The Experimental Chemotheraphy of Filariasis *Bancrofti*[1]

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WHEN ACCOMPANIED by its frequent complications, the form of filariasis caused by *Wuchereria bancrofti* is one of the most serious tropical diseases. In the endemic areas, which are widely dispersed throughout the tropical zone, fairly high percentages of the general population usually harbor the parasite, and many individuals exhibit the serious or disabling symptoms or sequelae of the infection—lymphangitis, lymphadenitis, and elephantiasis.

Hitherto, little or no success has apparently attended the many efforts to eradicate this infection by chemotherapeutic procedures. A wide range of drugs has been tried in therapy, including compounds of antimony, arsenic, mercury, copper, zinc, tin, and other metals, germanin, acridine derivatives, plasmochin, aniline dyes, sulfonamides, iodine compounds, emetine, cobra venom, and many other substances.[2] Of all these materials, only antimony compounds have in the past appeared to exert significant effects on the disease and, even with these, the effects—as judged by the microfilaria levels—have almost invariably been distinctly temporary.[3] Unfortunately, patients have usually been followed for but short periods—two weeks or so—after treatment ceased, so that long-term effects escaped notice, even if they occurred.

As the result of experimental studies performed in this laboratory in the therapy of a naturally occurring filariasis (*Litomosoides carinii*) of cotton rats, it became apparent that observations on

1. Received for publication May 7, 1946. The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the College of Physicians and Surgeons, Columbia University.

2. O. Temkin, A report on the medicinal treatment of filariasis *bancrofti*. National Research Council, Office of Medical Information, Washington, D. C., September 1945.

3. R. N. Chopra and S. S. Rao, Chemotherapy of filarial infection. Indian J.Med.Res., 27:549–562, 1939.

peripheral blood must be continued for some weeks or months before an adequate evaluation of the effects of treating this rodent form of filariasis is possible. In the animal infection, the pentavalent antimony compounds, neostibosan and neostam, exerted but little immediate effect on the circulating microfilariae, yet they manifested a powerful action upon the adult filarial worms, killing those that occurred in the pleural space after a few days of administration.[4] Sometimes microfilariae circulated for weeks or months after treatment had ceased and long after the parent worms had been killed. Although microfilariae gradually decreased in number following therapy and were finally no longer seen in the blood, their disappearance was largely attributable to the fact that the parent worms were dead and were no longer shedding embryos into the circulation.[5] Those embryos present in the blood, when the adult worms died, were gradually eliminated, not by direct action of the drug on them, but probably by immunological or other antagonistic forces which the host was bringing into play against them. However—and this point is critical in the interpretation of data that will be offered presently on the human cases—it was invariably found when the animals were autopsied, after microfilariae had finally disappeared from their circulating blood, that the adult worms had been killed. This observation is important since, in the human disease, all known pathology is related to the prolonged presence of the adult parasite. The early destruction of this adult phase of the worm, which is the primary end sought through chemotherapy, can evidently be accomplished in the rodent infection by the administration of drugs. Furthermore it appears that the death of the adult parasites can safely be assumed, if microfilariae permanently disappear from the blood as a consequence of treatment.

As a result of these observations in animals, for which data given in Table 1 are representative, a program for the extended investigation of the experimental therapy of filariasis was devised. In this, it was proposed to test first a fairly wide range of drugs for therapeutic activity in the cotton rat filariasis. Compounds which showed promise in the therapy of the animal infection were then to be tried in the human disease. The results of the program form the substance of this report.

4. J. T. Culbertson and H. M. Rose, Chemotherapy of filariasis in the cotton rat by administration of neostam and neostibosan. J.Pharmacol. and Exper. Therapeutics, **81**:189–196, 1944.

5. *Ibid.*

TABLE 1

Effect of Neostibosan and of Neostam on Filariasis (Litomosoides carinii) *of Cotton Rat*

Cotton Rat No.	*Drug*	*Day treatment began*	*No. of Microfilariae Seen in 100 Fields of Tail Blood (x 430)*							*Recovery of Adult Filarial Worms at Autopsy*
			Days after treatment							
			6	11	14	21	41	62	81	
1	Neostibosan	36	34	16	10	22	18	2	0[a]	4: all dead; enveloped in fat
2	Neostibosan	186	40	66	44	42	28	1	0[a]	25: all dead; enveloped in exudate
3	Neostibosan	76	98	48	34	64	30	2	0[a]	30: all dead; enveloped in exudate
4	Neostibosan	26	16	12	18[a]					20: all dead; enveloped in exudate
5	Neostibosan	60	26	80	8[a]					15: all dead; enveloped in exudate
6	Neostibosan	14	14	10	12[a]					10: all dead; enveloped in exudate
7	Neostam	90	41	11	4	0	0[a]			25: dead; massed in exudate
8	Neostam	105	100	85	62	26	0[a]			40: dead; massed in exudate
9	Neostam	126	52	31	0	0[a]				20: dead; massed in exudate
10	Neostam	52	56	24[a]						20: dead; massed in exudate
11	Neostam	6	23	16[a]						6: dead; massed in exudate
12	Neostam	22	20	16[a]						12: 6 dead in exudate; others living

[a]Day of autopsy.

TREATMENT

NEOSTIBOSAN: Rats Nos. 1–3: 40 mg. given intramuscularly on alternate days for three weeks; after rest period of 3 weeks, 80 mg. given every third day for the next 3 weeks.
Rats Nos. 4–6: 40 mg. given on alternate days until autopsy.

NEOSTAM: Rats Nos. 7–9: 60 mg. four times weekly.
Rats Nos. 10–12: 40 mg. three times in one week.

TABLE 2

Results of Testing Selected Drugs for Action on Litomosoides carinii *in Cotton Rat*

Drug No.[a]	*Drug Name*	*No. of Rats Used*	*Route and Schedule of Administration*	*Days of Treatment*	*Effect on Number of Microfilariae*	*Day of Autopsy*	*Effect on Adult Worms*	*Apparent Value of Drug*
338	Streptothricin	5	Intramuscular; 5000 units daily	10	None	11–26	A few killed in each rat; some fibrin deposited	Little or none
354	Urea stibamine	4	Intramuscular; 20 mg. on alternate days	11	Slight or none	13	Mostly dead, matted together	Active on adults
385	Vanadium gluconate	5	*Per os*; 20 mg. on alternate days	20	90% reduction in 1 rat	22–38	None	None
388	Acranil	5	Intramuscular or *per os*; 20 mg. on alternate days	14	Some reduction	15	None, although adults stained	None
390	Plasmochin	5	*Per os*; 10–20 mg. on alternate days	20	Reduced 75% by 10th day	16–28	A few dead in 4 rats; some fibrin deposited	Chiefly on microfilariae
421	Stibanose	13	Intramuscular; 60 mg. daily	6	Reduced by 50%	21	Mostly dead; some fibrin deposited	Active on adults
460	p-(-phenylphenoxy) aniline	2	*Per os*; 10 mg. daily for 2 weeks, then 20 mg. daily for 2 wks.	14, 28	None	14, 28	A few (10%) dead after 28 days	None
504	Phthalic acid, butyl ester, copper salt	2	Same as 460	12, 28	None	15, 29	None	None
527	Penicilin	5	Intramuscular; 300 units daily	6–17	None	7–18	None	None
637	chloro-N-B-dimethylphenethylamine hydrochloride	4	Intraperitoneal; 15 mg. daily	14, 21	Reduced 30%	21	None	None

[a]Numbers were assigned by Dr. L. R. Farquhar, Chemotherapeutic Center, National Research Council, Washington.

