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Sulfanilamide and Sulfapyridine in Treatment of Experimental *B. typhosus* (*Eberthella typhosus*) Infections of Mice.

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Buttle, Parish, McLeod and Stephenson[1] found sulfanilamide in dose of 0.025 g by oral administration somewhat effective in the treatment of mice inoculated intraperitoneally with 100 lethal doses of *B. typhosus* (3 strains) when given immediately after inoculation in a single dose, or when the drug was given in the same dose twice daily; of 20 treated mice 15 were alive 12 days later while all of 10 untreated controls died within 2 days. When mucin was used as a diluent for the culture, protection was obtained against a slightly larger number of fatal doses of culture. Ten mice infected with 500,000 organisms survived for 12 days when treated with 2 daily oral doses of 0.025 g sulfanilamide. In one experiment in which treated mice were observed for one month, no deaths occurred after the twelfth day. A single oral dose of 0.025 g shortly after infection was found almost as effective as the same oral dose repeated twice daily for 6 days, but when treatment was delayed 5 hours after the infection, the result was not as good as with immediate treatment, although some protection was observed. Taking 25 g as the average weight of the mice employed, the dose of 0.025 g per mouse was equivalent to approximately 1.0 g per kilo. Schmidt[2] has reported improvement in 3 cases of typhoid fever following treatment with prontosil 1. One of these, thought to be dying, improved in 24 hours and recovered in 6 weeks.

Our experiments were conducted with a motile strain of *B. typhosus (Eberthella typhosus)* isolated about 8 months previously from a case of typhoid fever. The minimal lethal dose of 24-hour broth culture by intraperitoneal inoculation was approximately 0.1 cc (Table I) and 0.2 cc by intraperitoneal inoculation was employed in treatment experiments with sulfanilamide and sulfapyridine.

Since difficulty was experienced in giving mice accurate doses by mouth, the compounds were administered in solution by subcutaneous or intraperitoneal injection. For this purpose 0.4 g of sulfanilamide was dissolved in 50 cc of hot saline giving 0.008 g per cc; 0.2 g

[1] Buttle, G. A. H., Parish, H. J., McLeod, M., and Stephenson, D., *Lancet*, 1937, **1**, 681.

[2] Schmidt, J., *Munch. Med. Wchn.*, 1936, **83**, 2122.

TABLE I.
Virulence of *B. typhosus* for Mice.

Wt, g	Dose,* cc	Results in Days					
		1	2	3	4	5	6
26	0.005	—	—	—	—	—	—
25	0.005	—	—	—	—	—	—
28	0.01	—	—	—	—	—	—
24	0.01	—	—	—	—	—	—
21	0.05	—	—	—	—	—	—
23	0.05	—	—	—	—	—	—
19	0.1	—	—	D			
22	0.1	—	—	—	D		
23	0.1	—	—	D			
25	0.2	—	—	D			
22	0.2	—	D				
24	0.2	—	—	D			
26	0.3	D					
21	0.3	—	D				
20	0.4	D					
22	0.4	D					

* Of 24-hour broth culture by intraperitoneal inoculation.

sulfapyridine was dissolved in 200 cc of hot saline solution giving 0.001 g per cc.

In one experiment summarized in Table II, 6 mice were given 2 doses of 0.160 g *sulfanilamide* by *subcutaneous* injection 6 hours apart before intraperitoneal inoculation with 0.2 cc of 24-hour broth culture followed by a third dose 12 hours thereafter and repeated at 6-hour intervals. Two additional mice were kept as untreated infection controls and both succumbed in 48 to 72 hours after inoculation. Two more were included as drug controls and survived 12 days when

TABLE II.
Effect of Sulfanilamide by Subcutaneous Injection in Treatment of *B. typhosus* Infections of Mice.

Wt, g	Dose per kilo,* g	Results in Days								
		1	2	3	4	5	6	8	10	12
24	.160	—	—	—	—	—	D			
25	”	—	D							
25	”	—	—	—	D					
23	”	—	—	D						
26	”	—	—	—	—	D				
24	”	—	D							
24	”	—†	—	—	—	—	—	—	—	—
26	”	—†	—	—	—	—	—	—	—	—
23	Control	—	D							
25	”	D								

*By subcutaneous injection; 2 doses given 6 hours apart before intraperitoneal inoculation with 0.2 cc of 24-hour broth culture of *B. typhosus* followed by third dose 12 hours thereafter and repeated at 6-hour intervals.

†Drug controls.

the experiment was terminated. Of the 6 treated animals, 4 survived for 1 to 2 or 3 days beyond the untreated controls, indicating that sulfanilamide in the dose administered probably showed some therapeutic effect although the results were not as encouraging as those reported by Buttle and his colleagues, probably because the dose employed was about 6 times smaller per kilo of weight.

In a second experiment 8 mice were inoculated intraperitoneally with 0.2 cc of 24-hour broth culture; 2 kept as untreated controls died in 48 to 72 hours. Six of the mice were given 0.160 g *sulfanilamide* by *subcutaneous* injection immediately after inoculation and the dose repeated every 6 hours; 1 survived for about 4 days but the remaining 5 succumbed in 2 to 3 days after inoculation (Table III); 2 drug controls lived for 12 days, when the experiment was terminated.

