CHEMOTHERAPY OF MURINE LEPROSY.

IV. THE EFFECTS OF AMITHIOZONE (TB1/698), *p*-AMINOSALICYLIC ACID (PAS), B283 (A PHENAZINE PIGMENT), FIVE ANTIBIOTICS AND THREE DIPHENYLTHIOUREA COMPOUNDS ON MOUSE LEPROSY

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The results of treatment of murine leprosy in the mouse with streptomycin, certain sulfones and isonicotinylhydrazines, nicotinamide and pyrazinamide have been reported previously (6, 7). The present paper deals with amithiozone (TB1/698), *p*-aminosalicylic acid (PAS), a phenazine pigment (B283), five antibiotics (chlortetracycline, oxytetracycline, chloramphenicol, penicillin and erythromycin) and three diphenylthiourea derivatives (SU-1795, SU-1906 and SU-2358).

Several reports on the effects of thiosemicarbazone compounds and of *p*-aminosalicylic acid on murine leprosy have appeared, but the value of these drugs has not been established. Variation in screening techniques used by different investigators probably explains the discordant results reported. There are differences in the species of animal used and in routes of inoculation, and in dosage of drugs, mode of administration, and length of treatment.

Amithiozone (*p*-acetylaminobenzaldehyde thiosemicarbazone) has been used in seven series of experiments, four in rats (8, 9, 21, 22) and three in mice (2, 11, 12), but in no two instances with either species were the experimental conditions the same. The drug was reported active in one experiment in rats and in two in mice, inactive in three experiments in rats and one in mice. Two other thiosemicarbazones have been tested: 4-ethyl-sulfonylbenzaldehyde thiosemicarbazone, found to be inactive in mice (10), and *p*-pyridine aldehyde thiosemicarbazone, found active in the rat (16).

Contradictory results have been reported also with PAS. Three experiments were performed in rats and two in mice, the results being successively inactive, active, active, inactive and slightly active (8, 17, 22, 11, 15).

Of the five antibiotics dealt with in the present report, two have previously been reported to be inactive: penicillin, in three experiments in rats (20, 4, 13), in which dosages and duration of treatment differed; and oxytetracycline, in one experiment in mice (12).

A summary of the principal experimental conditions and findings of various authors who have used thiosemicarbazones, PAS, penicillin and oxytetracycline is given in Table 1.

The use of B283, the hydrochloride of 2-anilino-3-amino-5-phenylphenazine, in murine leprosy has not previously been reported. It has been said to be effective in experimental tuberculosis in mice (3), in

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urinary-tract tuberculosis in man (14), and in human leprosy (1). Recently diphenylthiourea derivatives were reported to be effective in experimental tuberculosis of mice and of guinea pigs (19), and these compounds are

TABLE 1.—*Summary of published reports on the effects of thiosemicarbazones, PAS, penicillin and oxytetracycline on murine leprosy.*

Drug	Activity	Animal and route of infection	Daily dose and route of administration	Duration of treatment	Reference
Amithiozone (TB-1)	Inactive	Rat H	20 mgm/rat O	6 mo.	8
	Inactive	Rat H?	(No data)	(?)	9
	Active	Rat H	0.3 mgm/rat O	60 da.	22
	Inactive	Rat H	0.1-0.2 gm/rat H	3-10 mo.	21
	Active	Mouse IV	10 mgm/mouse F	180 da.	2
	Active	Mouse IP	0.5 gm/kgm F	28 da.	11
	Inactive	Mouse IP	10-50 mgm/mouse O/H	30-42 da.	12
4-Ethyl-sulfonyl-benzaldehyde thiosemicarbazone	Inactive	Mouse IE	0.1% F	4 mo.	10
p-Pyridine aldehyde thiosemicarbazone	Active	Rat IM	50 mgm/kgm H	171 da.	16
PAS	Inactive	Rat H	400 mgm/rat O	6 mo.	8
	Active	Rat IP	1.3 gm/kgm F	8 mo.	17
	Active	Rat H	25 mgm/rat O	60 da.	22
	Inactive	Mouse IP	2.5 gm/kgm F	28 da.	11
	Slight	Mouse IC	20 mgm/mouse H	77 da.	15
Penicillin	Inactive	Rat IP &H	800 u/rat IP	10 wk.	20
	Inactive	Rat H	1000 u/rat H	5 mo.	4
	Inactive	Rat H	25000 u/kgm twice weekly H?	2-3 mo.	13
Oxytetracycline	Inactive	Mouse IP	20 mgm/mouse H/O	30-42 da.	12

Code: F = Food; H = Hypodermically; IC = Intracerebrally; IE = Intracorneally; IM = Intramuscularly; IP = Intraperitoneally; IV = Intravenously; O = Orally by tube; u = Units.

said also to be effective in murine leprosy (18). No report has been found on the action of chlortetracycline, chloramphenicol or erythromycin in murine leprosy.