LABORATORY STUDIES WITH *Litomosoides Carinii*, THE FILARIA OF THE COTTON RAT

The laboratory work performed with the cotton rat filarial worm can conveniently be divided into two parts: that concerned with treatment of the infection in the living cotton rat, and that performed *in vitro* upon parasites freshly removed from the animal body.

In Vivo Studies. Altogether, 40 drugs were tested for therapeutic activity against filariasis in the living cotton rat. In general, each drug was given by an appropriate route as intensively as possible for from two to four weeks. During this time, microfilaria counts were made on the tail blood of the animals at regular intervals, and finally, the treated animals were autopsied and searched for adult worms so that effects, if any, could be observed upon the mature parasites. The data obtained with certain representatives of the drugs tested are given in Table 2.

Of those tested, the only drugs which manifested significant activity upon the adult parasites in the cotton rat filariasis were those that contained antimony. Neostibosan, stibanose, neostam, and urea stibamine—all compounds of pentavalent antimony—showed marked effects on the adult worms, the effects being apparently the same, qualitatively, in all cases. These drugs also caused a gradual decline in the number of circulating microfilariae in the cotton rat. A few other drugs appeared to cause the microfilaria level to drop without affecting the adult parasites.

In Vitro Studies. The *in vitro* studies were performed upon adult parasites removed aseptically from the cotton rat pleural space and transferred to 50 cc. Erlenmeyer flasks containing 10 cc. of sterile Simms' physiological serum-salt solution. Provided the flasks remained bacteriologically sterile, the adult parasites often continued viable for a week or so at 37° C. At room temperature, the parasites lived even longer. Drugs were added to the flasks in known concentration and the effects on the viability of the worms noted by observations at appropriate intervals.[6]

Only 13 drugs, as shown in Table 3, were tested by the *in vitro* method. In general, the method did not appear useful for the screening of drugs, since some compounds—neostibosan and neostam, for example—were almost inactive upon the worms *in vitro* yet quite effective upon the infection in the animal, whereas others—

6. H. M. Rose, J. T. Culbertson, and E. Molloy, An *in vitro* method for the bio-assay of chemotherapeutic agents in filariasis. J.Parasitol., **30** (Supp.):16–17, 1944.

TABLE 3

Results of Testing Drugs for Action upon Litomosoides carinii *in Vitro*

Drug No.[a]	*Drug Name*	*Concentration Tested*	*Results*
79	Anthiomaline	Molar x 10^{-5}	Adults dead in 3 days
338	Streptothricin	100 units per cc.	Adults survived 4 days
354	Urea stibamine	Molar x 10^{-5}	Adults survived 10 days
385	Vanadium gluconate	1–20,000	Adults survived 4 days
386	Neostibosan	1–100,000	Adults survived 10 days
388	Acranil	(a) 1–20,000, (b) 1–100,000, (c) 1–1,000,000	Adults (a) dead in 1 hour, (b) dead in 36 hours, and (c) survived 4 days
392	6-chloro-9-4(diethylaminobutylamino)-2 methoxyacridine dihydrochloride trihydrate	(a) 1–20,000, (b) 1–100,000, (c) 1–1,000,000	Adults (a) dead in 1 hour, (b) dead in 18 hours, and (c) survived 4 days
395	3-(2-dimethylaminoethylamino)-7-dimethyl-aminophenothiazine, hydroiodide dihydrate	(a) 1–20,000, (b) 1–100,000, (c) 1–1,000,000	Adults (a) dead in 3 hours. (b) dead in 3 days, and (c) survived 4 days
403	7-iodo-8-hydroxy-5-quinoline sulfonic acid, sodium bicarbonate	1–20,000	Adults survived 4 days
421	Stibanose	Molar x 10^{-5}	Adults survived 10 days
486	Neostam	1–100,000	Adults dead 10 days
527	Penicilin	100 units per cc.	Adults survived 4 days
	Atabrine	(a) 1–20,000, (b) 1–100,000, (c) 1–1,000,000	Adults (a) dead in 24 hours, (b) dead in 48 hours, and (c) survived 4 days

[a] Numbers were assigned by Dr. L. R. Farquhar, Chemotherapeutic Center, National Research Council, Washington.

atabrine and acranil—exerted strong effects *in vitro* but were without activity in the highest tolerated doses against the parasites in the living cotton rat. However, one rather significant point was learned from the *in vitro* studies: all of the drugs tested had greater action upon the adult parasites than upon the microfilariae. This was apparent because microfilariae, transferred along with the adult worms from the pleural space of the cotton rat to the serum-salt-drug suspensions (or else which escaped from the adult worms after such transfer), continued their usual flexing movements long after the adult parasites had died. This observation is compatible with the fact that microfilariae in the living rodent are less susceptible to an administered drug—at least, to certain pentavalent antimony compounds—than are the adult worms in the pleural space.

STUDIES UPON PATIENTS INFECTED WITH *Wuchereria Bancrofti*

It was apparent from the foregoing work in the cotton rat filariasis that several of the compounds of pentavalent antimony deserved trial in the treatment of human filariasis. Meanwhile, experimental studies performed by investigators in other laboratories[7] revealed that several compounds of trivalent antimony—tartar emetic, fuadin, and anthiomaline—as well as a number of arsenical preparations—melarsen oxide, mapharsen, and tryparsamide—also killed adult worms in the cotton rat filariasis and were therefore also potentially useful in treating the human disease. Accordingly, arrangements were made to carry on therapeutic tests in human filariasis in Puerto Rico, West Indies, where infection with *Wuchereria bancrofti* is comparatively common among the general population. Work was begun in April 1944, and, with occasional interruptions, continued until June 1945.

The Patients. All of the subjects included in this study were native Puerto Ricans (except No. 12 HB, Table 5, who had been born in Martinique). Those below 18 years of age (the youngest was 8 years old) were students at either the Insular Home for Boys at Guaynabo or the Insular Home for Girls at Santurce, Puerto Rico. The ones 18 years old or over (the oldest was 37 years of age) were males who had been rejected by the military because of filariasis. All patients had microfilariae in their nocturnal blood, and all but 3 were free of symptoms of filariasis. Two of those with symptoms (Nos.

7. Personal communications from Dr. R. N. Bieter, University of Minnesota; Dr. G. F. Otto, Johns Hopkins University; Dr. H. J. Robinson, Merck Institute, and Dr. A. D. Welch, Western Reserve University (through Dr. L. R. Farquhar, National Research Council).

20 RMA, Table 6, and 35 CM, Table 8) reported recurrent lymphangitis with moderate swelling of the legs. The third patient with symptoms (No. 11 CP, Table 6) had periodic chyluria. One group of 15 patients was kept untreated as a control on the effects of treatment.

The Drugs Employed. The following antimony-containing drugs were employed for treating the cases of human filariasis: *pentavalent compounds:* neostibosan (Winthrop), stibanose (Winthrop), neostam (Wellcome), and urea stibamine (Squibb; Brahmachari); *trivalent compounds:* fuadin (Winthrop), anthiomaline (Merck; Specia), and tartar emetic (Abbott). The only non-antimonial preparation used for treating the patients was a trivalent arsenical compound, melarsen oxide (Parke-Davis).

