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Sulfone and Sulfonanilide Therapy in Streptococcal Infections.

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Recent reports[1-4] have indicated that 4,4'-di-(acetylamino)-diphenylsulfone and 4,4'-diamino-benzenesulfonanilide are high in chemotherapeutic efficacy and relatively low in toxicity.

In order to contribute further data on these points, the two above mentioned drugs* were tested parallel with sulfanilamide against experimental hemolytic streptococcal infections of mice.

All animals were infected intraäbdominally with 0.5 cc. of various dilutions (10^{-8}, 10^{-6}, 10^{-4}, and 10^{-2}) of 18-hour broth cultures of strain C 203.[5, 6, 7] However, a different culture was used for each experiment. Each dilution involved the use of 40 to 45 mice divided into equal groups: one control and 3 treated. In one experiment (Fig. 1 A) there were only 2 treated groups.

Oral treatment was begun 2 to 4 hours after infection and continued daily as indicated in Fig. 1. All chemicals were suspended in 15% aqueous gum acacia; the sulfone as 2.5 and 5% suspensions, and the anilide as well as the sulfanilamide as 5% suspensions. Because the anilide proved unstable in suspension, the latter was freshly prepared prior to each treatment. The therapy was continued for 10 days except in the case of the smallest infecting dose where it was discontinued after 5 days.

The therapeutic results were good with all 3 drugs (Fig. 1 A and B) when the infecting dose was low or moderate (10^{-8} to 10^{-4} dilution of the culture). However, in one of 2 experiments performed at different times, each involving the use of a heavy in-

1 Whitby, L. E. H., *Lancet*, 1937, **1**, 1517.

2 Fourneau, E., Tréfouël, J., Tréfouël, J., Mme., Nitti, F., and Bovet, D., *Compt. rend. Acad. d. sc.*, 1937, **205**, 299.

3 Fourneau, E., Tréfouël, J., Tréfouël, J., Mme., Nitti, F., and Bovet, D., *Bull. Acad. de méd.*, Paris, 1937, **118**, 210.

4 Bauer, H., and Rosenthal, S. M., *Pub. Health Rep.*, 1938, **53**, 40.

* These chemicals were synthesized and donated to us by the Monsanto Chemical Company of St. Louis, Missouri.

5 Long, P. H., and Bliss, E. A., *J. A. M. A.*, 1937, **108**, 32.

6 Raiziss, G. M., Severac, M., and Moetsch, J. C., *J. Chemotherapy*, 1937, **14**, 1.

7 McKinney, R. A., and Mellon, R. R., PROC. SOC. EXP. BIOL. AND MED., 1937, **37**, 33.

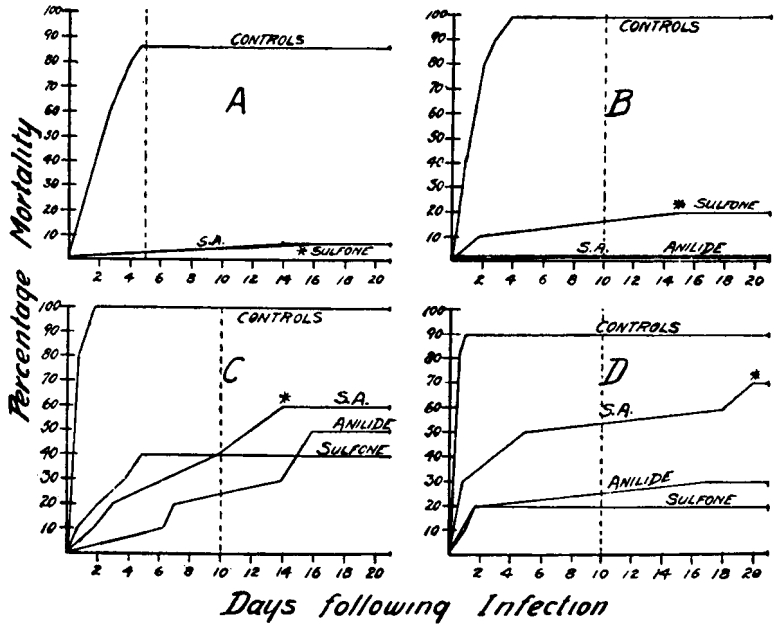

FIG. 1.

A: Culture diluted 10^{-8}
14 mice per group
Daily *Dosage* (oral) mg.
Sulfanilamide 10
Sulfone 5

B: Culture diluted 10^{-4}
10 mice per group
Daily *Dosage* (oral) mg.
Sulfanilamide 10
Anilide 10
Sulfone 5

C: Culture diluted 10^{-2}
10 mice per group
Daily *Dosage* (oral)
Sulfanilamide 10
Anilide 10
Sulfone 5

D: Culture diluted 10^{-2}
10 mice per group
Daily *Dosage* (oral)
Sulfanilamide 10
Anilide 10
Sulfone 10

All mice injected with 0.5 cc. of diluted culture, intraäbdominally. The vertical broken lines indicate cessation of therapy.
S.A.: Sulfanilamide.
*Death not due to streptococcal infection.

fecting dose (10^{-2} dilution of the culture), somewhat divergent results were obtained. Although both, the anilide and the sulfone, showed a suggestion of superiority over sulfanilamide (Fig. 1 C), a more definite indication of this was shown in the other experiment (Fig. 1 D), where all dosages were equal.

The difference in the results of the anilide therapy in these 2 experiments (Fig. 1 C and D) is perplexing because other conditions were so nearly alike. In C (Fig. 1), 3 out of 5 deaths in the anilide group occurred 14 to 17 days after infection, whereas in D (Fig. 1), this group had only 3 deaths, of which one occurred after the second day.

The livers and kidneys of some of the treated mice from each group were examined histologically for lesions attributable to the medications, but all changes found in the various treated animals were also represented in the untreated controls.

Attempts to determine the maximum tolerated single oral dose of the sulfone were discontinued when it was found that 20 gm. mice tolerated 400 mg. of the drug without the slightest untoward effect. Similarly, 100 mg. were tolerated subcutaneously. The latter injections, however, resulted in firm, subcutaneous nodules which after 2 weeks consisted essentially of chalky white deposits of sulfone crystals. Microscopically, in 24 to 48 hours following such injection, there was marked local edema with moderate leukocytic exudation in the region of the crystalline sulfone deposits.

The anilide was somewhat more toxic than sulfanilamide. Four out of 5 mice which received 100 mg. of the anilide by mouth died, whereas of 5 mice receiving 80 mg. sulfanilamide, none died; and of 4 mice receiving 120 mg. sulfanilamide by mouth, only one died. Subcutaneously, mice tolerated 60 mg. of the anilide without symptoms except for the development of a small, firm nodule at the site of injection.

The sulfone appeared to be more effective than the anilide against infections in mice caused by the C 203 strain, and because of the extremely low toxicity the sulfone appears to hold more promise of finding practical application.

Our results are in general agreement with the conclusions drawn by Bauer and Rosenthal.[4]

Conclusions. 1. 4,4'-di-(acetylamino)-diphenylsulfone is more efficacious than sulfanilamide against certain hemolytic streptococcal infections of mice. 2. Against these same infections, the 4,4'-diamino-benzenesulfonanilide is as good as or better than sulfanilamide. 3. The sulfone is less toxic than either the anilide or sulfanilamide. 4. Medication of mice with these drugs produced no demonstrable hepatic or renal lesions.