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Response of Sulfonamide-fast Pneumococci to Penicillin.

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Schmidt and Sesler[1] have shown that hydroxyethylapocupreine is effective against both sulfonamide-fast and parent strains of pneumococci; however, the degree of effectiveness against parent strains was less and the toxicity was more than that of sulfapyridine in comparable chemotherapeutic dosage.

We have conducted similar comparative experiments with penicillin and sulfapyridine in mouse infections with Types I, II, and III pneumococci, a "fast" and parent strain of each type being used. The penicillin was prepared by Dr. J. M. McGuire and Mr. F. G. Jones of the Lilly Research Laboratories; this substance comprised a brown powder about 200 times as bacteriostatic for staphylococci as the culture filtrate from which it was derived. The six strains of pneumococci were obtained through the kindness of Dr. L. H. Schmidt of Christ Hospital, Cincinnati. Our experiments are described briefly as follows:

The stock pneumococcus cultures were passaged through mice once each week. Directly after passage, 16-hour rabbit blood broth subcultures were prepared. For therapy, a group of 240 mice of about 20 g weight were each injected with 10^{-4} cc (about 10,000 M.L.D.) of the various subcultures of pneumococci. Subgroups of 20 mice infected with each strain were treated respectively with penicillin and sulfapyridine, as shown in the upper 3 sections of Table I. One hundred forty-four additional nontreated control mice were injected in groups of 4 with doses of 10^{-4} to 10^{-9} cc of the various pneumococcus strains to determine the degree of virulence. All of the strains proved of high virulence at the time of use, as shown in the lower section of Table I.

Penicillin therapy comprised 10 oral doses of 20 mg each, 4 doses being given at 2-hour intervals on each of the first and second days and 2 doses being given with an 8-hour interval on the third day. A dose of 5 mg of sodium bicarbonate was given with each dose of penicillin as a protection against gastric acidity. Sulfapyridine therapy comprised 5 oral doses of 30 mg each, 2 doses being given with an 8-hour interval on each of the first and second days and one dose

1 Schmidt, L. H., and Sesler, C. L., *J. Phar. and Exp. Therap.*, 1941, **72**, 311.

TABLE I.
Comparative Response of Parent and Sulfapyridine-fast Pneumococci to Penicillin and Sulfapyridine.

Pneumococcus 10⁻⁴ cc			Number of mice dead on days indicated or survived 14 days (S)										Mean length of life (days)
Type	Strain	Therapy	1	2	3	4	5	6	7	8-14	S	Per cent survived	
I, McGovern	parent	1					1				19	95	13.5
	"	2			1			2	2	2	13	65	11.6
	fast	1								3	17	85	13.6
	"	2	8	12							0	0	1.6
II, C H	parent	1				1					19	95	13.5
	"	2			2	4	12	2			0	0	4.7
	fast	1								1	19	95	14.0
	"	2	2	13	4	1					0	0	2.2
III. C H A	parent	1	1	1	2	3					13	65	10.1
	"	2		5	5	5	5				0	0	3.5
	fast	1	1	2	3	3					11	55	9.0
	"	2	12	6	2						0	0	1.5

Virulence controls; all types and strains (cc)	Type I, McGovern		Type II, C H		Type III, C H A	
	Parent	Fast	Parent	Fast	Parent	Fast
10^{-4}	4/4*	4/4	4/4	4/4	4/4	4/4
10^{-5}	4/4	4/4	4/4	4/4	4/4	4/4
10^{-6}	4/4	4/4	4/4	4/4	4/4	4/4
10^{-7}	4/4	4/4	4/4	4/4	4/4	4/4
10^{-8}	4/4	3/4	3/4	3/4	2/4	3/4
10^{-9}	0/4	1/4	0/4	0/4	1/4	3/4

Therapy: 1 = penicillin 20 mg × 10 doses.
2 = sulfapyridine 30 mg × 5 doses.
*Mice dead/mice used.

being given on the third day. Initial drug doses in both instances were given within an hour after infection, and all overnight intervals when no drug was given were 16 hours. Details of pneumococcus mouse infections of this order and effective sulfonamide chemotherapy have already been described.[2, 3]

It is observed from the results in Table I that sulfapyridine has a decreasing order of antipneumococcal effectiveness against Type I parent strain, Type II parent strain, Type III parent strain, and Types I, II, and III fast strains; the degree of effectiveness against these 3 latter strains in fact is practically *nil*. Penicillin, in contrast, appears highly effective against both parent and fast strains of Types I and II and moderately effective against both parent and fast strains of Type III pneumococci.

[2] Powell, H. M., and Chen, K. K., *J. Ind. State Med. Assn.*, 1940, **33**, 503.
[3] Powell, H. M., and Chen, K. K., *J. Ind. State Med. Assn.*, 1941, **34**, 602.

Further experiments with *Streptococcus hemolyticus* and *Staphylococcus aureus* will be reported in the near future.

The penicillin employed has now been concentrated by chemical means, thus permitting the oral administration of substantially smaller doses than those reported here.

We desire to express to Dr. G. H. A. Clowes our indebtedness for advice and suggestions in the conduct of these experiments.

Conclusions. Penicillin is an effective chemotherapeutic agent against both parent and sulfonamide-fast pneumococci in mouse infection experiments.

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Formation of Angiotonin-like Pressor Substance from Action of Crystalline Pepsin on Renin-Activator.

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The interesting communication of Croxatto and Croxatto[1] in which they describe the formation of a pressor substance similar in properties to angiotonin or hypertensine prompted us to repeat their work. We wished to ascertain whether the same results could be obtained by using crystalline pepsin instead of the commercial product. Further, the effect of pH on this reaction as well as on that between renin and renin-activator was studied.

Methods. Preparation of the Renin-activator. For the preparation of renin-activator ox serum[2, 3] was used. One volume of 3 M potassium phosphate at pH 6.5 was added to an equal volume of ox serum and the resulting precipitate discarded. To each liter of the clear filtrate 500 cc of 3 M phosphate was added to raise the phosphate concentration to 2 molar. This precipitate which contains the active material was collected on Buchner funnels.

The precipitate was dissolved in distilled water and dialyzed against running tap water. The precipitate which forms in the sac was discarded and the residual solution reprecipitated between 1.5 and 2

1 Croxatto, H., and Croxatto, R., *Science*, 1942, **95**, 101.

2 Kohlstaedt, K. G., Helmer, O. M., and Page, I. H., PROC. SOC. EXP. BIOL. AND MED., 1939, **39**, 214.

3 Kohlstaedt, K. G., Page, I. H., and Helmer, O. M., *Am. Heart J.*, 1940, **19**, 92.