METHODS AND MATERIAL

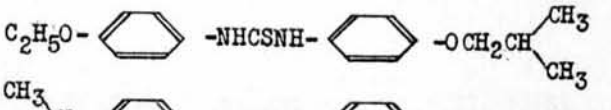
The technique of chemotherapeutic assay in intraperitoneally infected mouse leprosy previously described by me (5) was employed. Female albino mice of National Institutes of Health general-purpose strain, weighing 20±2 gm., were used in groups of 20, each group being caged separately. Inoculations were made with 0.5 cc. of a 1:30 suspension made from the omenta and pelvic fatty pads of mice which had been infected four to five months before with the Hawaiian strain of *Mycobacterium leprae murium*.

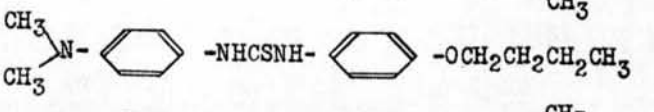
Except when otherwise stated, treatment was started on the day after inoculation. Streptomycin was injected subcutaneously, daily, five days a week. All other drugs

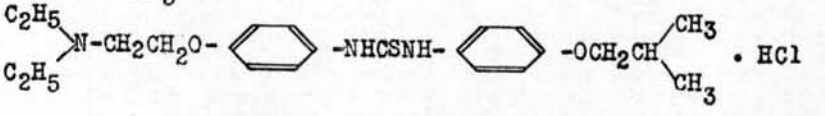
were mixed in the food except penicillin, which was given in the drinking water. With amithiozone, four dose levels were employed. Small doses, 0.05 and 0.1 per cent, were tested in one experiment in duplicated groups. Moderate doses, 0.3 per cent, were screened in three repeated experiments. The large dose of 1 per cent was tested in two experiments in which treatment was delayed for one and one-half months after inoculation and therapy then given for only one and one-half months. The dosage with PAS was 0.6 per cent. B283 was begun at a level of 0.5 per cent, but loss of body weight was noted early and the dose was reduced to 0.2 per cent in the second week and to 0.1 per cent thereafter. Of the antibiotics, chlortetracycline was used in 0.1 per cent concentration, and oxytetracycline and chloramphenicol at 0.3 per cent. The concentration of penicillin in the water was 200 units per cc., given five days per week. Stock solutions were prepared once a week and kept at 4°C. Erythromycin, also in the food, was 0.5 per cent. Of the diphenylthiourea derivatives, SU-1795 was begun at 2 per cent concentration, SU-1906 at 0.5 per cent, and SU-2358 at 0.1 per cent; changes proved necessary, as will be noted later.

Animals were sacrificed approximately three months after inoculation. Autopsies were performed by me without knowledge of the treatment the animals had received. The mortality rate, body weight, weights of omenta and pelvic fatty pads, and the bacillus and leprosy indices, were recorded, and the omenta and pelvic fatty pads were photographed. The bacillus index represents the total score (graded as 0 to 5 for each smear) given to smears made from the following sites and organs: site of inoculation, omentum, pelvic fatty pads, portal lymph nodes, paravertebral lymph nodes, thymus gland (bronchotracheal lymph nodes in some early experiments), spleen, liver, lung and kidney. The leprosy index is the total score given to gross pathologic lesions in various sites and organs graded as follows: site of inoculation and lymph nodes, each, 0-2; omentum and mesentery, 0-6; pelvic fatty pads, spleen and liver, each, 0-4; miscellaneous, including lungs, kidneys, diaphragm, pericardium, retrosternal region, and thymus gland, each, 0-1. The data presented in Tables 2 to 6 represent the averages of all animals of each group except the bacillus indices, which are averages of two representative animals of each group.

Amithiozone (Myvizone) was supplied by E. R. Squibb & Sons; PAS and chloramphenicol (Chloromycetin) by Parke, Davis & Co.; B283 by Geigy Pharmaceutical Laboratories; erythromycin (Ilotycin) by Eli Lilly & Co.; chlortetracycline (Aureomycin) by Lederle Laboratories; oxytetracycline (Terramycin) and penicillin, crystalline G, by Chas. Pfizer & Co.; and streptomycin sulfate by Merck & Co.; while Ciba Pharmaceutical Products supplied the following three diphenylthiourea compounds:

SU-1795, 

SU-1906, 

SU-2358, 

RESULTS

Evaluation of amithiozone.—Of 380 animals included in these experiments, 31 died. Twenty-seven of these deaths were caused by intercurrent diseases, and only four by leprous involvement: two in the control group of Experiment 2, and one each in the control group and Group B (0.1%