The Estimation of Microfilariae. The number of microfilariae in all patients was estimated in 60 cmm. of nocturnal finger blood taken before treatment, at intervals during treatment, and periodically after cessation of treatment. Similar blood samples were obtained at intervals from the untreated control patients. The films prepared from these blood samples were dehemoglobinized in water, fixed in alcohol-ether (50 percent each), stained with Bullard's hematoxylin, and destained with acid alcohol. The number of microfilariae shown in the tables represents the number counted after search of the entire film under 100 x magnification.

From a few patients, 10 cc. of nocturnal blood were drawn by syringe, laked by several washings with saponin and physiological salt solution, and centrifuged. The sediment resulting from centrifugation was then carefully searched in its entirety for microfilariae, under 100 x magnification, successive portions of sediment being transferred to a slide with a capillary pipette.

Comment. The first group of cases studied were treated with neostibosan, the drug being given in the same dosage but for a considerably longer period than that recommended in the treatment of kala-azar. Only one (No. 11 CP, Tables 4 and 6) of the 30 patients in this first group was hospitalized during treatment, all other individuals continuing their usual activities as students or workmen throughout the period of treatment. In all subsequent work, not only with neostibosan but also with other drugs as well, treatment was carried on much more intensively, indeed the purpose being to press each drug to the limit of tolerance in each patient. These patients were generally hospitalized and were kept under treatment for from one to three but, generally, for two weeks.

last, some symptoms recorded as reactions to drug (fever, cough, fatigue) may have had other causes.

Results. Table 6 shows that, eighteen months after treatment, 16 of the 20 patients given a single prolonged light course of neostibosan had lost all microfilariae and were therefore, presumably, free of the infection. The remaining 4 patients all lost more than 85 percent of the microfilariae originally present and showed some likelihood of finally losing the remainder.

Four of 10 patients in Table 7, given 2 courses of drug, lost all microfilariae by the eighth month after the end of the second course. The remaining 6 patients all lost more than 75 percent of the microfilariae originally present.

Of 5 patients in Table 8 given a single intensive course of drug, 3 were negative for microfilariae after nine months, and the remaining 2 had lost by that time 86 percent and 57 percent, respectively, of the number of microfilariae originally present.

Taken altogether, of the 35 patients treated with neostibosan, 23 became negative for microfilariae, and 7 others lost during the period of observation more than 90 percent of the microfilariae originally present. Of 5 remaining treated patients, 4 lost more than 75 percent, and one lost over half the microfilariae in the same period of eighteen months.[8]

Examination of Larger Blood Volumes for the Presence of Microfilariae. It is apparent from the data in Tables 6, 7, and 8 that microfilariae declined in number in the blood of patients following treatment with neostibosan. From the blood of some patients, all microfilariae evidently have disappeared. However, the absence of microfilariae from the standard 60 cmm. blood sample used in this work by no means proves that all embryos have been eliminated from the total blood of a given patient. Accordingly, it was decided to examine for the presence of microfilariae much larger blood volumes from certain patients. From these individuals, 10 cc. of nocturnal blood were obtained, the usual 60 cmm. samples likewise being procured, simultaneously, for purposes of comparison. Both blood samples were examined in the manner described earlier under "The Estimation of Microfilariae." The results are given in Table 9.

As would be anticipated, the data show that the chance of finding microfilariae is somewhat greater through examining a larger blood

8. J. T. Culbertson, H. M. Rose, and J. Oliver González, Chemotherapy of human filariasis by the administration of neostibosan. First report. Am.J.Trop.Med., 25:271–274, 1945; Chemotherapy of human filariasis by the administration of neostibosan. Second report. *Ibid.*, 403–406.

TABLE 6

Data on Twenty Patients with Filariasis Given One Comparatively Light Course of Neostibosan

Case No.	*Age*	*Wt. (Lb.)*	*Drug Given (G.)*	*Days of Treatment*	*Number of Microfilariae in 60 cmm. Blood from Treated Patients at Designated Times*							*Microfilaria Level, Percent of Change over Entire Period of Observation*
					Before Treatment	*At End of Treatment*	*Months After End of Treatment*					
							2.5	*6.0*	*9.0*	*12.0*	*15.0*	*18.0*	
1 LET	11	60	7.2	40	3	0	0	0	0	0	0	0	—100
2 MR	8	50	4.6	25	9	0	0	0	0	0	0	0	—100
3 VR	10	48	5.8	34	24	6	0	0	0	0	0	0	—100
4 AEB	16	106	7.2	40	15	36	8	0	0	0	0	0	—100
5 RT	14	100	7.2	40	41	36	9	0	0	0	0	–	—100
6 JT[a]	17	134	8.1	40	27	42	27	0	0	0	0	0	—100
7 CIR	13	102	7.2	40	216	204	141	6	0	0	0	0	—100
8 EMD[a]	18	138	10.4	48	18	42	21	2	0	0	0	0	—100
9 MSC[a]	26	112	10.5	48	150	120	66	10	0	0	0	0	—100
10 GM[a]	15	114	8.1	40	33	15	15	10	1	0	0	–	—100
11 CP[a]	21	125	7.6	49	15	61	—	1	2	0	0	–	—100
12 CAR	15	93	6.8	40	231	207	81	21	4	1	0	0	—100
13 JOA[a]	20	133	9.2	54	82	8	91	52	13	1	0	0	—100
14 OA[a]	21	146	7.2	38	36	12	0	1	1	1	1	0	—100
15 PB[a]	11	58	6.9	39	177	96	114	111	104	22	4	0	—100
16 RRC[a]	26	168	9.2	54	24	6	—	17	5	—	1	0	—100
17 JG[a]	13	79	8.1	39	255	204	57	14	3	0	0	1	—99
18 JL[a]	13	76	7.5	40	297	294	171	111	28	18	6	–	—97
19 DG[a]	12	73	7.5	40	21	51	6	0	0	0	0	1	—95
20 RMA	11	68	1.3	9	57	35	—	0	4	9	0	7	—87

[a]Males

TABLE 7

Data on Ten Patients with Filariasis (Wuchereria bancrofti) *Given Two Courses of Neostibosan*

Case No.	Age	Sex	Weight (Lb.)	First Course of Therapy						Second Course of Therapy						Microfilaria Level, Percent of Change over Entire Period of Observation
				Drug Given (G.)	Days of Treatment	No. of Microfilariae in 60 cmm. Blood at Designated Times				Drug Given (G.)	Days of Treatment	No. of Microfilariae in 60 cmm. Blood at Designated Times				
						Before Treatment	At End of Treatment	Months after End of Treatment				Before Second Course	At End of Second Course	Months after End of Second Course		
								2.5	6.0	9.0					1	5	8	
21 MN	12	F	74	6.5	40	27	54	18	13	13	7.9	10	13	1	2	0	0	—100
22 ME	16	F	102	6.9	40	136	126	111	49	65	12.5	14	65	11	16	0	0	—100
23 HRR	11	M	56	7.3	34	18	9	9	15	16	5.9	9	16	1	0	1	0	—100
24 DR	13	M	76	8.1	40	72	120	72	39	67	11.5	15	67	9	13	4	0	—100
25 CF	8	F	52	6.4	33	123	93	90	109	65	9.0	11	65	0	0	0	1	—99
26 CD	16	F	112	7.1	40	120	126	72	42	31	12.0	14	31	21	11	15	2	—98
27 FG	13	M	71	8.1	40	630	624	345	217	284	11.1	15	284	60	70	35	15	—97
28 IO	14	F	138	7.2	40	129	156	84	87	71	12.0	14	71	57	41	15	4	—96
29 JR	16	F	85	6.0	33	154	129	138	81	69	10.0	14	69	39	41	28	25	—83
30 BM	14	F	91	7.1	40	78	87	90	56	75	12.5	14	75	40	63	41	18	—76

