CHEMOTHERAPY OF MURINE LEPROSY II. THE EFFECTS OF STREPTOMYCIN, SULFONES AND ISONICOTINYLHYDRAZINES ON MOUSE LEPROSY

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INTRODUCTION

The effectiveness of the sulfones in the treatment of human leprosy is well known (9, 11). The antileprosy activity of streptomycin has been reported by several workers (6, 9, 11, 18). However, the action of these drugs on murine leprosy is still not established. Promin has been reported to have an inhibitory action on rat leprosy (2, 5) and on mouse leprosy (8). Diasone has been considered effective in rat leprosy when administered intraperitoneally (13), but ineffective when given subcutaneously (2). It was also ineffective in mouse leprosy (8). Antileprosy activity was demonstrated by 4,4'-diaminodiphenyl sulfone (DDS) in rat leprosy (7, 13, 14), and in intracerebrally-infected mouse leprosy (8).

A similar uncertainty also appears regarding chemotherapy with streptomycin or dihydrostreptomycin. This antibiotic has been reported ineffective in rats and mice inoculated by the usual routes (2, 4, 8), but definitely effective in mice inoculated intracerebrally (10).

As these compounds have been widely used in the treatment of leprosy, their chemotherapeutic actions in murine leprosy seem to merit careful study.

Recently isonicotinic acid hydrazide and its propyl derivative have been proved of suppressive value in experimental and clinical tuberculosis (1, 17, 21). It is, therefore, important to know whether they will reveal similar activity in the leprosy field. Clinical trials of these drugs have been undertaken in many places (23), but experimental data on murine leprosy are lacking.

The chemotherapeutic methods used by different investigators in the study of murine leprosy have not been uniform. In some studies rats have been used, in others mice. Various routes

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International Journal of Leprosy

of inoculation have been employed, i.e., subcutaneous, intramuscular, intraperitoneal, and intracerebral. The periods of treatment have ranged from 28 days to 18 months, and the basis of evaluation of activity has not been uniform. These variations may be responsible, in whole or part, for the conflicting results which have been reported. It seems clear that, unless a reliable technique is developed, uniformity can hardly be accomplished.

During the past one-and-one-half years we have studied the chemotherapeutic actions of various drugs on intraperitoneallyinfected mouse leprosy, and a simple and reliable test has been developed (3). The present report is concerned with studies of the actions of sulfones (DDS and diasone), streptomycin, and their combinations; isonicotinic acid hydrazide (Nydrazid) and 1-isonicotinyl-2-isopropylhydrazine (Marsilid) are also included.

METHODS AND MATERIAL

The technique of chemotherapeutic assay in the intraperitoneally-infected mouse has been described (³). The treatment usually is started on the day after inoculation, although in some instances it has been delayed or interrupted due to shortage or toxicity of drugs. Streptomycin has been given daily by subcutaneous injection, 5 days a week. The other drugs have been mixed in the food.

The drugs used were obtained from the following sources: streptomycin sulfate from Merck & Co.; 4,4'-diaminodiphenyl sulfone and diasone sodium phosphate from the Abbott Laboratories; Nydrazid from E. R. Squibb & Sons; and Marsilid from Hoffmann-LaRoche.

In the four successive experiments reported on in this article, the young female white mice of the National Institutes of Health general-purpose strain, weighing 20 ± 2 gm., were used in groups of 20. Inoculations were intraperitoneal, 0.5 ml. of the seed suspensions. In each experiment one group of inoculated mice was left untreated as the leprosy control, and one group of uninoculated, untreated animals was used to obtain normal weights. In certain of the experiments drug-toxicity control groups were used.

Experiment 1.—In this first experiment streptomycin and DDS were tested separately. The dose of streptomycin was 3 mgm.; the food concentration of DDS was 0.01 per cent. The animals were inoculated on March 12, 1951, with a suspension made from the omenta and pelvic fatty pads of 5 mice inoculated intraperitoneally 4½ months previously. The experiment was terminated June 11 to 14, 1951.

Experiment 2.—The drugs used in this experiment were streptomycin, in the 3 mgm. dose; DDS, 0.1% concentration; diasone, 0.3%; streptomycin and DDS in the same dosages as when used alone; and streptomycin and diasone, also in the same dosages. The mice were inoculated on August 20, 1951, with a suspension of the usual lesions from 4 mice infected 5 months before. The experiment was terminated between November 26 and December 3, 1951.