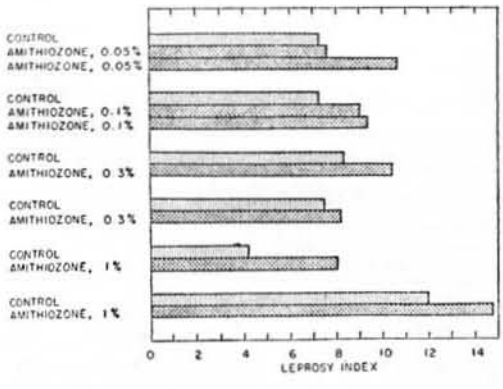
TABLE 2.—*Evaluation of amithiozone.*

Exp. No.	Group	Dose in food	No. died/ used	Body wt. gm.	Weight of omentum gm.	Weight of pelvic fatty pads gm.	Bacillus index	Leprosy index								ICE[a]
								Site of inoculation	Omentum and mesentery	Pelvic fatty pads	Lymph nodes	Spleen	Liver	Misc.	Total index	
1	Normal mice		1/20	24.4	0.01	0.75										
	Leprosy control, untreated		1/20	25.7	0.19	1.60	19.7*b*									
	Amithiozone	0.3%	2/20	22.9	0.20	1.43	23.7*b*									
	Amithiozone, toxicity control	0.3%	0/20	23.9	0.02	0.71										
2	Leprosy control, untreated		3/20	23.2	0.13	1.00	13.3	0.76	3.00	2.47	0.83	0.18	1.00	0	8.24	
	Amithiozone	0.3%	2/20	20.8	0.17	1.06	24.0	1.39	2.86	2.33	0.72	1.33	1.44	0.31	10.38	0.8
3	Leprosy control, untreated		1/20	25.8	0.17	1.67		1.42	2.05	2.95	0.53	0.21	0.31	0	7.47	
	Amithiozone	0.3%	1/20	22.2	0.16	1.68		0.61	2.11	2.95	0.15	1.15	0.79	0.37	8.13	0.9
	Streptomycin	3 mg[c]	1/20	26.4	0.09	1.22		0.42	0.98	1.26	0.05	0	0	0	2.71	2.8
	Streptomycin and amithiozone	3 mg[c] 0.3%	0/20	27.4	0.10	1.25		0.75	1.25	1.10	0	0	0.05	0.05	3.20	2.3
4	Leprosy control, untreated		1/20	21.1	0.11	0.84	18.0	0.79	2.92	1.58	0.42	0.66	0.76	0.11	7.24	
	Amithiozone, Group A	0.05%	2/20	23.8	0.12	0.90	17.5	0.67	3.50	1.58	0.28	0.58	0.63	0.36	7.60	1.0
	Amithiozone, Group B	0.05%	1/20	23.4	0.22	0.99	19.0	0.76	4.08	2.50	0.37	1.11	0.95	0.84	10.61	0.7
	Amithiozone, Group A	0.1%	0/20	21.9	0.12	0.98	22.5	0.86	3.15	2.13	0.33	1.10	0.90	0.50	8.97	0.8
	Amithiozone, Group B	0.1%	1/20	21.7	0.12	0.75	14.5	0.95	3.53	1.68	0.47	0.89	0.92	0.89	9.33	0.8
5	Leprosy control, untreated		0/20	27.0	0.08	0.64	18.3	0.55	1.73	0.78	0.23	0.30	0.63	0	4.22	
	Amithiozone[d]	1.0%	0/20	24.0	0.13	0.73	19.5	0.68	3.15	2.15	0.18	1.05	0.68	0.15	8.04	0.5
6	Leprosy control, untreated		5/20	24.1	0.19	0.95	24.0	0.93	4.53	2.87	0.53	0.77	0.73	1.63	11.99	
	Amithiozone[d]	1.0%	9/20	20.9	0.14	0.82	28.0	1.05	5.09	3.14	0.77	1.00	1.23	2.50	14.78	0.8

a Index of chemotherapeutic effectiveness; see text.
b The bacillus index in this case is the average of the whole group of animals.
c Injected subcutaneously.
d Treatment started one and one-half months after the inoculation.

dosage) of Experiment 4. The drug was well tolerated, as shown by the experience of the toxicity control group given 0.3 per cent of the drug in Experiment 1, and that of the group treated with 1 per cent in Experiment 5.

The average weights of the omenta of all animals treated with different doses of amithiozone were either equal to or larger than the comparable weights for the controls except in the treated group of Experiment 6. The weights of pelvic fatty pads of all amithiozone-treated groups were likewise similar to or greater than those of the untreated controls. The rougher appearance and the larger sizes of omenta and pelvic fatty pads of representatives of the treated groups are shown in comparison with normals and untreated controls in Plates 7 and 8. Leprosy indices of all treated groups, especially those of Experiments 2, 5 and 6, and of Group B (0.05%) in Experiment 4, were larger than those of corresponding controls (Text-fig. 1). The bacillus indices of all treated groups, except two groups receiving the smaller doses of the drug, were likewise slightly higher than those of the controls.



TEXT-FIG. 1. Comparison of the leprosy indices of animals treated with various doses of amithiozone, with those of their corresponding controls. All the leprosy indices of treated groups are definitely larger than those of the controls except 2 groups which are only slightly larger than those of the controls. These were one treated with 0.05 per cent in the food, and another with 0.3 per cent.

The average index of chemotherapeutic effectiveness (ICE)[3] of all the treated groups was 0.8, with a range of 0.5 to 1. This indicates that the administration of various doses of amithiozone resulted in an increase of about 25 per cent in the growth of the leprosy lesions.

