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Bacteriostatic Effects of Sulfathiazole upon Various Micro-Organisms. Its Therapeutic Effects in Experimental Pneumococcal Infections.*

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McKee and her coworkers[1] have reported briefly that sulfathiazole is bacteriostatic *in vitro*. In Table I are recorded data regarding the comparative bacteriostatic effects of sulfanilamide, sulfapyridine and

TABLE I.
Comparative Bacteriostatic Effects of Sulfanilamide, Sulfapyridine and Sulfathiazole upon Various Bacteria in Broth.

Organism	Inoculum Orgs./cc	Growth—Colonies/cc 17-24 hours: Sulfanilamide 10 mg %	Sulfapyridine 10 mg %	Sulfathiazole 10 mg %	Controls
Hem. Strept. Group A					
C203	42	75,000	70,000	30,000	810 million
"	108	74 million	20 million	800,000	550 "
Bart	60	70,000	40,000	23,000	560 "
"	66	65 million	1 million	1 million	500 "
N.Y.5	42	80,000	90,000	123,000	590 "
"	46	74 million	16 million	1 million	320 "
Hem. Strept. Group D					
Zymogenes	420	2 billion	1.85 billion	1.75 billion	2.2 billion
"	8	1.07 "	1.46 "	1.34 "	1.02 "
Hem. Strept. Group G					
Dog	152	22,000	37,000	80,000	450 million
"	202	70,000	89,000	79,000	167 "
Pneumococci					
Type I	17,200	2 million	1 million	4 million	630 million
"	280	30 "	20,000	10,000	1.7 billion
SVI P/47	23,400	28 "	425 million	12 million	1.35 "
Type II	2,700	4,000	3,000	11,000	1.2 "
"	3,800	200,000	300,000	150,000	920 million
S. aureus	12	270 million	214 million	102 million	1 billion
"	18	900 "	510 "	380 "	1.8 "
E. coli	6	1.8 billion	2.9 million	1.4 million	2.2 billion
"	80	—	70 "	19 "	2.5 "
B. proteus	36	2 million	60,000	50,000	6 billion

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[1] McKee, C. M., Rake, G., Greep, R. O., and Van Dyke, H. B., PROC. SOC. EXP. BIOL. AND MED., 1939, 42, 417.

sulfathiazole upon the growth of certain bacteria in beef infusion, 2% Neopeptone 0.075% dextrose broth. A perusal of the results shown in this table indicates that sulfathiazole is an effective bacteriostatic agent *in vitro,* being equal in this respect to both sulfapyridine and sulfanilamide.

It is important, in attempting to evaluate the therapeutic effectiveness of any new sulfanilamide derivative, that data regarding the absorption and excretion of the compound be available. This point was recognized by McKee, *et al.,*[1] in their report upon the comparative therapeutic value of sulfathiazole and sulfapyridine in the control of experimental infections in mice, but was not taken into consideration by Cooper, Gross and Lewis.[2] Previous studies[3, 4] have shown that sulfathiazole is absorbed more promptly and excreted more rapidly than sulfapyridine. Hence, in evaluating the comparative therapeutic effects of these two compounds when they are administered to mice by the oral route in experimental infections, the question as to whether adequate concentrations of sulfathiazole were maintained in the blood of the experimental animals is of importance. Up to the present time, all reports dealing with the comparative therapeutic effects of sulfathiazole and sulfapyridine in experimental pneumococcal infections in mice show that the latter compound is slightly more effective, *when the drugs are administered perorally in acacia suspensions at stated intervals.* As will be shown in Table II this has been our experience also. In these tests we employed 2 strains of Type I pneumococci, SVI, which is highly lethal for mice, but kills them slowly, thus making the infections quite susceptible to chemotherapy, and a strain of the Type I pneumococcus which kills mice rapidly and produces an infection in them which is very difficult to cure. The characteristics of these 2 strains in mice have been described previously.[5] As is recorded in Table II, therapy with sulfapyridine gave slightly better results in experimental infections produced in mice by the intraperitoneal injection of these 2 strains of Type I pneumococci than did sulfathiazole. This slight therapeutic superiority of sulfapyridine was more noticeable in infections produced by the strain "Pneumo I" than it was in infections produced by strain SVI. With the latter strain there was no statistical difference in the number of mice surviving after treatment, although the average survival time of the mice treated with sulfathiazole was somewhat

2 Cooper, F. B., Gross, P., and Lewis, M., *Ibid.*, 1939, **42**, 421.

3 Van Dyke, H. B., Greep, R. O., Rake, G., and McKee, C. M., *Ibid.*, 1939, **42**, 410.

4 Long, P. H., Haviland, J. W., and Edwards, L. B., *Ibid.*, in press.

5 Long, P. H., and Bliss, E. A., *Ann. Int. Med.*, 1939, **13**, 232.

TABLE II.

The Comparative Therapeutic Effects of Sulfapyridine and Sulfathiazole upon Experimental Pneumococcal Infections in Mice.

Organism	No. Mice	Inoculum M.L.D.	Drug	Deaths—Days after infection										Survivals	
				1	2	3	4	5	6	7	8	9	10-30	No.	%
Pneu. SVI	15	570	S.T. D30			2		1	2	2	1		1	6	40
”	15	570	S.P. D30			1	1	1	2				2	9	60
”	50	615	S.T. D10		1	1	1			2	3		4	38	76
”	50	615	S.P. D10		1	1	1	2		2				43	86
”	50	615	Controls	16	34									0	0
Pneu. I	30	600	S.T. D30	1	19	10								0	0
”	30	600	S.P. D30		16	7	3	1					1	2	7
”	50	710	S.T. D10	1	22	10	5	6	1	2	1			2	4
”	50	710	S.P. D10		3	12	22	4		2	1			6	12
”	50	710	Controls	50										0	0

S.T. = Sulfathiazole
S.P. = Sulfapyridine
D30 = 30 mg *per os* immediately after infection and 6 hours later, then Q.D. for 3 days.
D10 = 10 mg *per os* T.I.D. for 5 days, B.I.D. for 1 day, Q.D. for 1 day.

less than that of those treated with sulfapyridine. However, in the infections produced by strain "Pneumo I", therapy with sulfapyridine proved superior to that with sulfathiazole, both in relation to average survival time and to the number of mice surviving at the end of the 30-day period of observation. However, we attribute this superiority to the fact that under the conditions of our tests, the concentrations of sulfapyridine were better maintained in the blood of the mice than were those of sulfathiazole.

McKee[1] found that when sulfapyridine and sulfathiazole are administered as 1% of the diet, the therapeutic effect of the 2 drugs in experimental pneumococcal infections in mice is the same. Preliminary tests which we have carried out tend to confirm this observation. While our experience has necessarily been limited, we have noted that sulfathiazole has a definite therapeutic effect in human pneumococcal pneumonia. However, it is too early to make any comparison of the therapeutic effects of sulfathiazole and sulfapyridine in this disease.

Conclusions. Sulfathiazole is as effective a bacteriostatic agent as is sulfapyridine in broth cultures of certain strains of Lancefield's Groups A, D, and G *beta* hemolytic streptococci, *E. coli, Staphylococcus aureus,* Types I and II pneumococci and *B. proteus.* Under the conditions of our tests sulfathiazole was slighly less effective than sulfapyridine in the control of experimental pneumococcal infections in mice. However, as has been pointed out, the more rapid absorption and excretion of sulfathiazole by the mouse, partially invalidate the results of comparative therapeutic tests in which the drug is administered *per os* in acacia suspensions at stated intervals.

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