1 Chang: Chemotherapeutic Test Results

Experiment 3.—In this experiment, a repetition of the second one, the four treated groups received streptomycin, DDS, diasone, and streptomycin and DDS combined, in the same dosages as before. Two uninfected drugtoxicity control groups were included, for streptomycin alone and DDS alone. The inoculations were made on January 7, 1952, the inoculum a suspension of lesions from 3 mice infected 4½ months previously. The experiment was terminated April 14 to 21, 1952.

Experiment 4.—This experiment was aimed to determine the effects of Nydrazid and Marsilid in different dosages in comparison with the streptomycin-DDS combination. Two groups of mice received Nydrazid in 0.014 per cent concentration, and two others in 0.028 per cent concentration; similarly, two groups received Marsilid in 0.2 per cent concentration, and two groups in 0.028 per cent concentration; for the streptomycin-DDS group, the former was given in doses of 2 mgm. (instead of the usual 3 mgm.), the latter in the usual 0.1 per cent concentration. Two uninfected toxicity control groups were included, one receiving Nydrazid in the 0.028 per cent concentration, the other receiving Marsilid in the 0.2 per cent concentration. The inoculum was a suspension of lesions from 3 mice infected $4\frac{1}{2}$ months previously. The inoculations were made on May 15, 1952; the treatment was started on the following day except for the Marsilid groups, which began 10 days after inoculation; the experiment was terminated August 18 to 25, 1952.

The leprosy index, the bacillus index, and the chemotherapeutic effectiveness index (I.C.E.) shown in the tables have been arrived at as explained in the first article of this series (³).

RESULTS

In the first experiment, in which streptomycin and DDS were tested separately, the former was found effective in the suppression of the leprous growth. As shown in Table 1, the weights of the omenta and pelvic fatty pads of the treated

 TABLE 1.—Chemotherapy of mouse leprosy, Experiment 1; evaluation of streptomycin and DDS, separately.

Drug	Dose	Number died/ used	Body weight gm.	Weight of omentum, gm.	Weight of pelvic fatty pads, gm.	Bacillus index
Normal mice		0/20	25.2	0.02	0.84	
Untreated leprosy control		1/20	25.7	0.19	1.60	19.7
Streptomycin	3 mgm.	2/17	27.5	0.09	1.05	18.2
DDS	0.01%	3/20	25.8	0.27	1.40	20.5

Note.—(a) All figures for weights and indices in this and the other tables represent averages for each group except where otherwise noted. (b) In all instances streptomycin was given by daily subcutaneous injection, 5 days a week; all other drugs were incorporated in the food in the concentrations indicated.

21, 1

group were considerably less than those of the untreated controls, although the difference in the bacillus indices of these two groups was not striking. Five out of 20 mice of the streptomycin-treated group died during the course of this experiment. Three of them were killed by accidents, and two died of pneumonia on the 46th and 63rd days of the infection. The remainder were sacrificed at the end of the experiment.

DDS in a concentration of 0.01 per cent in the diet did not show any inhibitory action. Three animals of this group died of respiratory infection in the early days of the experiment.

In the second experiment (Table 2), the inhibitory action of 3 mgm. of streptomycin was confirmed. As in the first experiment, the weights of the omenta and the pelvic fatty pads were markedly less than those of the control group, and the leprosy indices for the individual organs were likewise considerably smaller. The total leprosy index for the whole group was about one-third of that of the control. This gives a clearcut presentation of the inhibitory action of streptomycin in mouse leprosy.

While the small dose of DDS used in the first trial, 0.01 per cent concentration, was ineffective, the larger dose used here, 0.1 per cent, was highly effective. The total leprosy index was approximately one-fourth of that of the control and slightly superior to that for streptomycin.

Diasone, a derivative of DDS, showed definite antileprosy activity. It was less effective than its parent compound, although the dose used was approximately equivalent to that of DDS (36% of DDS was found by assay in diasone sodium phosphate).

An additive inhibitory action was obtained from the combined treatment of streptomycin and DDS. The index of chemotherapeutic effectiveness of this combination was 5, and only about 3 for each drug singly. On the other hand, the combination of streptomycin with diasone differed little in action from that of streptomycin alone. This will be discussed later.

Streptomycin and DDS were well tolerated in this experiment. One out of 20 of the streptomycin-treated group died of respiratory infection in the early days of the experiment. One of the control mice died within the first month from intercurrent disease. The average weight of the diasone-treated animals was lower than that of the controls. There were no deaths in the combined-treatment groups.

