it remained unchanged in one. Perhaps the minimum curative dose is about 0.6 mg./kg.

Arsenamide in doses of 1–2 mg./kg. daily is a potent filaricidal drug against *W. bancrofti*, but the danger of severe toxic action upon the liver is a contraindication to its use except under special conditions.

Two patients were treated with 4 g. and 5 g. respectively of suramin for trypanosomiasis. This treatment had no apparent effect during the next five months on the number of *bancrofti* microfilariae in their blood.

Grateful acknowledgments are made to Professor B. S. Platt for clinical facilities; to the Director of Medical Services, Gambia, for interest and encouragement; to Sisters S. E. Brewer and D. J. Fayers for nursing assistance; and to Dr. J. Niven for advice on morbid histology. The drug was kindly supplied by Eli Lilly & Co., Indianapolis, U.S.A. who also re-examined the material at our request.

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