TABLE 8

Data on Five Patients with Filariasis (Wuchereria bancrofti) *Given a Single Intensive Course of Neostibosan*

Case No.[a]	*Age*	*Weight (Lb.)*	*Drug Given (G.)*	*Days of Treatment*	*Number of Microfilariae in 60 cmm. Blood at Designated Times*						*Microfilaria Level, Percent of Change over Entire Period of Observation*
					Before Treatment	*At End of Treatment*	*Months after End of Treatment*				
							1.0	*3.0*	*6.0*	*9.0*	
31 EG	8	46	11.0	15	30	0	0	0	0	0	—100
32 MM	14	78	9.5	14	93	12	38	3	0	0	—100
33 JAA	21	134	15.5	13	79	26	10	9	3	0	—100
34 VN	11	65	11.0	15	651	150	267	234	197	90	—86
35 CM	36	162	12.3	12	194	144	98	24	93	82	—57

[a]All are males.

TABLE 9

Comparative Numbers of Microfilariae in 60 cmm. Blood Samples and in the Sediment from 10 cc. of Laked Blood, from Certain Patients Treated with Neostibosan

Case No.	No. in 60 cmm. Blood		No. in Sediment from 10 cc. of Blood (Laked with Saponin) 8 to 18 Months after Treatment
	Before Treatment	8 to 18 Months after Treatment	
1 LET	3	0	0
2 MR	9	0	0
3 VR	24	0	0
4 AEB	15	0	0
6 JT	27	0	3
7 CIR	216	0	2
12 CAR	231	0	0
15 PB	177	0	1
17 JG	255	1	88
19 DG	21	1	18
21 MN	27	0	0
22 ME	136	0	0
23 HRR	18	0	0
24 DR	72	1	70
25 CF	123	2	2
26 CD	120	2	31
31 EG	30	0	0
32 MM	93	0	5

sample than that routinely employed in this work. Occasionally, for example, when no embryos whatever were seen in 60 cmm. of blood, a small number of parasites were found in 10 cc. of blood. However, on the whole, the parasite yield from the large volume was not impressively greater. Indeed, when no parasite was found in the 60 cmm. blood sample, none likewise was recovered usually from the 10 cc. sample.[9] Additional evidence is thus supplied to show that the number of microfilariae is substantially reduced through treatment. Although a few embryos probably could be found in the presumably negative cases if still larger blood volumes were examined, it seems probable that, with the passage of more time, even these will disappear, rendering the patients absolutely free of all filarial parasites.

9. It should be appreciated that many of these patients had been negative on examination of repeated 60 cmm. blood samples for several months previously.

Neostam

Procedure. Eleven patients were treated intensively with neostam, all of these individuals being hospitalized for two weeks during therapy. Except for patient No. 9 AF, Table 5, who was discharged for irrelevant reasons after only a few injections, all patients received between 8.5 and 11.4 g. of the drug. Injections were made three times daily. Following 0.15 g. on the first day, doses were gradually increased until most patients received 0.5 g. on the fourth day and 1.0 g. on the seventh day. Thereafter, whenever possible, the daily dose of 1.0 g. was maintained until treatment ended.

Reactions to Drug. As can be seen in Table 5, neostam was not well tolerated by patients, the only individual in whom reactions were not seen being No. 9 AF, who was treated for only a few days. All the 10 remaining patients experienced severe nausea and vomiting, especially during the first days of treatment. Three patients were in shock on the first or third day, and the majority of them suffered from severe abdominal pain, fever, and a more or less extensive rash (Plate 1) over the hands, arms, and trunk. It was difficult to keep patients under treatment with this drug.

Results. The patients treated with neostam have now been followed for seven months since treatment ended. As the data in Table 10 reveal, 2 individuals have lost all microfilariae, 5 others have lost at least 80 percent of those originally present, and the remaining patients, except for No. 11 JMO who could not be followed, have lost 59 percent, or more.

Urea Stibamine

Procedure. Six patients were treated intensively for two weeks with urea stibamine, 3 of these receiving the original Brahmachari product and 3 receiving the Squibb preparation. The patients were hospitalized during treatment. Injections were made three times daily. On the first day only 0.1 g. was given, but 0.6 g. of the Squibb preparation was injected on the third day and from 0.75 to 0.9 g. was given on most subsequent days. The largest daily dose of the Brahmachari drug was 0.525 g., but on most days only 0.3 was injected.

Reactions to Drug. As shown in Table 5, the Squibb preparation of urea stibamine was much better tolerated by patients than was the Brahmachari drug. One patient treated with the Squibb drug had no reactions whatever, and the remaining 2 showed good tolerance. All 3 patients given the Brahmachari drug suffered severe reactions, with nausea, vomiting, abdominal pain, headache, and salivation.

TABLE 10

Data on Eleven Patients with Filariasis (Wuchereria bancrofti) *Treated with Neostam*

Case No.[a]	*Age*	*Weight (Lb.)*	*Drug Given (G.)*	*Period of Treatment (Days)*	*Number of Microfilariae in 60 cmm. of Blood from Treated Patients at Designated Times*						*Microfilaria Level, Percent of Change over Entire Period of Observation*
					Before Treatment	*At End of Treatment*	*Months after End of Treatment*				
							1	*3*	*6*	*7*	
1 ALB	23	107	10.6	14	62	14	61	—	0	0	—100
2 RNV	25	175	11.4	14	249	25	60	0	1	0	—100
3 MMR	22	113	10.6	14	366	121	276	123	16	9	—97
4 FT	22	140	7.7	15	189	175	48	5	1	8	—95
5 LMS	26	112	9.8	14	96	34	40	4	25	12	—87
6 JMG	21	115	8.5	15	55	34	180	46	39	4	—85
7 CBC	23	134	10.8	14	21	4	—	4	4	—	—80
8 AAR	19	137	11.0	14	35	8	29	21	17	11	—68
9 AF	25	146	2.1	5	33	—	19	10	31	13	—60
10 AVG	21	121	10.1	14	290	49	185	—	100	118	—59
11 JMO	19	128	8.7	15	166	47	187	—	—	—	+12

[a]All are males.

TABLE 11

Data on Six Patients with Filariasis (Wuchereria bancrofti) *Treated with Urea Stibamine*

Case No.[a]	*Age*	*Weight (Lb.)*	*Product Used*	*Drug Given (G.)*	*Days of Treatment*	*No. of Microfilariae in 60 cmm. Blood from Patients at Designated Times*							*Microfilaria Level, Percent of Change over Entire Period of Observation*
						Before Treatment	*At End of Treatment*	*Months after End of Treatment*					
								1.0	*3.0*	*6.0*	*9.0*	*10.0*	
1 RCA	25	146	Squibb	6.8	16	3	4	0	0	0	0	0	—100
2 JFL	19	144	Squibb	7.1	17	20	5	2	0	0	0	0	—100
3 ALV	30	141	Squibb	7.1	17	155	181	209	145	128	92	161	+3
4 JBM	19	120	Brahmachari	4.2	14	12	0	0	0	0	—	—	—100
5 MFT	20	127	Brahmachari	3.3	11	14	18	6	0	0	—	—	—100
6 HM	21	109	Brahmachari	4.9	16	334	96	163	153	163	176	56	— 83

[a] All are males.