Histologic studies revealed no qualitative changes in the lesions resulting from the amithiozone therapy. Quantitative evaluations of the involvement of tissues were not conclusive, although a slight increase in the lesions has been found in certain tissues (e. g., heart, thymus, etc.) of treated animals.

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[3] Index of chemotherapeutic effectiveness is calculated by: $\frac{\text{Total leprosy index of control group}}{\text{Total leprosy index of treated group}}$. The larger the figure, the higher is the activity of the drugs. Unity means no action. A figure below unity means enhancement of the leprous growth.

Streptomycin, on the other hand, had marked suppressive activity. The animals given combined therapy with streptomycin and amithiozone showed a slightly higher leprosy index and lower ICE than did those given streptomycin alone.

From these findings it may be concluded that the various dose levels of amithiozone employed produced no suppressive activity. On the contrary, there was a slight but definite stimulation of the infection. This was observed in animals receiving full treatment, as well as in those in which therapy was delayed. When amithiozone was used in combination with streptomycin, the suppressive activity of streptomycin was not enhanced.

Evaluation of PAS.—The effect of *p*-aminosalicylic acid, or PAS, was studied in three successive experiments the results of which are shown in Table 3. Four animals in the first two experiments and 17 in the third died of intercurrent diseases. That the drug was well tolerated, however, is shown by the mortality rate and the body weights of the PAS groups of the first two experiments.

In the first experiment, the over-all average weights of the omenta and of the pelvic fatty pads, and also the bacillus indices, had approximately similar values in the treated and untreated groups. The values of the weights of omenta and pelvic fatty pads, and of the leprosy index of the treated group, were slightly lower than those of the control group in the second experiment but slightly higher in the third one. Streptomycin alone showed a definitely suppressive effect, as before, but the combination of streptomycin and PAS was not advantageous.

Evaluation of B283.—The phenazine pigment B283 was tested in duplicate groups in one experiment, the results of which are also given in Table 3. Eleven animals, five in one of the duplicate treated groups, three in the other, and three in the control group, died of intercurrent diseases. The average body weight of the survivors in the two treated groups was lower than that of the control animals. No marked differences in the weights of omenta or of pelvic fatty pads, or in the bacillus and leprosy indices, were noted between the treated and untreated groups, indicating that this drug possesses no suppressive activity in mouse leprosy.

Evaluation of antibiotics.—Two successive experiments were performed to determine the effects of chlortetracycline, oxytetracycline and chloramphenicol, as shown in Table 4. All three of these antibiotics were well tolerated. One animal of the control group and two of the chloramphenicol group in the first experiment died of intercurrent diseases.

Two animals of the control group in Experiment 1 and one of the controls in Experiment 2 died because of extensive leprous involvement. In the first experiment, oxytetracycline showed a slight suppressive action on leprous growth, while the other antibiotics were inactive. In the second experiment, the leprosy indices of all three were slightly higher than that

TABLE 3.—*Evaluation of PAS and B283.*

Exp. No.	Group	Dose in food	No. died/ used	Body wt. gm.	Weight of omentum gm.	Weight of pelvic fatty pads gm.	Bacillus index	Leprosy index								ICE
								Site of inoculation	Omentum and mesentery	Pelvic fatty pads	Lymph nodes	Spleen	Liver	Misc.	Total index	
1	Leprosy control, untreated		1/20	25.7	0.19	1.60	19.7[a]									
	PAS	0.6%	1/20	25.0	0.23	1.53	21.3[a]									
2	Leprosy control, untreated		1/20	25.8	0.17	1.67		1.42	2.05	2.95	0.53	0.21	0.31	0	7.47	
	PAS	0.6%	0/20	24.1	0.14	1.43		1.05	1.60	3.00	0.35	0.20	0.40	0	6.60	1.1
	Streptomycin	3mg[b]	1/20	26.4	0.09	1.22		0.42	0.98	1.26	0.05	0	0	0	2.71	2.8
	PAS and streptomycin	0.6% 3mg[b]	0/20	27.4	0.13	1.32		0.65	1.50	1.00	0.25	0	0	0	3.40	2.2
3	Leprosy control, untreated		5/20	24.1	0.19	0.95	24.0	0.93	4.53	2.87	0.53	0.77	0.73	1.63	11.99	
	PAS	0.6%	12/20	25.4	0.19	1.10	24.5	0.69	4.75	2.69	0.75	1.00	0.81	2.38	13.07	0.9
1	Leprosy control, untreated		3/20	24.1	0.14	0.79	15.0	0.53	3.97	1.41	0.50	0.38	0.44	1.32	8.55	
	B283, Group A	0.5—0.1%	5/20	21.2	0.17	0.82	15.0	0.93	3.77	1.90	0.37	0.60	0.53	1.80	9.90	0.9
	B283, Group B	0.5—0.1%	3/20	22.1	0.13	0.52	14.0	0.62	3.85	1.65	0.38	0.44	0.21	1.00	8.15	1.1

a The bacillus index in this case is the average of the whole group of animals.
b Injected subcutaneously.

of the control. The average ICE's of the two experiments were, 1.0 for chlortetracycline, 1.2 for oxytetracycline and 1.0 for chloramphenicol. None of these antibiotics, therefore, was found to possess suppressive activity.