In this experiment, the weights of omentum and pelvic fatty

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Drugs	Dose	No. died/ used	Body wt. gm.	Weight of omen- tum, gm.	Weight of pelvic fatty pads, gm.	Site of inocu- lation	Omen- tum and peri- toneum	Pelvic fatty pads	Lymph nodes	Spleen	Liver	Misc.	Total index	I.C.E./a
Normal mice		3/20	22.7	0.01	0.59									
Untreated leprosy control		1/20	25.8	0.17	1.67	1.42	2.05	2.95	0.53	0.21	0.31	0	7.47	
Streptomycin	3 mgm.	1/20	26.4	0.09	1.22	0.42	86.0	1.26	0.05	0	0	0	2.71	2.8
DDS	0.1%	0/20	25.7	0.09	0.87	0.35	0.75	0.95	0	0	0	0	2.05 .	3.6
Diasone	0.3%	0/20	20.3	0.10	0.93	0.35	1.23	1.45	0.15	0	0.20	0	3.38	2.2
Streptomycin and DDS	3 mgm. 0.1%	0/20	26.7	0.07	1.10	0.25	0.65	0.50	0.10	0	0	0	1.50	5.0
Streptomycin and diasone	3 mgm. 0.3%	0/20	24.8	20.0	0.80	0.89	1.00	0.89	0.05	0	0	0	2.83	2.7

21, 1

Chang: Chemotherapeutic Test Results

61

a Index of chemotherapeutic effectiveness.

pads were in agreement with the total leprosy index. This is true usually of the weight of the omentum. The weight of pelvic fatty pads, however, varies greatly in normal mice and is probably dependent primarily upon the nutritional state. In infected mice the extent of involvement of the pads also varies greatly. The leprosy index reflects the quantity of leprous tissue in various organs and is a more precise guide than weights.

The third experiment was a repetition of the second one, to confirm the anti-leprosy activity of these compounds. Similar inhibitory effects were obtained, except that the activity of streptomycin was slightly stronger than that of DDS (Table 3). Diasone revealed low activity, as before. The combination of streptomycin and DDS remained the most effective, showing the same degree of chemotherapeutic effectiveness as in the second experiment. The appearance of the leprous tissues is shown in Plate 2.

Three out of the 20 mice of the untreated leprosy control group died in this experiment. One died of intercurrent infection about 2 months after inoculation. Two died just before the termination of the experiment, with a tremendous amount of leprosy growth over the abdominal viscera; death was apparently caused by the leprosy infection.

Streptomycin showed definite toxicity in the two leprosy groups of this experiment. Depression of physical activity and loss of body weight occurred in the third and the fourth weeks of the treatment. The antibiotic was suspended during the fifth week, and the animals then recovered completely. In the DDS group one animal died of respiratory infection 25 days after inoculation. Diasone was well tolerated.

In the toxicity controls of streptomycin and DDS included in the experiment, the drugs were given to normal mice for 3 months. The streptomycin group showed some toxic symptoms in the early period; three animals died on the 28th, 53rd and 61st days of the experiment. The 0.1 per cent DDS group also had 3 deaths: 2 on the 21st and 1 on the 25th day, due to intercurrent diseases. Enlarged, dark spleens were the only pathological findings in the animals given the sulfones. No gross pathological changes were found in the streptomycintreated animals.

Based on the evidence of this experiment, the inhibitory action of DDS, streptomycin, diasone, and the streptomycin-DDS combination in mouse leprosy seems to be definitely proved. Their comparative activities in terms of average chemothera-

21, 1

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Chang: Chemotherapeutic Test Results

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Drugs	Dose	No. died/ used	Body wt., gm.	Weight of omen- tum, gm.	Weight of pelvic fatty pads, gm.	Bacil- lus index	Site of inocu- lation	Omen- tum and peri- toneum	Pelvic fatty pads	Lymph nodes	Spleen	Liver	Misc.	Total index	I.C.E.
Normal mice		0/20	24.0	0.02	06.0										
Untreated leprosy control		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	
Streptomycin ·	3 mgm.	0/20	22.8	0.05	0.65	8.5	0.68	0.97	0.45	0.30	0	0	0	2.40	3.4
DDS	0.1%	1/20	25.6	0.13	0.82	6.0	0.82	1.37	0.42	0.42	0	0	0	3.03	2.7
Diasone	0.3%	0/20	23.6	0.13	0.83	12.0	06.0	2.28	1.17	0.35	0.25	0.20	0	5.15	1.6
Streptomycin and DDS	3 mgm. 0.1%	0/20	24.0	0.05	0.61	8.5	0.60	06.0	0.12	0.10	0	0	0	1.72	4.8
Streptomycin toxicity control	3 mgm.	3/20	21.1	0.01	0.39										
DDS toxicity control	0.1%	3/20	22.1	0.01	0.43										

63

a The bacillus index in this case is the average of 2 representative animals.

