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Therapeutic Effect of Sulfathiazole and Sulfapyridine.

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The pharmacology of the new thiazole analogue of sulfapyridine prepared by Lott and Bergeim[1] has been described in a preceding paper.[2] The therapeutic effect of this drug has been tested in a large number of mice against several different infections. In all cases the effect has been measured against that produced by the same amounts of sulfapyridine. The results are discussed below.

The drugs have been administered by several different methods. Thus the free acid has been injected by stomach tube as a suspension both in water and in gum acacia and also subcutaneously as an aqueous suspension. A solution of the sodium salt in water has been given by stomach tube. The results obtained when the drugs were given by any of these methods indicated that the new compound, sulfathiazole, was very promising (Table I). Several *in vitro* tests also gave results promising for sulfathiazole. However, the physical properties of sulfathiazole are such that its administration as a suspension proved to be technically difficult. The insoluble powder settled out more rapidly than did the sulfapyridine, rendering it difficult to give the full doses indicated or to measure the actual dose given. Moreover, in certain experiments the sodium salt was found to be precipitated in the stomach in the form of a curd much of which remained for several days so that the mice did not absorb the anticipated amount of drug. The technical difficulties outlined above might account for some of the less favorable results obtained with sulfathiazole as compared with sulfapyridine (Table I). In addition, however, was the fact that sulfathiazole disappears from the circulating blood after single administrations much more rapidly than does sulfapyridine.[2] In all the above experiments the drugs were administered twice a day at 9 a.m. and 5 p.m., leaving an interval of 16 hours when no drug was given and the blood level of sulfathiazole probably dropped to low levels. It was thought that better results would be obtained were more repeated administration assured and it was, therefore, decided to adopt the method of mixing the drug with

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

[2] van Dyke, H. B., Greep, R. O., Rake, Geoffrey, and McKee, C. M., Proc. Soc. Exp. Biol. and Med., 1939, **42**, 410.

TABLE I.

Infecting organism	Therapy: Route of administration	Therapy: Amt per day mg/k	Therapy: Days treatment	Number of mice treated with: Sulfathiazole: Lived, No.	Sulfathiazole: Died: No.	Sulfathiazole: Died: Avg life in days	Sulfapyridine: Lived, No.	Sulfapyridine: Died: No.	Sulfapyridine: Died: Avg life in days	Untreated: Lived, No.	Untreated: Died: No.	Untreated: Died: Avg life in days
Pneumococcus Type 1 P	*subcu.	1000	5	3	27	4.6	1	29	3.9	0	30	<1
Type 2 P	”	”	”	6	24	6.5	18	12	9.4	0	30	<1
Type 3 S	”	”	”	10	17	5.8	21	9	10.9	0	30	1.7
Meningococcus Type 1	”	”	”	11	18	4.0	8	20	2.1	0	29	1.4
Pneumococcus Type 1 P	†oral	1250	10	6	19	8.5	13	14	8.6	0	9	1.4
Lymphogranuloma venereum	”	”	7	13	0		13	0		11	19	8.9

* Suspension of free acid in distilled water.

† Suspension of free acid in gum acacia.

the food as described by Bieter and coworkers[3] and Litchfield and coworkers.[4]

The drugs were added in 1% concentrations to Sherman mouse-diet No. 1. Mice were placed on the diet 2 days before they were infected so that they would become accustomed to the food. Our observations agree with those of other workers[3, 4] that mice eat such a diet freely throughout the 24 hours with a peak of consumption around midnight and lowest consumption around 6 a.m. The amount of drug consumed daily by this method is approximately equal for sulfathiazole and sulfapyridine and averages around 1.85 g per kilo. Following infection mice were maintained on the drug diet for 10 days and were then returned to normal diet for a further 10 days' observations. All results are given up to the termination of the 20 days.

Infections with the following organisms have been tested: Pneumococcus Types 1 (4 strains), 2 (3 strains), 3 (5 strains), 5, 6, 7, 8, 14, and 26, meningococcus, and *Streptococcus hemolyticus*. All infection was by the intraäbdominal route. The dose varied, but for the pneumococcal strains was usually one cc of a $1:10^{-7}$ dilution of a 5-hour blood-broth culture. All strains used have been maintained in a state of constant virulence by frequent mouse-passage.

Table II shows representative results. It will be noted that there is little difference between the two drugs. In the case of some strains, *i. e.*, pneumococcus Type 2-807 and pneumococcus Type 8, little protection occurred with either drug; in others, *i. e.*, pneumococcus 7 and the *Streptococcus hemolyticus*—C203, perfect protection was obtained with both drugs.