Penicillin was tested in three successive experiments (Table 5). Four animals of the treated group in the first experiment and two animals of the control group in the second experiment died shortly before termination of the experiments from extensive leprous involvement. Eight other deaths were caused by intercurrent diseases. The leprosy index of the treated group in the first experiment was definitely higher than that of the control, definitely lower in the second, and only slightly lower in the third, showing that activity of penicillin, if any, was inconsistent. The average ICE of the three experiments taken together was 1.2, and it is concluded that penicillin had no marked suppressive action.

Erythromycin, tested in one experiment in duplicate groups (Table 5), was well tolerated. Three control animals and two of the treated groups died in the first two months of the experiment of intercurrent diseases. Identical results were obtained in the weights of omenta and of pelvic fatty pads, and in the bacillus and leprosy indices, for the treated and untreated groups, showing that erythromycin has no activity in mouse leprosy.

In short, none of the five antibiotics—chlortetracycline, oxytetracycline, chloramphenicol, penicillin and erythromycin—revealed any significant activity.

Evaluation of diphenylthiourea compounds.—The three derivatives of diphenylthiourea employed were tested in one experiment, duplicate groups being used for each drug and also for the control. With SU-1906, started at 0.5 per cent, marked loss of body weight was noted in both groups within two weeks; the drug was then stopped for 10 days and resumed with the reduced dose of 0.2 per cent. With SU-1795, started at 2 per cent, both groups showed some loss of body weight, and the dose was reduced to 1 per cent from the fourth week. SU-2358 was well tolerated. The results are shown in Table 6.

Two animals receiving SU-1906, Group B, and three receiving SU-2358, Group A, died of intercurrent diseases in this experiment, two in the early days and three shortly before the termination of the experiment. The average leprosy index of the two control groups was 9.04, which was the same as that of the two groups treated with SU-1795. The SU-1906 animals had leprosy indices slightly higher, and the SU-2358 animals slightly lower, than those of the controls. In general, the three derivatives of diphenylthiourea showed no marked activity.

DDS, 0.1 per cent in the food, was used as a standard of reference for this experiment. Its suppressive activity on the leprous growth is also shown in Table 6.

TABLE 4.—*Evaluation of chlortetracycline, oxytetracycline and chloramphenicol.*

Exp. No.	Group	Dose in food	No. died/ used	Body wt. gm.	Weight of omentum gm.	Weight of pelvic fatty pads gm.	Bacillus index	Leprosy index								ICE
								Site of inoculation	Omentum and mesentery	Pelvic fatty pads	Lymph nodes	Spleen	Liver	Misc.	Total index	
1	Leprosy control, untreated		3/20	23.2	0.13	1.00	13.3	0.76	3.00	2.47	0.83	0.18	1.00	0	8.24	
	Chlortetracycline	0.1%	0/20	23.7	0.15	1.24	18.0	1.20	2.25	2.05	0.35	0.40	1.20	0.10	7.55	1.1
	Oxytetracycline	0.3%	0/20	24.9	0.11	1.21	18.5	1.55	1.68	1.93	0.35	0.15	0.33	0	5.99	1.4
	Chloramphenicol	0.3%	2/20	25.4	0.16	1.07	27.5	1.67	2.25	2.22	0.72	0.50	1.22	0	8.58	1.0
2	Leprosy control, untreated		1/20	21.1	0.11	0.84	18.0	0.79	2.92	1.58	0.42	0.66	0.76	0.11	7.24	
	Chlortetracycline	0.1%	0/20	24.4	0.13	1.03	13.0	0.96	3.82	1.90	0.35	0.25	0.33	0.58	8.19	0.9
	Oxytetracycline	0.3%	0/20	24.1	0.13	1.16	18.0	0.99	3.25	2.23	0.58	0.53	0.38	0.53	8.49	0.9
	Chloramphenicol	0.3%	0/18	23.3	0.13	1.02	17.5	0.92	3.44	2.44	0.08	0.56	0.61	0.47	8.52	0.9

