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Bacteriostatic Effects of Sulfanilamide, Pyridine and Thiazol Derivatives upon Colon-Typhoid-Dysentery Group.*

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Chemotherapeutic studies of a series of thiazol derivatives of sulfanilamide under conditions of experimental infections in animals with *beta* hemolytic streptococci (strain C203), *Staphylococcus aureus,* and pneumococci Types I, II and III as reported by Fosbinder and Walter,[1] McKee, *et al.*,[2] and Barlow and Homburger[3, 4] suggested that at least 2 of these compounds merited careful clinical examination. A comparison of the *in vitro* effects of these compounds on the above organisms indicated that they were superior to either sulfanilamide or sulfapyridine (Lawrence[5]).

The present investigation was undertaken to determine the comparative *in vitro* effects of the thiazol compounds (sulfathiazol, sulfamethylthiazol and sulfaphenylthiazol) with those of sulfanilamide and sulfapyridine upon additional groups of organisms, namely, the gram negative bacilli representative of the colon-typhoid-dysentery group. These included 5 strains of *Eberthella typhosa,* one culture of which had recently been isolated from a typhoid patient (No. 1006), 2 cultures each of *Escherichia coli* and *Aerobacter aerogenes,* and one strain each of *Salmonella paratyphi, S. schottmuelleri, S. suipestifer, S. psittacosis, S. enteritidis, Shigella dysenteriae* and *Proteus vulgaris.*

Method. Ten mg % drug-broth solutions were prepared by adding the dry powders to 100 cc quantities of veal dextrose broth of pH 7.4 and containing bacto peptone.† Since preliminary cultural

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1 Fosbinder, R. F., and Walter, L. A., *J. Am. Chem. Soc.*, 1939, **61**, 2033.

2 McKee, G. M., Rake, G., Greep, R. O., and Van Dyke, H. B., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 417.

3 Barlow, O. W., and Homburger, E., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 792.

4 Barlow, O. W., and Homburger, E., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 317.

5 Lawrence, C. A., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 92.

† A few crystals remaining at the bottom of the flask containing the sulfaphenyl-broth solution, after autoclaving and cooling to 37°C, indicated this solution to be slightly supersaturated.

studies indicated that the particular strain of dysentery organisms used in this investigation grew more luxuriantly in a dextrose-free veal medium, the carbohydrate was omitted from the broth in which this organism was studied. The medicated culture media were autoclaved at 10 lb for 10 minutes and upon cooling 1 cc of an 18-hour broth diluted culture of one of the several organisms was added to each drug-broth and drug-free control broth medium.

The inoculated solutions were incubated at 37°C for 23-25 hours. In order to estimate the degree of bacteriostasis at this time, the following procedures were carried out. One-tenth and 1.0 cc of appropriate broth dilutions were placed in each of 2 petri dishes and melted and cooled (45°C) veal dextrose agar added. The contents were mixed thoroughly by swirling and the agar allowed to solidify. The plates were incubated at 37°C for 72 hours at which time the growing colonies were counted.

Results. In Table I are presented the results of the *in vitro* effects

TABLE I.

Comparison of *In Vitro* Effects of the Several Compounds upon *E. typhosa*, *E. coli*, and *S. dysenteriæ*.

		10 mg% concentrations. 23-25 hrs. 37°C. Organisms/cc.					
Organism	Inoculum Bacteria/cc	Sulfanilamide	Sulfapyridine	Sulfathiazol	Sulfamethylthiazol	Sulfaphenylthiazol	Control
E. typhosa	45	420 M	125,000	35,000	20,000	—	570 M
"Rawling" "B"	75	330 M	450	0	250	320,000	670 M
E. typhosa	40	500 M	780 M	110 M	100 M	610 M	660 M
"Rawling" "M"	80	725 M	490 M	120 M	40 M	410 M	590 M
E. typhosa	40	520 M	670 M	340 M	350 M	530 M	600 M
"Hopkins"	60	450 M	660 M	40 M	135 M	370 M	490 M
E. typhosa	70	620 M	460 M	370 M	410 M	640 M	930 M
No. 305	60	630 M	375 M	215 M	170 M	380 M	650 M
E. typhosa	70	620 M	750 M	370 M	440 M	580 M	830 M
No. 1006	60	750 M	620 M	230 M	290 M	620 M	890 M
E. coli	17	368 M	28 M	3 M	6 M	46 M	754 M
"B"	90	740 M	1 M	490,000	720,000	250,000	1.1 B
E. coli	23	1.1 B	112 M	3.3 M	4.7 M	32 M	1.2 B
"M"	75	1 B	40 M	4 M	17 M	86 M	1.2 B
S. dysenteriæ	4	484 M	308 M	130 M	122 M	145 M	425 M
	14	595 M	342 M	112 M	144 M	122 M	518 M

— = Compound not tested.
0 = No growth in plate inoculated with 0.1 cc. of the undiluted drug broth solution or dilutions thereof.
M = Million.
B = Billion.

of the several compounds upon *E. typhosa, E. coli* and *S. dysenteriae.* While the differences in the degree of bacteriostasis produced by most of these compounds under these experimental conditions are not striking, there is a definite trend which indicates a greater inhibitory effect on the part of sulfathiazol and sulfamethylthiazol than that of the other compounds.

