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## Effect of Sulfapyridine in Pneumococcus Type I Infections In Rabbits.

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(Introduced by Hobart A. Reimann.)

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Since much of the experimental work with sulfapyridine has been done with mice, it was decided to test the chemotherapeutic action of this drug against bacteremia with Type I pneumococcus in rabbits.

According to the method of Goodner[1] 0.1 cc of a 1:1000 dilution of an 18-hour blood broth culture of Type I pneumococcus was inoculated endermally into the shaved skin of 40 rabbits. Twenty were kept as controls and the remaining 20 were given sulfapyridine at intervals ranging from 12 to 24 hours following inoculation. Blood cultures were made just before the onset of treatment and daily thereafter. A record was kept of the number of colonies of pneumococci per cubic centimeter of blood each day. The drug was suspended in 60 to 80 cc of physiologic salt solution and administered by stomach tube 2 or 4 times a day at 4-hour intervals. The amount of sulfapyridine in the blood, determined by the method of Marshall and Litchfield,[2] was measured just before each treatment in every animal. Rectal temperatures were recorded twice daily. In every instance bacteremia was present before the onset of therapy.

As a preliminary step to determine the rate of absorption and excretion of the drug 2 uninfected rabbits were given 0.25 g of sulfapyridine per kilo of body weight in 2 equally divided doses 4 hours apart. While the maximum concentration appeared in the blood one and one-half hours after administration of each dose, a level almost as high was present one-half hour following treatment. Although the ability to conjugate the drug varied in different rabbits, the maximum amount of conjugation occurred in the first half hour. Twenty hours after treatment only a trace of the drug in its conjugated form was left in the blood.

*Group I.* Three pairs of infected animals were treated according to the above program, 16, 19 and 21 hours respectively following inoculation. Bacteremia was present and the infection was apparently overwhelming. One treated and one control animal of the

[1] Goodner, K., *J. Exp. Med.*, 1928, **48**, 413.

[2] Marshall, E. K., Jr., and Litchfield, J. T., Jr., *Science*, 1938, **88**, 85.

series treated 16 hours after infection survived. The surviving treated animal maintained a level of 6 to 10 mg of total sulfapyridine in its blood, largely in the free state for approximately 8 hours a day, which dropped back to a low level at the end of each 24-hour period.

*Group II.* Because of the inefficiency of therapy as just described when the concentration of the drug in the blood was allowed to drop over a period of 16 hours, another group of rabbits was treated 12 to 24 hours following infection with larger quantities of sulfapyridine given in 4 equal doses at 4-hour intervals, allowing only 8 hours during which an effective level might not be maintained. An attempt was made to obtain a high level in the blood at once by giving 0.75 g per kilo per day for the first day followed by 0.50 g per kilo thereafter. By this method the level in the blood rose 2 to 3 mg higher during the first 8 hours than when 0.5 g per kilo per day was given from the beginning of treatment. Of the 24 animals observed in this group 4 of the treated (33.3%) died while 8 of the controls (66⅔%) died.

*Group III.* Two controls and 2 infected rabbits treated with 0.75 g of sulfapyridine per kilo per day were observed. Both treated animals maintained levels of 11 to 15 mg in the blood over several hours of the day for 5 days. Blood cultures became sterile but the concentration of sulfapyridine rose in the blood to as high as 30 mg, including 10 to 12 mg of the conjugated form. The animals became weak, emaciated and one developed urinary retention. Both of the treated and one of the control animals died.

*Comment.* There is some benefit to be ascribed to treating pneumococcus Type I bacteremia in rabbits with sulfapyridine if a level of 7 to 10 mg of total sulfapyridine is maintained for most of the 24-hour period of the day. To do this most effectively 0.75 g per kilo per day in 4 equal doses at 4-hour intervals should be given the first day followed by 0.5 g per kilo per day thereafter until blood cultures are negative for 3 days. The proportion of free and conjugated drug is apparently of little importance in rabbits in relation to bacteriostatic efficiency. However, in those animals believed to manifest toxic symptoms from high concentrations of total sulfapyridine (20 to 30 mg) it was observed that the conjugated drug was often as high as 10 to 14 mg. The animals which recovered were able to utilize and eliminate the drug and showed a progressive diminution in the number of pneumococci in the blood over a period of 3 to 5 days when the blood culture ordinarily became sterile. With very high concentrations of sulfapyridine, bacteremia at times persisted, suggesting the possibility that the high levels of the drug are so toxic, or that the amount of polysaccharide capsular substance is so

large that the animal is overwhelmed and cannot utilize the normal protective mechanism which might be sufficient ordinarily to control the infection. The temperatures of the treated animals were usually 1 to 2 degrees F lower than the controls. The skin lesions of the treated animals are ordinarily less extensive, while the controls frequently presented more edema, swelling and necrotic areas.

*Conclusion.* 1. A blood level of 7 to 10 mg total sulfapyridine is effective in controlling bacteremia with Type I pneumococcus in 66.6% of treated rabbits. 2. In animals treated with sulfapyridine the local skin lesions are usually less extensive and the temperatures are 1 to 2 degrees lower than the controls.

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## Observations on the Toxicology of Sulfathiazole and Sulfapyridine.

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Fosbinder and Walter as well as Lott and Bergeim[1] have prepared the thiazole analogue of sulfapyridine, 2(*p*-amino-benzene-sulfonamido)thiazole, which in this and the following report will be called sulfathiazole. The pharmacology of this drug is of interest because it resembles sulfapyridine in respect of its chemotherapeutic efficacy in combating pneumococcus and other infections in mice.[2]

Experiments which have been performed to determine the acute lethal effects of a single dose of the sodium salt of either drug are listed in Table I.* Each experiment represents observations in a single group of albino mice homogeneous as to breed and size. In experiments B, C, D, and E, the toxicity of the sodium salts of sulfapyridine and sulfathiazole after subcutaneous injection was compared at the same dose levels. In experiment B, the drugs appeared to be equally toxic; however, in experiments C, D, and E, when larger

[1] Fosbinder, R. J., and Walter, L. A., *J. Am. Chem. Soc.*, 1939, **61**, 2032; Lott, W. A., and Bergeim, F. H., in press.

[2] McKee, C. M., Rake, Geoffrey, Greep, R. O., and van Dyke, H. B., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 417.

* The molecular weight of sulfathiazole is 2.5% greater than sulfapyridine. Usually doses were corrected for this difference.