TABLE 5.—*Evaluation of penicillin and erythromycin.*

Exp. No.	Group	Dose[a]	No. died/ used	Body wt. gm.	Weight of omentum gm.	Weight of pelvic fatty pads gm.	Bacillus index	Leprosy index								ICE
								Site of inoculation	Omentum and mesentery	Pelvic fatty pads	Lymph nodes	Spleen	Liver	Misc.	Total index	
1	Leprosy control, untreated		5/20	24.1	0.19	0.95	24.0	0.93	4.53	2.87	0.53	0.77	0.73	1.63	11.99	
	Penicillin	100 u/cc.	4/20	23.4	0.20	1.48	29.5	1.31	5.41	3.06	0.94	1.72	1.31	2.38	16.13	0.7
2	Leprosy control, untreated		2/20	23.7	0.13	1.00	20.0	1.14	4.72	2.28	0.83	0.67	0.72	1.64	12.00	
	Penicillin	100u/cc.	1/20	23.6	0.12	1.05	12.0	0.95	3.39	1.03	0.39	0.11	0.37	0.84	7.08	1.7
3	Leprosy control, untreated		1/20	24.8	0.18	1.56	20.0	0.53	3.92	2.47	0.08	0.58	0.61	1.34	9.53	
	Penicillin	100u/cc.	1/20	23.7	0.13	1.11	13.5	0.58	3.45	1.82	0.11	0.82	0.29	1.11	8.18	1.2
1	Leprosy control, untreated		3/20	24.1	0.14	0.79	15.0	0.53	3.97	1.41	0.50	0.38	0.44	1.32	8.55	
	Erythromycin, Group A	0.5%	1/20	23.1	0.14	0.76	19.0	0.50	3.68	1.58	0.34	0.53	0.29	1.45	8.37	1.0
	Erythromycin, Group B	0.5%	1/20	23.1	0.14	0.77	14.5	0.61	3.89	1.58	0.29	0.32	0.50	1.37	8.56	1.0

a Penicillin was dissolved in drinking water, the erythromycin was given in the food.

TABLE 6.—*Evaluation of diphenylthiourea compounds.*

Group	Dose in food	No. died/ used	Body wt. gm.	Weight of omentum gm.	Weight of pelvic fatty pads gm.	Bacillus index	Leprosy index								ICE
							Site of inoculation	Omentum and mesentery	Pelvic fatty pads	Lymph nodes	Spleen	Liver	Misc.	Total index	
Leprosy control, untreated, Group A		0/20	24.0	0.20	1.32	14.0	0.73	3.93	1.80	0.13	0.28	0.35	1.20	8.42	
Leprosy control, untreated, Group B		0/20	25.5	0.18	1.21	18.0	0.58	4.20	2.40	0.30	0.60	0.55	1.03	9.66	
DDS	0.1%	0/20	24.7	0.11	0.87	12.0	0.55	2.93	0.93	0.05	0	0.05	0.70	5.21	1.8
SU-1795, Group A	2-1%	0/20	22.9	0.18	1.34	18.0	0.70	3.70	2.15	0.13	0.45	0.20	1.48	8.81	1.0
SU-1795, Group B	2-1%	0/20	24.3	0.17	1.56	15.5	0.84	3.63	2.34	0.08	0.74	0.26	1.39	9.28	
SU-1906, Group A	0.5—0.2%	0/20	21.0	0.14	1.14	12.0	0.53	3.83	2.60	0.13	1.25	0.53	1.15	10.02	0.9
SU-1906, Group B	0.5—0.2%	2/20	21.2	0.16	1.42	22.0	0.75	3.61	2.42	0.11	1.33	0.31	1.78	10.31	
SU-2358, Group A	0.1%	3/20	22.9	0.18	1.22	10.5	0.53	3.32	1.71	0.06	0.06	0	1.09	6.77	1.2
SU-2358, Group B	0.1%	0/20	24.2	0.15	1.14	10.5	0.55	3.60	1.83	0.18	0.25	0.28	0.98	7.67	

DISCUSSION

The results of all the experiments presented in this report are summarized in Table 7. The average index of chemotherapeutic effectiveness (ICE) of each dose of each drug or of each combination of drugs is shown. The averages, excepting those for streptomycin and DDS, are for two or three groups of animals tested in different experiments or for duplicate groups screened in a single test. Forty animals were usually used for each

TABLE 7.—*Combined results concerning the activity of the drugs dealt with in Tables 2 to 6.*

Drug	Dose		No. of mice used	ICE[b]
	Per cent in food	Mgm./kgm.[a]		
Amithiozone	0.05	100	40	0.8
Amithiozone	0.1	200	40	0.8
Amithiozone	0.3	600	40	0.9
Amithiozone	1.0	2000	40	0.7
PAS	0.6	1200	40	1.0
B283	0.5-0.1	1000-200	40	1.0
Chlortetracycline	0.1	200	40	1.0
Oxytetracycline	0.3	600	40	1.2
Chloramphenicol	0.3	600	40	1.0
Penicillin[c]	100 u/cc.	20000 u/kgm.	60	1.2
Erythromycin	0.5	1000	40	1.0
SU-1795	2-1	4000-2000	40	1.0
SU-1906	0.5-0.2	1000-400	40	0.9
SU-2358	0.1	200	40	1.2
Streptomycin		150	20	2.8
Streptomycin and amithiozone	0.3	150 600	20	2.3
Streptomycin and PAS	0.6	150 1200	20	2.2
DDS	0.1	200	20	1.8

a Calculated on the basis of an average food intake of 4 gm., or an average water intake of 4 cc., daily per 20-gram mouse.

b Index of chemotherapeutic effectiveness. The higher the figure the more the activity; unity means no action; less than unity means enhancement of the infection (see text).

c Drug dissolved in drinking water.

dose of a single compound, and 20 animals for a combination of two compounds. ICE values above unity, indicating suppressive action, are seen only with streptomycin and DDS.