International Journal of Leprosy

peutic effectiveness are as follows: streptomycin-DDS combination, 4.9; DDS, 3.2; streptomycin, 3.1; diasone, 1.9.

In the fourth experiment, in which the actions of Nydrazid and Marsilid on mouse leprosy were studied—administration of Marsilid being unavoidably delayed for 10 days—two different doses of each drug were tested in a total of 160 mice, using 40 mice (2 groups) for each dose. As the standard of reference, one group was treated simultaneously with 2 mgm. streptomycin combined with 0.1 per cent DDS, the dose of streptomycin being reduced because of the toxicity observed in the third experiment.

Unfortunately, the animals of the Nydrazid-treated groups, one Marsilid-treated group (Group A of small dose), and one spare untreated leprosy group were attacked by a respiratory infection about three weeks after the inoculation. They were thin, nervous, and lost weight. Labored respiration showed in the severe cases. Congested lungs and mottled liver were the main findings. The control groups were free from the infection.

The isonicotinylhydrazines were discontinued twice for a total of 15 days in the second month of the experiment. The respiratory infection was controlled in the majority of the animals, but mild symptoms persisted in some mice. Penicillin was then given in the drinking water, in a concentration of 100 units per ml., to all the affected groups mentioned for two weeks in the later part of the experiment. All the animals were healthy in appearance at the time of autopsy. The total number of deaths in all eight groups treated with isonicotinylhydrazines was 26; 23 were caused by the respiratory infection, and 3 by accidents.

Some nervous symptoms and impairment of appetite were observed in the toxicity-control groups. The drugs were given continuously, without interruption, and no penicillin was given. Five of 20 mice of the Nydrazid group (0.028%) died in the middle part of the experiment. The Marsilid group (0.2%)had one death at the beginning of the experiment. Dark spleens were found in all the Marsilid-treated animals.

It is possible that the resistance of infected animals was lowered by the drugs, making them susceptible to the intercurrent infection. Discontinuance of the drugs for 15 days apparently controlled this condition but it probably played an important role in producing the high mortality rate of this experiment, because the same respiratory disease occurred also

										Leprosy	index				
Group	Dose	No. died/ used	Body wt.,	Weight of omen- tum, gm.	Weight of pelvic fatty pads, gm.	Bacil- lus index	Site of inocu- lation	Omen- tum and peri- toneum	Pelvic fatty pads	Lymph nodes	Spleen	Liver	Misc.	Total index	I.C.E.
Normal mice		0/20	25.0	0.02	0.62										
Untreated leprosy control		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	
Streptomycin and DDS	2 mgm. 0.1%	0/20	24.7	0.04	0.54	8.0	0.13	0.78	0.05	0	0	0.08	0	1.04	4.0
Nydrazid, Group A	0.014 %	7/20	23.9	0.04	0.41	6.0	0.24	1.03	0.24	0.24	0	0	0	1.75	2.4
Nydrazid, Group B	0.014%	3/20	23.2	0.03	0.36	0.7	0.21	0.88	0.27	0.27	0	0	0	1.63	2.6
Nydrazid, Group A	0.028%	3/20	24.3	0.03	0.44	7.5	0.11	0.50	0.12	0.03	0	0	0	0.76	5.6
Nydrazid, Group B	0.028 %	4/19	23.9	0.03	0.35	7.5	0.03	0.50	0	0.17	0	0	0	0.70	6.0
Marsilid, Group A	0.2%	2/20	24.4	0.02	0.66	8.0	0	0.33	0.06	0	0	0	0	0.39	10.8
Marsilid, Group B	0.2%	0/18	24.7	0.03	0.64	7.5	0	0.39	0	0.06	0	0	0	0.45	9.4
Marsilid, Group A	0.028%	3/20	22.0	0.04	0.25	10.0	0.41	1.29	16.0	0	0	0.06	0	2.67	1.6
Marsilid, Group B	0.028%	1/20	23.5	0.03	0.44	6.0	0.39	0.74	0.08	0.05	0	0.05	0	1.31	3.2
Nydrazid toxicity control	0.028%	5/20	29.4	0.02	0.73										
Marsilid toxicity control	0.2%	1/20	23.8	0.02	0.41										

21, 1 Chang: Chemotherapeutic Test Results

International Journal of Leprosy

in one spare untreated group with a mortality approaching the above-mentioned rate.