In a third experiment 14 mice were inoculated intraperitoneally with 0.2 cc of 24-hour broth culture; 4 kept as untreated controls died in 24 to 72 hours. Ten of the mice were given 0.160 g *sulfanilamide* by *intraperitoneal* injection 2 hours after inoculation with a second dose 4 hours later and thereafter at 6-hour intervals. Of these 3 survived 12 days, while the remaining 7 succumbed within 4 days (Table IV); 2 drug controls survived 12 days, when the experiment was terminated.

In a fourth experiment 14 mice were inoculated intraperitoneally with 0.2 cc of 24-hour broth culture; 4 kept as untreated controls died in 24 to 48 hours. Ten of the mice were given 0.169 g *sulfapyridine* by *intraperitoneal* injection immediately after inoculation with a second dose 4 hours later and thereafter at 6-hour intervals. Of

TABLE III.

Effect of Sulfanilamide by Subcutaneous Injection in Treatment of *B. typhosus* Infections of Mice.

Wt, g	Dose per kilo,* g	Results in Days								
		1	2	3	4	5	6	8	10	12
22	.160	—	—	D						
25	”	—	D							
25	”	—	D							
24	”	—	—	—	D					
22	”	—	D							
26	”	—	D							
24	”	—†	—	—	—	—	—	—	—	—
24	”	—†	—	—	—	—	—	—	—	—
22	Control	D								
24	”	—	D							

*By subcutaneous injection begun immediately after intraperitoneal inoculation with 0.2 cc of 24-hour broth culture of *B. typhosus* and repeated every 6 hours.

†Drug controls.

these one survived for 12 days, while the remaining 9 succumbed in 24 to 72 hours (Table V); 2 drug controls survived 12 days, when the experiment was terminated.

TABLE IV.
Effect of Sulfanilamide by Intraperitoneal Injection in Treatment of *B. Typhosus* Infections of Mice.

Wt, g	Dose per kilo,* g	Results in Days								
		1	2	3	4	5	6	8	10	12
22	.160	—	—	—	—	—	—	—	—	—
24	”	—	D							
25	”	—	D							
21	”	—	—	D						
24	”	D								
24	”	—	D							
25	”	—	—	—	—	—	—	—	—	—
26	”	—	—	D						
23	”	—	—	—	—	—	—	—	—	—
22	”	—	—	—	D					
25	”	—†	—	—	—	—	—	—	—	—
25	”	—†	—	—	—	—	—	—	—	—
25	Control	—	D							
24	”	—	—	D						
21	”	D								
22	”	D								

*By intraperitoneal injection. First dose 2 hours after inoculation with 0.2 cc of 24-hour broth culture of *B. typhosus;* second dose 4 hours later and repeated at 6-hour intervals.

†Drug controls.

TABLE V.
Effect of Sulfapyridine by Intraperitoneal Injection in Treatment of *B. Typhosus* Infections of Mice.

Wt, g	Dose per kilo,* g	Results in Days								
		1	2	3	4	5	6	8	10	12
23	.160	—	D							
22	”	D								
24	”	—	—	D						
24	”	—	—	—	—	—	—	—	—	—
24	”	—	D							
23	”	D								
25	”	D								
25	”	—	D							
22	”	—	—	D						
24	”	—	D							
20	”	—†	—	—	—	—	—	—	—	—
24	”	—†	—	—	—	—	—	—	—	—
22	Control	D								
20	”	—	D							
25	”	D								
22	”	D								

*By intraperitoneal injection. First dose immediately after inoculation with 0.2 cc of 24-hour broth culture of *B. typhosus;* second dose 4 hours later and repeated at 6-hour intervals.

†Drug controls.

Summary. Sulfanilamide by subcutaneous injection in dose of 0.160 g per kilo apparently prolonged the lives of some mice when given in 2 doses 6 hours apart before intraperitoneal inoculation with *B. typhosus* in a dose fatal in about 48 hours, followed by subsequent doses at 6-hour intervals. But when the compound in the same dose was given by subcutaneous injection immediately after inoculation followed by subsequent doses at 6-hour intervals there was much less evidence of therapeutic activity. However, sulfanilamide was much more effective when given intraperitoneally in the same dose 2 hours after intraperitoneal inoculation followed by a second dose 4 hours later and subsequent doses at 6-hour intervals. Of the total of 22 treated mice in 3 experiments, 3 survived and the lives of 7 were prolonged, whereas all of 8 untreated controls succumbed in 1 to 2 days after inoculation.

Sulfapyridine was less effective. Of 10 mice given 0.160 g by intraperitoneal injection immediately after inoculation, followed by a second dose 4 hours later and subsequent doses at 6-hour intervals, one survived and the lives of 2 were prolonged about 24 hours beyond the survival of 4 untreated controls which succumbed in 24 to 48 hours after inoculation.

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Sulfapyridine and Sulfanilamide in Experimental Pneumococcal, Meningococcal, Welch Bacillary and Friedländer's Bacillary Infections in Mice.*

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We[1, 2] have discussed the comparative therapeutic efficiency of sulfapyridine and sulfanilamide in the treatment of experimental hemolytic streptococcal and Type I pneumococcal infections in mice. These reports were based upon results obtained in mice the origins of

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1 Long, P. H., Bliss, E. A., and Feinstone, W. H., *Penna. Med. J.*, 1939, **42**, 483.

2 Long, P. H., *J. A. M. A.*, 1939, **112**, 538.