Every attempt to raise the dose of drug above 0.3 g. per day brought fresh reactions and higher doses were believed hazardous.

Results. After observation for ten months, 2 of the patients who received the Squibb preparation were free of microfilariae (Table 11), but the third had evidently 3 percent more embryos than were originally present. Of the 3 patients who received the Brahmachari drug, 2 also were negative for microfilariae; the third had lost 83 percent of the original number of embryos. It should be pointed out that all patients in these groups, who became negative, had comparatively light initial infections.

Stibanose

Procedure. Five patients were treated with stibanose. They were all students at the Insular Home for Boys at Guaynabo, Puerto Rico, and were not hospitalized during treatment. On the first day, 4 cc. of drug (6.67 percent solution) were given in a single injection; on the second day, two injections, each of 8 cc., were given; on all subsequent days, 2 injections each of 10 cc. were administered (Table 5).

Reactions to drug. No reactions whatever were seen in any patient treated with stibanose.

Results. Of 5 patients given stibanose, one became negative in five months from the end of treatment, another lost 60 percent of his microfilariae, and the remaining 3 lost smaller percentages of their embryos, as shown in Table 12.

Fuadin

Procedure. While hospitalized, 15 patients were treated with fuadin (6.3 percent solution). Five cc. (0.315 g.) of the drug were regularly injected in a single dose in all patients on the first day and 2 doses of this size given for the next two or three days. A few patients received 2 injections each of 7.5 cc. on the fifth day. In no case could such an intensive schedule be maintained, and generally from the fifth to the eighth day little or no drug was given. Thereafter, moderate dosage—4 to 6 cc. per day—was resumed until the end of the course (Table 5).

Reactions to Drug. In most patients, no reactions whatever to fuadin were recorded before the fourth day of treatment. From that day on, however, reactions were seen in every patient. Treatment had to be stopped in one individual on the sixth day, and another patient refused further treatment on the seventh day. Practically all patients reported nausea, vomiting, abdominal or bone pain,

TABLE 13

Data on Fifteen Patients with Filariasis (Wuchereria bancrofti) *Treated with Fuadin*

Case No.[a]	*Age*	*Weight (Lb.)*	*Drug Given (G.)*	*Period of Treatment (Days)*	*Number of Microfilariae in 60 cmm. of Blood from Treated Patients at Designated Times*						*Microfilaria Level, Percent of Change over Entire Period of Observation*
					Before Treatment	*At End of Treatment*	*Months after End of Treatment*				
							1	*2*	*4*	*7*	*8*	
1 JJ	29	124	2.7	11	145	44	69	—	91	—	2	—98
2 GMF	18	122	4.8	14	154	40	55	64	27	0	8	—94
3 JRC	19	123	1.6	6	298	123	280	—	130	32	16	—94
4 SVA	31	144	4.5	13	287	132	184	181	117	—	13	—92
5 LFCR	22	126	4.2	12	389	29	99	56	15	52	59	—84
6 RRZ	21	120	3.3	13	181	44	171	—	—	45	31	—82
7 SSP	22	132	4.2	13	493	46	218	74	—	16	99	—79
8 PRD	26	169	3.8	11	133	10	10	70	5	50	38	—71
9 MNR	18	142	5.2	13	112	51	16	25	56	38	33	—70
10 GG	30	113	6.1	14	234	31	141	100	67	109	68	—70
11 BAC	21	140	3.5	14	273	33	102	3	79	29	95	—61
12 EMC	27	118	4.0	11	64	54	25	18	29	—	—	—54
13 JRA	18	127	5.0	14	517	161	508	276	—	225	240	—53
14 ARH	23	126	4.2	13	852	89	460	—	165	276	315	—51
15 SRM	24	133	2.5	7	233	79	219	274	174	—	—	—25

[a] All are males.

headache, fever, and salivation; several had anorexia and a persistent rash.

Results. By the eighth month after the end of treatment, no patient was entirely free of microfilariae (Table 13), but 4 of 15 patients had lost over 90 percent of the original number of circulating embryos. Of the 11 remaining patients, 10 had lost over half, and, of these, 6 had lost at least 70 percent of the microfilariae originally present.

Anthiomaline (Specia)

Procedure. Ten patients were treated with anthiomaline Specia (6.0 percent solution). Seven of these individuals were hospitalized. The 3 not hospitalized (Nos. 1 VG, 2 CAC, and 5 GG, Tables 5 and 14) were students at the Insular Home for Girls at Santurce, Puerto Rico, who had been treated for filariasis nine months previously with neostibosan, apparently with little effect. The patients were given 1.5 cc. of drug the first day in a single dose and thereafter, 3.0 cc. daily in a single injection. It was originally proposed to treat all patients for twenty days.

Reactions to Drug. No reactions were recorded for any of the 10 patients before the seventh day of treatment. Thereafter, progressively more severe effects were noted in all patients (Table 5) and only 4 of the 10 patients were able to carry through the full schedule of injections. Treatment was stopped in one case on the seventh day, in one on the fourteenth day, in one on the sixteenth day, in 2 on the seventeenth, and in one on the eighteenth day. Two patients experienced shock.

Results. Eight months after treatment ended, 2 patients (both of whom had been previously treated with neostibosan) were free of microfilariae and all but one of the remaining 8 had lost over 50 percent of the microfilariae initially present (Table 14).[10]

Anthiomaline (Merck)

Procedure. Ten patients were treated with the Merck preparation of anthiomaline (6.0 percent solution). These individuals were hospitalized for two weeks and as much drug as possible given in this time. In most patients, 1 or 2 cc. were given on the first day, 3 to 5 cc. on the second, and from 4 to 8 cc. on the third day. Thereafter,

10. H. W. Brown, The treatment of filariasis (*Wuchereria bancrofti*) with antimony lithium thiomalate. J.A.M.A., **125**:952–958, 1944; Tropical diseases with special references to filariasis (*Wuchereria bancrofti*). New York State J.Med., **45**:2405–2411, 1945.

TABLE 14

Data on Ten Patients with Filariasis (Wuchereria bancrofti) *Treated with Anthiomaline Specia*

Case No.	*Age*	*Weight (Lb.)*	*Drug Given (G.)*	*Period of Treatment (Days)*	*Number of Microfilariae in 60 cmm. of Blood from Treated Patients at Designated Times*						*Microfilaria Level, Percent of Change over Entire Period of Observation*
					Before Treatment	*At End of Treatment*	*Months after End of Treatment*				
							1	*3*	*7*	*8*	
1 VG[a]	17	118	3.1	17	47	3	3	1	0	0	—100
2 CAC[a]	18	106	2.3	16	33	4	4	—	—	0	—100
3 FVB	22	139	3.0	17	433	199	133	54	0	3	—99
4 BCR	23	133	3.6	20	289	15	56	44	47	63	—77
5 GG[a]	15	143	1.1	7	139	115	113	67	36	40	—74
6 GSM	35	107	3.6	20	722	163	438	334	69	239	—66
7 JLT	20	111	3.6	20	677	132	397	356	212	257	—62
8 PF	18	111	2.4	14	951	180	528	344	166	377	—60
9 RRM	22	124	3.6	20	1094	134	641	536	489	—	—55
10 DVG	22	124	3.0	18	22	10	17	—	—	—	—22

[a]Females.