It will be noted that the ICE values of amithiozone are below unity. All the doses of this drug used in these experiments showed some stimulating effect on mouse leprosy, producing an average of 25 per cent increase in the lesions. No other drug in the present series showed this effect. This apparent stimulating action of amithiozone is not in agreement with the findings of others, who have found that the drug is either suppressive or inactive (Table 1). Nor does it agree with the findings in human leprosy, in which definite effectiveness has been reported by several investigators. No satisfactory explanation can be given at present; further studies may throw some light on the reason for these discrepancies.

SUMMARY

Studies have been made of the therapeutic effects on murine leprosy of several drugs and antibiotics, employing the intraperitoneally-infected mouse. The following results were obtained:

Amithiozone (TB1/698) seemed to cause some stimulation of the infection.

PAS (*p*-aminosalicylic acid), B283 (a phenazine pigment), chlortetracycline (Aureomycin), oxytetracycline (Terramycin), chloramphenicol (Chloromycetin), penicillin, erythromycin (Ilotycin), and three derivatives of diphenylthiourea, i. e., SU-1795, SU-1906 and SU-2358, revealed no significant activity.

RESÚMEN

Estos estudios versan sobre los efectos terapéuticos de varias drogas, incluso antibióticos, en la lepra murina, habiéndose empleado para ellos ratones infectados intraperitonealmente. Se obtuvieron los siguientes resultados:

La amitiozona (Tb1/698) pareció ocasionar alguna excitación de la afección.

El PAS (ácido *p*-aminosalicílico), el B283 (pigmento fenacínico), la clortetraciclina (Aureomicina), la oxitetraciclina (Terramicina), el cloranfenicol (Cloromicetina), la penicilina, la eritromicina (Iloticina) y tres derivados de la difeniltiourea, a saber, SU-1795, SU-1906 y SU-2358, no revelaron mayor actividad.

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DESCRIPTION OF PLATES

PLATE (7)

Comparison of the pelvic fatty pads and omenta of untreated leprosy mice with those treated with small doses of amithiozone three months after inoculation. In each photograph the upper part is of the pelvic fatty pads, the lower one of the omenta.

FIG. 1. Pelvic fatty pads and omenta of 19 normal mice.

FIG. 2. Untreated leprosy control group of Experiment 4.

FIG. 3. Amithiozone, 0.05 per cent, group B. The lesions in the pelvic fatty pads and omenta are larger than those of the controls (Fig. 2).

FIG. 4. Amithiozone, 0.1 per cent, group A. The lesions here are also larger than those of the controls.