In spite of this complication, the antileprosy activity of the isonicotinylhydrazines was remarkable (Table 4). The leprosy infection was retarded in each animal of all the eight groups. Gross pathological lesions were so scanty that one could find nothing abnormal except some tiny leprous nodules over the mesentery or omentum. Nydrazid in the larger dose revealed high activity in the suppression of leprous growth, but it was less potent than the larger dose of Marsilid. The smaller doses of these two compounds also showed definite effectiveness; 0.4-0.6 mgm. of Nydrazid or 0.8-1.1 mgm. of Marsilid per mouse per day had a chemotherapeutic effectiveness only slightly less than that of streptomycin or DDS.

Photographs of the omenta and pelvic fatty pads of the treated and untreated groups, shown in Plate 3, illustrate these findings.

Histological sections showed very few leprosy lesions in the animals treated with the larger doses of the isonïcotinylhydrazines. Small leprous foci were found at the site of inoculation, in the omentum, the retroperitoneal lymph nodes, the pelvic fatty pads and occasionally in the liver and spleen. Scattered acid-fast bacilli were found in all these areas except the last two. They were mostly extracellular, and typical lepra cells were rare. Some degenerated acid-fast bacilli and acid-fast granular masses were seen. No leprosy lesions were found in the heart, lung, kidney, intestine or thymus. The histological findings suggested that active multiplication of *M. leprae murium* was suppressed. Some degeneration of the acid-fast bacilli seemed to have occurred where they were present after three months of treatment with these drugs.

Regarding the group of mice treated with streptomycin (2 mgm.) combined with DDS, an additive action was again obtained, but the activity was slightly less than that shown by the 3 mgm. dose of streptomycin in the combined therapy of the earlier experiments.

No eradication of the infection has been obtained in the treated animals. Even in the most favorable response, acid-fast bacilli were still found in various tissues. Whether the organisms were dead or alive was not determined.

In the first experiment, the bacillus index was based upon nine smears from each mouse. No significant differences were

found between the control group, the group given 3 mgm. of streptomycin and that given 0.01% DDS.

In the third and fourth experiments, because of the labor involved, bacillus indices were based upon nine smears from each of two mice of each group. In this experiment, the indices point to suppressive action of 3 mgm. of streptomycin, 0.1% DDS and their combination in these dosages, but not of 0.3% diasone. In the fourth experiment the bacillus index was definitely lower in all treated groups than in the control, but does not indicate differences in effectiveness of the various drugs.

Further study of the bacillus index is necessary but from these experiments it appears that whereas the leprosy index distinguishes between drugs of variable effectiveness in suppressing murine leprosy, the bacillus index does not.

Table 5 summarizes the results of all the four experiments. Drug activity was proportional to the size of the dose. If the drugs are compared according to their maximum tolerated doses, which are approximately the same as the highest doses used in the experiments, the order of their antileprosy activity would be as follows: Marsilid, Nydrazid, streptomycin combined with DDS, DDS, streptomycin, diasone.

Drug	Dose	Number of mice used	Index of chemotherapeutic effectiveness
Marsilid	0.2%	40	10.1
Nydrazid	0.028%	40	5.8
Streptomycin and DDS	3 mgm. 0.1%	40	4.9
DDS	0.1%	40	3.2
Streptomycin	3 mgm.	40	3.1
Marsilid	0.028%	40	2.5
Nydrazid	0.014%	40	2.4
Diasone	0.3%	40	1.9

 TABLE 5.—Combined results of the antileprosy activity of the drugs tested

 in Experiments 2, 3 and 4.

DISCUSSION

Within each group the variations of the extent of the leprous lesions in individual animals were great. The best way to reduce the influence of these variations on the experimental

results is to use large numbers of animals. A total of 640 mice has been used in this study, and in each experiment the groups were of sufficient size to give statistical validity to the results.

Penicillin was used in one of the experiments to combat a respiratory complication. The question of whether the administration of this antibiotic in drinking water for two weeks had any influence on our test merits consideration. An adequately controlled experiment was not done, but the evidence obtained indicates that penicillin has no effect on the progress of murine leprosy.