TABLE 15

Data on Ten Patients with Filariasis (Wuchereria bancrofti) *Treated with Anthiomaline Merck*

Case No.[a]	*Age*	*Weight (Lb.)*	*Drug Given (G.)*	*Period of Treatment (Days)*	*Number of Microfilariae in 60 cmm. of Blood from Treated Patients at Designated Times*						*Microfilaria Level, Percent of Change over Entire Period of Observation*
					Before Treatment	*At End of Treatment*	*Months after End of Treatment*				
							1	*3*	*6*	*7*	
1 PPP	36	146	3.3	13	74	0	3	0	2	0	—100
2 EGG	20	125	4.2	13	99	5	46	1	1	0	—100
3 MADB	19	153	2.9	13	317	175	234	17	0	1	—99
4 MASR	27	130	2.0	13	99	78	1	—	—	—	—98
5 PRR	20	126	2.7	9	324	104	167	61	3	47	—79
6 MNR	21	119	2.3	13	133	111	63	—	6	30	—77
7 FF	21	129	1.6	6	348	248	173	142	—	—	—59
8 SGC	32	106	2.7	13	163	53	136	73	61	108	—33
9 HGC	19	126	1.9	11	365	376	283	172	132	261	—28
10 LRS	18	139	2.3	13	1036	867	—	—	—	—	—16

[a]All are males.

TABLE 16

Data on Four Patients with Filariasis (Wuchereria bancrofti) *Treated with Tartar Emetic*

Case No.[a]	*Age*	*Weight (Lb.)*	*Drug Given (G.)*	*Period of Treatment (Days)*	*Number of Microfilariae in 60 cmm. of Blood from Treated Patients at Designated Times*						*Microfilaria Level, Percent of Change over Entire Period of Observation*
					Before Treatment	*At End of Treatment*	*Months after End of Treatment*				
							1	*3*	*6*	*7*	
1 MJF	21	121	0.77	14	65	45	46	13	—	0	—100
2 EPD	27	140	0.73	14	215	177	257	108	39	59	—72
3 RCF	37	140	0.79	14	174	120	174	157	69	117	—32
4 RDM	25	137	0.88	14	281	267	208	83	172	271	—3

[a]All are males.

the amount of drug administered varied considerably (Table 5). Some patients were tried with injections of fairly large amounts (6 to 8 cc.) on alternate days to see whether they could tolerate the drug better than by smaller daily injections.

Reactions to Drug. In general, patients reacted poorly during treatment with anthiomaline Merck. Only 2 patients of the 10 treated were considered to have tolerated the drug well, these receiving 70 cc. (4.3 g.) and 56 cc. (3.7 g.), respectively, in fourteen days. Reactions were severe in all others, and the drug had to be discontinued in 2 patients by the ninth day.

Results. Of the 10 patients treated, 7 lost at least 50 percent of their microfilariae by the seventh month after treatment and, of these, 2 were negative (Table 15). One patient, No. 10 LRS, did not return to the hospital for check at any time after discharge.

Tartar Emetic

Procedure. Only 4 patients were treated with tartar emetic. Although all 4 were hospitalized during fourteen days of treatment, the drug was not applied intensively.

Reactions to Drug. Serious reactions were seen in only one patient, No. 3 RCF, who was in shock lasting about five minutes immediately after injection was administered on the eighth day of treatment. All patients had an extensive rash from the sixth or eighth day till the end of treatment, and most of them suffered from headache, abdominal pain, or bone pain (Table 5).

Results. One of the 4 patients became free of microfilariae by the seventh month from the end of treatment and another, within this period, lost 72 percent of his circulating microfilariae. The remaining 2 patients lost only 32 percent and 3 percent, respectively, of their microfilariae as the result of treatment (Table 16).

Melarsen Oxide

Procedure. The only compound used for treatment, which did not contain antimony, was melarsen oxide. This preparation, which contained trivalent arsenic, was administered to eighteen persons. Three patients (Nos. 1 PRM, 2 MMM, and 3 SJ in Tables 5 and 17) received the drug orally: one 50 mg. capsule 3 times daily for one week, and, after a few days of rest, for several additional days. The remaining patients were given the drug (7.5 or 10 mg.) dissolved in propylene glycol by vein for seven or nine successive days.

Reactions to Drug. Eleven of the 15 patients treated intravenously with melarsen oxide manifested no ill effects whatever (Table 5). Of

TABLE 17

Data on Eighteen Patients with Filariasis (Wuchereria bancrofti) *Treated with Melarsen Oxide*

Case No.[a]	*Age*	*Weight (Lb.)*	*Drug Given (G.)*	*Period of Treatment (Days)*	*Number of Microfilariae in 60 cmm. of Blood from Treated Patients at Designated Times*							*Microfilaria Level, Percent of Change over Entire Period of Observation*
					Before Treatment	*At End of Treatment*	*Months after End of Treatment*					
							1	*2*	*3*	*6*	*7*	*8*	
1 PRM[b]	19	143	1.50	14	9	15	4		0		—	0	—100
2 MMM[b]	28	127	1.05	8	92	12	16		14		15	25	—72
3 SJ[b]	23	139	1.20	13	409	537	302		415		238	361	—11
4 LEO	22	126	.09	9	8	24	8	0		0	0		—100
5 LFSD	19	117	.09	9	10	—	0	0		—	—		—100
6 RL	25	118	.09	9	31	12	47		4	0	0		—100
7 VCH	22	130	.08	8	125	0	0			0	0		—100
8 PBC	32	141	.06	7	20	33	10		1	3	0		—100
9 MOP	27	145	.09	9	51	29	53		0	0	1		—98
10 TC	24	125	.09	9	51	39	32	9	—	30	5		—90
11 MAB	24	148	.06	7	78	155	119		70	—	22		—71
12 HB	27	129	.08	9	8	57	20		—	3	3		—62
13 VCS	24	131	.06	7	1128	1060	878		696	602	479		—57
14 RFS	30	145	.06	7	109	149	97		35	44	49		—55
15 FMC	25	114	.09	9	38	66	23		1	11	19		—50
16 AGC	21	116	.06	7	142	106	129		93	—	—		—34
17 MCD	24	147	.06	7	418	464	349		35	202	285		—31
18 JBP	30	133	.06	7	99	141	134		37	56	77		—22

[a]All are males.
[b]Treated orally.

the 4 who had reactions, one (No. 14 RFS) showed generalized adenopathy and malaise lasting for two or three days following the final injection on the seventh day; the 3 others had occipital headache on the eighth or ninth day of treatment. One of these last three recovered uneventfully, but the other 2 developed encephalitis. Fortunately, both patients finally survived, although in one case there were residual effects for at least seven months.

Of the 3 who received melarsen oxide orally, one reported no ill effects, but the other 2 had severe headache and abdominal pain, with dermatitis, after several days of treatment. Because of apparently serious effects in 2, the drug was stopped in all patients by the ninth day of treatment.

Results. Of the 18 patients treated with melarsen oxide (Table 17), 6 lost all microfilariae, and 4 others lost over 70 percent by the sixth or seventh month after treatment ended. The remaining 8 patients lost smaller percentages of embryos.

EFFECTS ON ADULT FILARIAL WORMS

In most of the treated patients, no effects whatever, which could be interpreted as indicative of activity by the drug upon the adult worms, were seen. In certain patients under intensive treatment, however, reactions were noted that seemed to indicate that adult worms were seriously affected by treatment. These reactions were not seen in the younger patients, but in adult males only, and consisted of swellings, usually painful, of the testis, spermatic cord, or epididymis, and the subsequent development in the scrotum of nodules sometimes one centimeter or more in diameter.