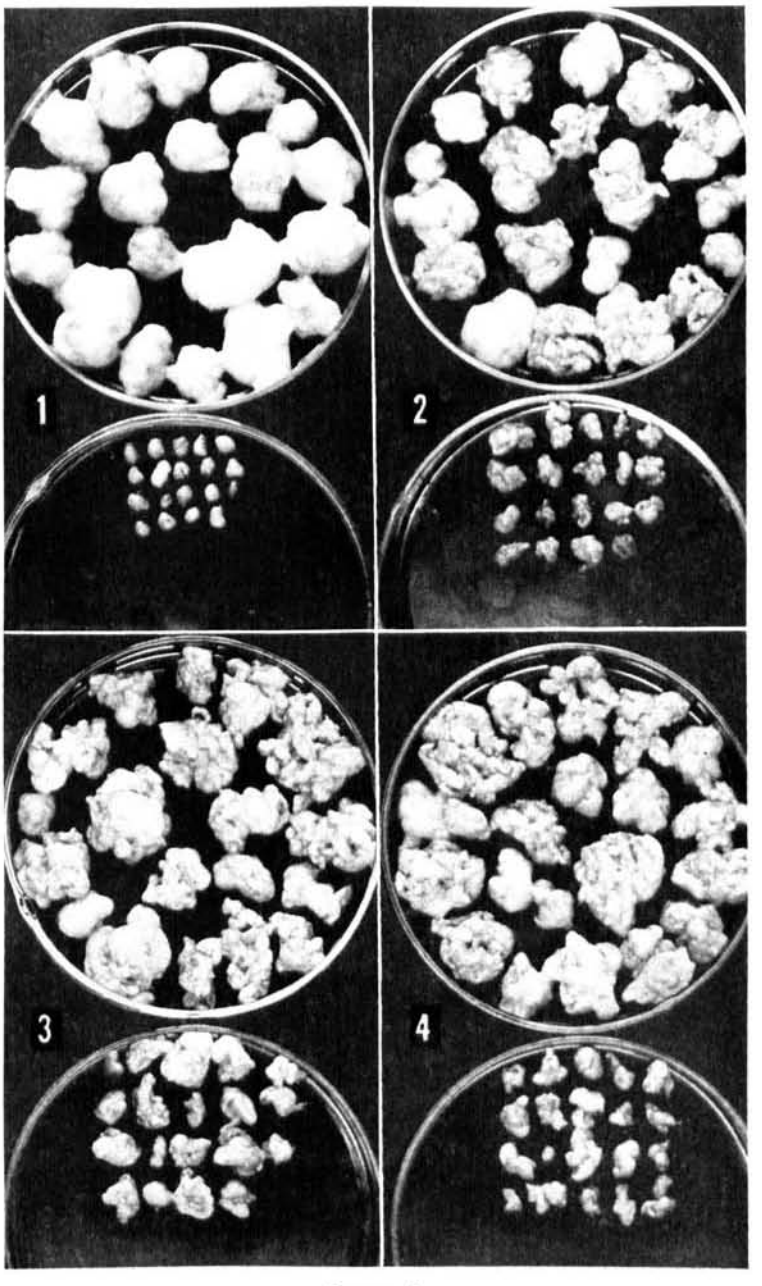

PLATE 7.

PLATE (8)

Comparison of the pelvic fatty pads and omenta of untreated leprosy mice with those treated with moderate and large doses of amithiozone three months after inoculation. In each photograph the upper part is of the pelvic fatty pads, the lower one of the omenta.

FIG. 5. Untreated leprosy control group of Experiment 2.

FIG. 6. Amithiozone group, 0.3 per cent. The lesions in the pelvic fatty pads and omenta are larger than those of the controls (Fig. 5).

FIG. 7. Untreated leprosy control group of Experiment 5.

FIG. 8. Amithiozone group, 1 per cent. The lesions in the pelvic fatty pads and omenta are larger than those of the controls (Fig. 7).

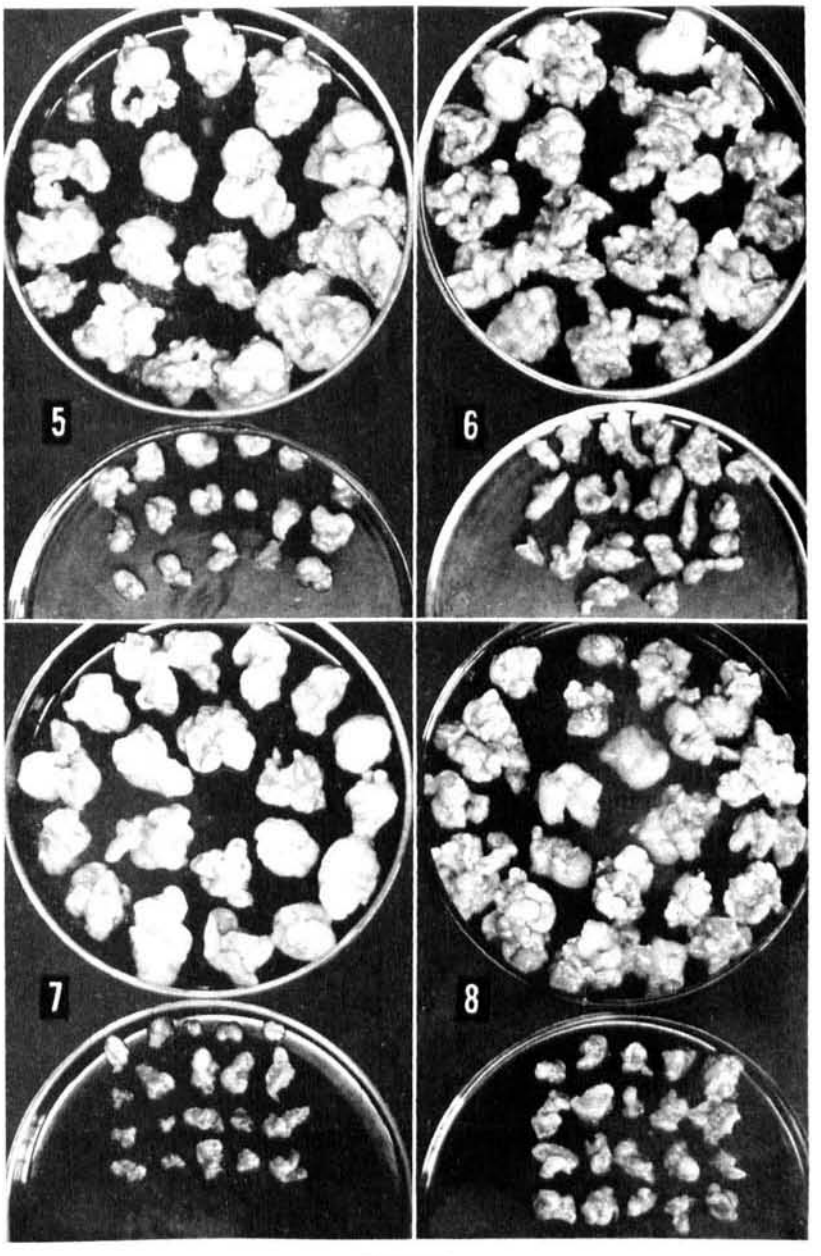

PLATE 8.