Since the antileprosy activity of the several drugs used can be repeatedly demonstrated almost quantitatively in mouse leprosy, the test employed may be considered to give reproducible results. The material for inoculation can be obtained conveniently and adequately from infected mice. The assay method is simple, and definite results can be obtained in a reasonably short time.

Smith and his associates (20) of this laboratory, reported that several of the DDS derivatives showed a potentiating action with streptomycin in guinea-pig tuberculosis. As reported in the present paper, an additive action was obtained with the combination of streptomycin and DDS in mouse leprosy. Encouraging clinical results with the use of streptomycin combined with sulfones have been reported in tuberculosis (12, 15, 16, 22), and in leprosy (6, 11, 18).

Diasone given orally was not as effective as DDS in these experiments. The former was mixed with sodium phosphate. It is known (19) that the absorption of diasone from the gut is poor, which may explain its low efficacy in the treatment of mouse leprosy.

Of the drugs tested, the isonicotinylhydrazines have been found to possess the highest antileprosy activity in mouse leprosy. Studies are in progress to determine whether the combination of isonicotinylhydrazines with streptomycin or with DDS will give a potentiating action.

SUMMARY

A comparison has been made of the antileprosy activity of streptomycin, 4,4'-diaminodiphenyl sulfone (DDS), diasone, Nydrazid (isonicotinic acid hydrazide), and Marsilid (1-isonicotinyl-2-isopropyl hydrazine) in mouse leprosy, employing the intraperitoneally-infected mouse. The isonicotinylhydrazines were found to be the most effective of these drugs in the suppression of the leprosy infection.

Streptomycin was found to have a degree of activity similar to DDS; diasone was the least active.

Combined therapy with streptomycin and DDS showed an additive effect.

The order of the antileprosy activity of these different drugs was as follows: Marsilid, Nydrazid, streptomycin combined with DDS, DDS, streptomycin, diasone.

RESÚMEN

Se comparó la actividad antileprosa de las drogas estreptomicina, 4,4-diamino-diphenyl sulfone (DDS), diasone, nydrazid (isonicotinic acid hydrazide) y marsilid (1-isonicotinyl-2-isopropyl hydrazine) en la lepra murina, empleándose el ratoncillo infectado por vía intraperitoneal.

Las isonicotinylhydrazines fueron las más efectivas en la supresión de la infección leprosa.

La estreptomicina tuvo una actividad comparable al DDS, el diasone fué la droga menos activa.

Terapia combinada de estreptomicina y DDS demostró effecto aditivo.

El orden de actividad anti-leprosa de estas drogas fué como sigue: marsilid, nydrazid, estreptomicina combinada con DDS, DDS, estreptomicina, diasone.

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PLATE 2.

Comparison of the pelvic fatty pads and the omenta of untreated and treated leprosy mice three months after infection, Experiment 3. In each pair of pictures the upper one is of the pelvic fatty pads, the lower one of the omenta.

FIG. 1. Leprosy control group, untreated.

FIG. 2. Streptomycin group, the lesions distinctly smaller than those of the controls, and slightly smaller than those of the DDS group (Fig. 3).

FIG. 3. Sulfone (DDS) group.

FIG. 4. Streptomycin-DDS groups, showing an additive effect of the combination of these two drugs. (Dosage of streptomycin, 3 mgm.)

Note that the leprous tissues of the treated groups are smaller and smoother than those of the control group.

CHANG]

[INTERNAT, J. LEPROSY, VOL. 21, NO. 1



PLATE 2.

PLATE 3.

Comparison of the pelvic fatty pads and the omenta of untreated and treated leprosy mice three months after infection, Experiment 4. In each pair of pictures the upper one is of the pelvic fatty pads, the lower one of the omenta.

FIG. 5. Leprosy control group, untreated.

FIG. 6. Streptomycin-DDS group, showing the same additive effect as in Fig. 4. (Dosage of streptomycin, 2 mgm.)
FIG. 7. Nydrazid-treated mice, Group A of the 0.028 per cent dosage.

FIG. 7. Nydrazid-treated mice, Group A of the 0.028 per cent dosage. The results with this drug are superior to those with the combination of streptomycin and DDS.

FIG. 8. Marsilid-treated mice, Group B of the 0.2 per cent dosage. Note the apparently normal appearance of the tissues in this group.

CHANG]





PLATE 3.