Scrotal involvement developed only near the close of the period of treatment or during the first two weeks after treatment ended. The swellings generally subsided within a week or so after appearance, although the nodules once formed often persisted for several months, meanwhile diminishing in size to become a minute hard granule. This granule was palpable in some individuals for as long as six months.

Scrotal effects will be described in 11 treated patients (Table 18), although several additional individuals reported lesser degrees of involvement. Five of these 11 persons had received neostam, one was given fuadin, 3 had anthiomaline Specia, and one was treated with anthiomaline Merck. It is important that one patient on melarsen oxide also showed an entirely similar scrotal reaction. All the patients who presented scrotal involvement also gave high microfilaria counts before treatment. Such counts, in the authors' opinion,

TABLE 18

Scrotal Signs Interpreted as Indicative of Effect upon Filarial Worms

Case No.	*Drug Used in Treatment*	*During Treatment (Day of Treatment in Parenthesis)*	*After End of Treatment (Days after Treatment in Parenthesis)*
1 ALB	Neostam	Left inguinal nodes enlarged and tender (13). Three nodes biopsied (14); negative for filarias. Both testes painful and swollen (14).	Bilateral swelling of epididymis with scrotal edema (4) gradually subsided; no residual effects when seen after 6 months.
2 RNV	Neostam	Left testis and epididymis swollen and painful (14).	Nodule in left epididymis, some tenderness (7), gradual subsidence, with no effects when seen after 6 months.
3 MMR	Neostam	Left testis and epididymis painful and swollen (14).	Nodule in left epididymis, with induration of right cord (7). Gradual subsidence, with no effects when seen after 6 months.
5 LMS	Neostam	None	Left epididymis enlarged, especially at upper pole; left cord enlarged; vas deferens indurated, with 2 small nodules in lower part near epididymis (3). Gradual subsidence. No effects after 6 months.
10 AVG	Neostam	Pain in testes 8–14. Right epididymis enlarged and tender (11). Nodule in right epididymis (14).	Nodule in right epididymis (7), gradual subsidence. No effects after 6 months.
11 BAC	Fuadin	None	Nodule of 1 cm. diameter excised from scrotum (14). See description of section in text and Plate 2.
4 BCR	Anthiomaline (Specia)	Left testis swollen and funiculitis (14). Nodule in left epididymis (18). Testis and cord improved (20).	Left cord still indurated (11). Very small nodule in left epididymis (37). Entirely negative after 6 months.
6 GSM	Anthiomaline (Specia)	Swollen left testis and cord tender (8, 20).	Negative (9).
9 RRM	Anthiomaline (Specia)	None	Both testes and cords swollen; had funiculitis and epididymitis (9).
3 MADB	Anthiomaline (Merck)	None	Orchitis and funiculitis (14). Subsided (24).
18 JBP	Melarsen oxide	None	Right epididymis and testes markedly swollen; large nodule in upper pole of epididymis (17). Negative after 6 months.

indicated either long sustained infection or else infection with many adult filariae.

A nodule was removed surgically by Dr. Julio S. Colón, Urologist of the University Hospital, from the scrotum of one patient (No. 11 BAC) who was treated with fuadin. Sections of this nodule prepared by Dr. Enrique Koppisch, Pathologist of the School of Tropical Medicine, revealed one or more adult filarial worms in the uteri of which microfilariae could be distinctly seen. In some parts of the section there was an extensive area of inflamation about the worm, which was apparently dead, suggestive of an acute Arthus reaction. Elsewhere, apparently dead worms were found in distended vessels, where they were enveloped by thrombi. Because of the condition of the nuclei in the ovary and other structures of the worms, it was believed the parasites had died recently, when the nodule was excised. Plate 2 reveals some details of the pathology.

OBSERVATIONS ON THE UNTREATED (CONTROL) CASES OF FILARIASIS

Fifteen patients with filariasis were kept untreated as a control group. All of these individuals were students at the Insular Home for Boys at Guaynabo, Puerto Rico. They were between 8 and 17 years of age. All were symptom-free but had microfilariae in their nocturnal blood.

Most of these individuals have been observed for the past twenty months. At intervals during this time, the number of microfilariae had been determined in 60 cmm. of finger blood. The relevant data on the patients are shown in Table 19.

It is significant that at no time during the twenty months of observation has any control patient failed to present microfilariae in the nocturnal blood sample. After twenty months, three of the 15 cases had somewhat fewer parasites than when first seen, but the remaining 12 persons all showed a rise in the over-all microfilaria level, this rise in half the cases amounting to 100 percent of the number first seen.

In the light of the regular persistence of the infection in these control cases—even in those with small infections—the disappearance of microfilariae from treated individuals can hardly be ascribed to anything except the effects of treatment.[11]

11. No signs whatever in the scrotum or elsewhere, referable to adult filarias, were seen in the control cases. Although all control cases were males and some had quite high microfilaria counts, the comparative youth of these persons may have precluded the possibility of such scrotal signs, the adult worms not having as yet made their way to the scrotum. In treated male patients of similar age to these controls, no scrotal involvement was likewise seen, despite the intensive administration of drug (neostibosan) and the eventual disappearance of all microfilariae from the circulating blood.

the cotton rat, is more vulnerable to the administered drug than is the microfilaria. The disappearance of microfilariae from the blood of treated patients is evidently not the result of a direct action of the drug on the microfilariae but rather the consequence of the death of the adult worms. Since no new microfilariae will be formed after the adults die, embryos will not be found in the blood after those present during treatment are lost. Following treatment, the long period required for the final disappearance of microfilariae—up to fifteen or eighteen months in some patients (Table 6)—suggests a corresponding longevity for these embryos.

It is unfortunate that through the tests in experimental animals (filariated cotton rats, dogs, and so forth) or by *in vitro* studies, drugs of greater effectiveness in filariasis have not been found. The practical therapy of filariasis requires a compound that can be more easily administered than neostibosan, and one that is more promptly effective. Yet, in the estimation of the authors, neostibosan is a reasonably effective therapeutic agent for filariasis *bancrofti*, one that may be used safely and with fairly good likelihood of success. The use of this compound in filariasis is, therefore, recommended until such time as a more favorable therapeutic agent is discovered, whenever treatment is deemed advisable.

SUMMARY

The present report summarizes the results of a study designed to discover chemotherapeutic agents effective in filariasis *bancrofti*. Preliminary tests were conducted upon a naturally occurring filariasis (*Litomosoides carinii*) in the cotton rat. These tests, carried on by ourselves and others, showed that a number of drugs containing antimony or arsenic are effective in the therapy of the rodent filariasis. Certain of these compounds were then employed in the treatment of human filariasis.

One hundred and fourteen patients with filariasis *bancrofti* have been treated with various drugs, the entire group being divided as follows: 35 were treated with neostibosan, 11 with neostam, 6 with urea stibamine, 5 with stibanose, 15 with fuadin, 20 with anthiomaline, 4 with tartar emetic, and 18 with melarsen oxide. Fifteen additional patients with filariasis *bancrofti* have been left untreated to serve as a control group on the effects of therapy. All of the 129 patients, who ranged from 8 to 37 years of age, had microfilariae in the nocturnal blood. Only 3 individuals presented symptoms of filarial infection.

It was the plan of the investigation to press each drug as intensively as possible. With some drugs, quite severe reactions, as de-

scribed above, were seen, and therapy had to be discontinued in some cases. The drugs which were best tolerated were the pentavalent antimonials, neostibosan and stibanose.