In the few experiments in which 0.5% of the drugs have been used in the diet the results with sulfathiazole have been slightly but consistently less favorable than those with sulfapyridine, a result to be expected in view of what occurs to the blood-levels of the two drugs in mice on a 1% diet. Single experiments on mice fed the drug in the diet, and the blood-curves following injection[2] indicate that the sulfathiazole blood-level is more dependent on the intake of drug in the food. During periods of low food-consumption the level of sulfathiazole will be lower than that of sulfapyridine; at other times the level of the two drugs is probably similar. Only representative experiments have been given in any detail in the tables and they show only a part of the work which has been carried out.

[3] Bieter, R. N., Larson, W. P., Cranston, E. M., and Levine, Milton, *J. Pharm. and Exp. Ther. Proc.*, 1939, **66**, 3.

[4] Litchfield, J. T., Jr., White, H. J., and Marshall, E. K., Jr., *J. Pharm. and Exp. Ther. Proc.*, 1939, **66**, 23.

TABLE II.

Infecting organism*	Number of mice treated with: Sulfathiazole diet† Lived No.	Sulfathiazole diet† Died No.	Sulfathiazole diet† Died Avg life in days	Sulfapyridine diet† Lived, No.	Sulfapyridine diet† Died No.	Sulfapyridine diet† Died Avg life in days	Normal diet Lived, No.	Normal diet Died No.	Normal diet Died Avg life in days
Pneumococcus Type 1 P	15	31	3.3	14	31	3.9	0	38	.82
" 748	15	5	6.	15	5	5.1	0	20	1.66
" 2 P	16	8	11.8	21	3	6.3	0	23	.77
" 807	0	20	2.2	0	20	2.	0	20	< .75
" 3 S	21	1	15.	21	1	9.	1	21	1.8
" 750	1	19	7.	3	17	6.2	0	20	.97
" 5 752	17	3	5.2	16	4	3.	0	20	.9
" 6	8	12	11.2	13	7	16.7	0	20	1.37
" 7 754	20	0		20	0		0	20	1.49
" 8 755	1	19	3.7	0	20	4.2	1	13	1.4
" 14 848	10	0		10	0		1	7	1.7
" 26	14	6	13.3	11	9	13.4	1	19	2.79
Meningococcus Type II	16	2	1.5	12	6	2.3	1	9	1.0
Streptococcus hemolyticus	14	0		13	0		0	14	.9

* Dose varied from 10^{-5} to 10^{-7} of a 5-hour culture depending on virulence.
† One percent drug in food.

Thus, 650 mice have been used in tests of the efficacy of the drugs when administered by methods other than that of addition to the diet. Approximately 1200 mice have been used in experiments with a 1% diet and 200 on a 0.5% diet.

As has been shown in Table I both sulfathiazole and sulfapyridine have an appreciable therapeutic effect against the agent of *lymphogranuloma venereum*. In tests with this agent 85 mice have been used. These results are in agreement with those obtained by others with sulfanilamide. Neither sulfathiazole nor sulfapyridine, however, has shown any activity against swine-influenza virus or *herpes simplex*. In these tests 300 mice have been used. Further virus-studies are in progress.

Conclusions. It has been shown that when the compounds which have been studied are administered as 1% of the diet, the therapeutic effect of sulfathiazole is equal to that of sulfapyridine. In view of the comparative toxicity and metabolism of these two compounds[2] it is possible that sulfathiazole may be a more desirable therapeutic agent than sulfapyridine.

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Chemotherapeutic Evaluation of Sulfanilamide Derivatives of Heterocyclic Amines.

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The therapeutic success with which sulfanilamide has been used in a number of unrelated bacterial and several viral diseases has stimulated the search for more effective and less toxic drugs. The trend of these investigations has generally been to modify the sulfanilamide nucleus by substitution in the amine or amide group, replacement of the amide group or degradation of the sulfone group. These substitutions have generally been of the alkyl, aryl, or substituted-alkyl or substituted-aryl type. The few compounds formed by the substitution of heterocyclic radicals for amino or amide hydrogens were of no especial interest, prior to the advent of sulfapyridine, because of their relatively feeble therapeutic activity.

Of these, the heterocyclic azo compounds *p*-sulfonamidophenylazodihydrocupreine,[1, 2] *p*-sulfonamidophenylazoapoquinine,[2] *p*-sulfonam-

[1] Heidelberger, M., and Jacobs, W. A., *J. Am. Chem. Soc.*, 1919, **41**, 2145.

[2] Buttle, G. A. H., Gray, W. H., and Stephenson, D., *Lancet*, 1936, **1**, 1286.