A comparison of the effects of the compounds upon the *Salmonella, Aerobacter* and *Proteus vulgaris* organisms is given in Table II. In general sulfathiazol and sulfamethylthiazol were again found to be somewhat more effective than sulfapyridine, and distinctly more active than sulfaphenylthiazol and sulfanilamide in their bacteriostatic actions upon the organisms studied.

These findings, in part, confirm the results obtained by Helmholz[6] who, under different experimental conditions, was able to show that sulfathiazol and sulfamethylthiazol were more effective than sulfanilamide and sulfapyridine in their *in vitro* actions upon many of the organisms associated with urinary infections.

TABLE II.

Comparison of the *In Vitro* Effects of the Several Compounds upon *Salmonella, Aerobacter* and *Proteus vulgaris* Organisms.

		10 mg% concentrations. 23-25 hrs. 37°C. Organisms/cc.					
Organism	Inoculum Bacteria/cc	Sulfanil-amide	Sulfa-pyridine	Sulfa-thiazol	Sulfa-methyl-thiazol	Sulfa-phenyl-thiazol	Control
S. paratyphi	110	1.3 B*	520 M	770,000	7 M	810 M	1.1 B
	155	1 B	600 M	260 M	225 M	520 M	1.1 B
S. schottmuelleri	160	1.6 B	730 M	8 M	115 M	860 M	1.6 B
	185	1.5 B	650 M	460 M	690 M	1.2 B	2 B
S. suipestifer	95	180 M	1,200	150	400	1,150	890 M
	100	340 M	80	40	270	10	740 M
S. psittacosis	70	380 M	350 M	15 M	60 M	700 M	580 M
	75	610 M	278 M	67 M	195 M	500 M	725 M
S. enteritidis	120	1 B	37 M	270,000	600,000	680 M	1.2 B
	47	690 M	630 M	50 M	105 M	400 M	720 M
A. aerogenes "B"	17	446 M	286 M	120 M	132 M	355 M	512 M
	26	425 M	224 M	94 M	160 M	376 M	489 M
A. aerogenes "M"	90	160 M	74 M	35 M	78 M	83 M	940 M
	150	1.4 B	430 M	60 M	90 M	900 M	1.2 B
Proteus vulgaris	37	460 M	13 M	1.5 M	1.5 M	15 M	290 M
	5	472 M	220 M	151 M	135 M	22 M	460 M

*See legend under Table I.

[6] Helmholz, H. F., *Proc. Staff Meetings, Mayo Clinic,* 1940, **15**, 65.

In a more recent publication Long and Bliss[7] also found that the unsubstituted thiazol derivative was equal to, or slightly superior to, sulfanilamide and to sulfapyridine in its bacteriostatic action upon cultures of *E. coli* and *B. proteus* in broth.

Conclusions. On the basis of *in vitro* studies sulfathiazol and sulfamethylthiazol have been found to be somewhat more effective than sulfapyridine, sulfaphenylthiazol and sulfanilamide in their *in vitro* effects upon bacteria representative of the colon-typhoid-dysentery group. In general, the unsubstituted thiazol derivative appears to be the most active compound, being followed in decreasing order of effectiveness by sulfamethylthiazol, sulfapyridine, sulfaphenyl thiazol and sulfanilamide.

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Changes Produced by Desoxycorticosterone Overdosage in the Rat.*

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Kuhlmann, *et al.*,[1] found recently that dogs chronically treated with very high doses of desoxycorticosterone acetate show definite signs of damage and reveal blood chemical changes which appear to be the opposite of what is seen in adrenal insufficiency. Thus they noted " . . . . a striking decrease in serum potassium, a slight increase in serum sodium, a slight decrease in serum protein and non-protein nitrogen . . . . ". In this connection it appears of interest to mention our experiments in the rat which indicate that treatment with as high a dose as 10 mg of desoxycorticosterone acetate daily given for 20 days fails to produce any externally visible signs of damage and that, contrary to expectations, the blood chlorides prove to be consistently low. Meanwhile we have no explanation for the fact that although desoxycorticosterone prevents hypochloremia in the adrenalectomized rat, chronic overdosage with this

7 Long, P. H., and Bliss, E. A., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 324.

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1 Kuhlmann, D., Ragan, C., Ferrebee, J. W., Atchley, D. W., and Loeb, R. F., *Science*, 1939, **90**, 496.