With every drug, some patients showed marked reductions, presumably permanent, in the numbers of circulating microfilariae and, with every drug except fuadin, at least one patient apparently lost all microfilariae from the blood. Usually, these reductions in microfilaria levels occurred slowly, and the blood of some patients was negative for embryos only after from twelve to eighteen months from the end of treatment. The most satisfactory results thus far have been shown by patients treated with neostibosan. Twenty-three of 35 in this group lost all parasites, apparently with little likelihood of relapse, and 7 others showed good promise of soon becoming negative. In contrast, none of the 15 untreated control patients has yielded a negative blood sample during the twenty months the controls have been followed. At the end of this period, a small reduction in the number of circulating embryos was seen in 3 of the controls, and an increase was observed in the remaining 12.

Scrotal involvement was seen in certain adult patients after intensive treatment with various drugs, and dead filarial worms were observed in a nodule excised from the scrotum of one patient treated with fuadin. The scrotal symptoms subsided, apparently completely, within a few weeks in all cases, with no suggestion that the patients suffered permanent damage as the result of treatment.

It is concluded from this study that filariasis *bancrofti* can be eliminated from patients by the administration of certain compounds of antimony or arsenic. Of the various drugs tested in patients, the pentavalent antimonial, neostibosan, shows the greatest promise of practical use in the disease, because it exerts a strong antagonistic effect upon the filarial worm and can be used with comparative safety, being well tolerated, essentially, by all subjects.

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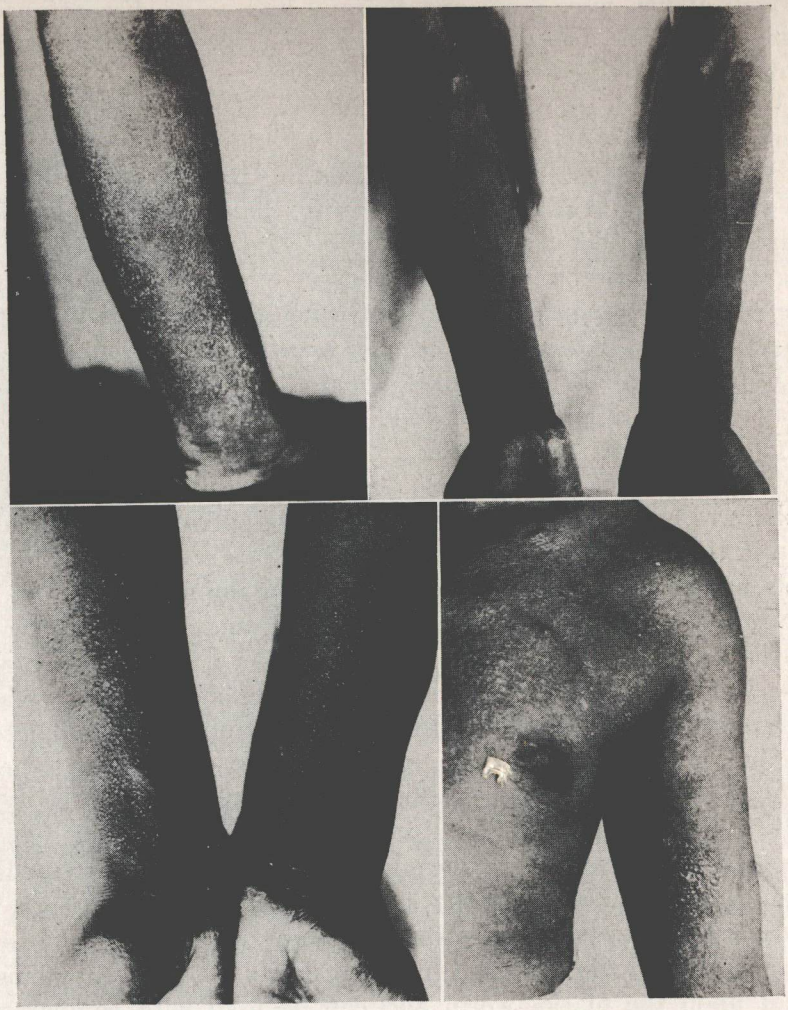

PLATE I

Dermatitis seen in patients with filariasis *bancrofti* during intensive administration of neostam. Identical reactions were seen in other subjects receiving other compounds of antimony.

LÁMINA I

Dermatitis observado en los sujetos parasitados con *W. bancrofti* durante la administración intensiva de neostam. Reacciones cutáneas análogas se presentaron en otros sujetos bajo la acción de otros compuestos de antimonio.

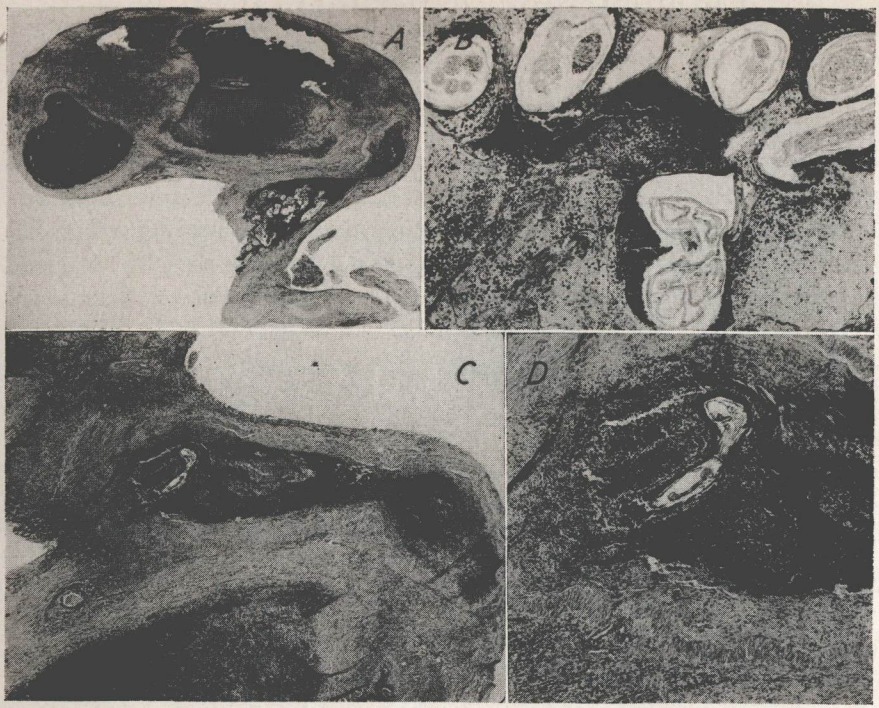

PLATE II

Photographs of Sections Prepared from Nodule Excised from Patient (No. 11 BAC) Treated with Fuadin.

A. (x 5) Section through nodule.
B. (x 50) Arthus-like appearance of reaction around worm.
C. (x 50) Worm in thrombus-like structure in vessel.
D. (x 100) Higher power of C, showing relationship of wall of vessel to worm in thrombus-like occlusion.

LÁMINA II

Fotograbados de cortes de un nódulo extirpado a un enfermo (número 11 BAC) tratado con fuadina.

A. (x 5) Corte longitudinal del nódulo.
B. (x 50) Reacción en torno al verme filárico, la cual se asemeja a la reacción de Arthus.
C. (x 50) Verme trombosando un vaso.
D. (x 100) El mismo fotograbado C en gran aumento demostrando la pared del vaso en relación con el verme trombosante.