extract had been added. After incubation for 5 days at 37.5° C, the organisms were centrifuged, washed with saline and transplanted to a solid medium. Whereas the controls grew out rapidly the organisms exposed to the extract failed to show any growth.

Thirty series of experiments were performed, using the material concentrated from as many separate harvests of mold substrate, representing a total of about 500 liters of original media.

The extract showed little deterioration when incubated for 2 weeks at 37.5° C or when autoclaved at 15 pounds pressure for 15 minutes. A slight lowering of antibiotic activity was noted when incubated with normal human serum or Sorensen phosphate buffer, pH 7.2 to 7.6. No effect on the extract was noted when treated with a Paulitsch borate buffer, pH 7.2 to 7.6.

Penicillin, which has already been shown to have no effect on the tubercle bacillus,[8] was tested against the strain used in our experiments. A concentration of 1,500 units per cc of Dorset's liquid medium failed to inhibit the growth of the standard inoculum used in these studies.

A strain of the human tubercle bacillus, isolated from the sputum of a patient with advanced pulmonary tuberculosis and shown to be highly pathogenic for guinea pigs, was inhibited *in vitro* by the mold extract in preliminary tests. Further experiments now in progress include isolation and purification of the active principle and the determination of the growth conditions necessary for optimum yield of the mold product.

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SULFONAMIDES AND EGG-SHELL FORMATION IN THE DOMESTIC FOWL

THE action of sulfa drugs on egg-shell formation in birds has been reported in papers which appeared in the last two years. Hinshaw and McNeil[1] first noted the laying of soft-shelled eggs by turkeys and White Leghorn hens following feeding of sulfanilamide. Scott *et al.*[2] published a more comprehensive study of the effect of feeding sulfanilamide to the laying fowl. These workers concluded that sulfanilamide appears to exert a specific inhibition on the secretory ability of the shell glands.

About the same time, Benesch *et al.*,[3] feeding sulfanilamide and sulfapyridine to laying hens, reported that carbonic anhydrase appeared essential for shell formation. Their working hypothesis was based on the following: (a) the suggestion of Meldrum and Roughton[4] that carbonic anhydrase might play a rôle in egg-shell formation; (b) the finding by Common[5] that the carbonic anhydrase activity of the uterine epithelium is higher than that of the remaining oviducal tissues, (c) the demonstration by Keilin and Mann[6] that sulfonilamides of the $R\text{-}SO_2NH_2$ type specifically inhibit carbonic anhydrase. This property, however, is absent in all compounds in which the sulfonamide group is substituted, as it is, for example, in sulfapyridine and sulfathiazole. Benesch *et al.*[3] fed single doses varying from 0.1 gm/kg to 0.2 gm/kg of sulfanilamide to laying hens and observed very thinned and pitted shells. The same birds were afterwards given a similar dose of sulfapyridine, and the shells obtained were normal throughout.

The writers undertook experiments with several sulfonamides of the unsubstituted and substituted type. The sulfonamides were fed at levels of 0.3 or 0.5 per cent. of the dry mash. The experimental period lasted one week and was preceded and followed by one-week control periods.

It was found that unsubstituted sulfonamides such as Soluseptazine and Neoprontosil caused thin rough-shelled eggs similar to those obtained upon feeding sulfanilamide. The substituted sulfonamides such as sulfathiazole, sulfaguanidine, sulfamerazine and sulfadiazine had a negligible effect on shell thickness. The shells were smooth, though they appeared slightly pitted when observed under low magnification.

These results so far confirmed the conclusions of Benesch *et al.*[3] On the other hand, repeated experiments with sulfapyridine consistently revealed a decrease in shell thickness as well as a rough surface, whether this compound was fed for several days or in a single dose. The data are presented in Table 1 and Fig. 1.

TABLE 1

EFFECT OF SULFAPYRIDINE ON SHELL THICKNESS

Per cent. sulfapyridine in dry mash	Bird number	Mean shell thickness (mm)		Per cent. decrease in shell thickness
		Control period	Experimental period	
0.3	1	0.343 ± 0.004*	0.275 ± 0.013	19.7
	2	0.354 ± 0.004	0.265 ± 0.006	25.0
	3	0.371 ± 0.004	0.283 ± 0.012	23.7
	4	0.354 ± 0.004	0.267 ± 0.016	24.4

*P. E. of the mean.

[8] E. P. Abraham, E. Chain, C. M. Fletcher A. D. Gardner, N. G. Heatley, M. A. Jennings and H. W. Florey, *The Lancet*, 241: 177, 1941.

[1] W. R. Hinshaw and E. McNeil, *Poultry Sci.*, 22: 291, 1943.

[2] H. M. Scott, E. Jungherr and L. D. Matterson, *Poultry Sci.*, 23: 446, 1944.

[3] R. Benesch, N. S. Barron and C. A. Mawson, *Nature*, 153: 138, 1944.

[4] R. U. Meldrum and F. J. W. Roughton, *Jour. Physiol.*, 80: 113, 1933.

[5] R. H. Common, *Jour. Agr. Sci.*, 31: 412, 1941.

[6] D. Keilin and T. Mann, *Nature*, 146: 164, 1940.

In four White Leghorns (Table 1), the decrease in shell thickness varied between 19 and 25 per cent. In Fig. 1, it is seen that a single dose of sulfapyridine affected the shell thickness for at least four days. The feeding of the same substance at 0.3 per cent. level in the dry mash for a period of six days gave thinner shells and upon withdrawal of the drug, the effect was observed for three to four days (Fig. 1). These findings are analogous to those of Benesch *et al.*[7] who note that sulfanilamide and sulfapyridine both inhibit to the same extent the calcification of the femurs in rat foetuses.

It is believed that this effect of sulfapyridine on shell formation, though not in agreement with the observations of Benesch *et al.*,[3] does not exclude carbonic anhydrase as a factor in shell formation. One is led to suggest, however, that certain sulfonamides such as sulfapyridine may interfere with normal shell formation by inhibiting enzymes other than carbonic anhydrase. A temporary vitamin deficiency always remains a possibility when dealing with sulfa drugs.

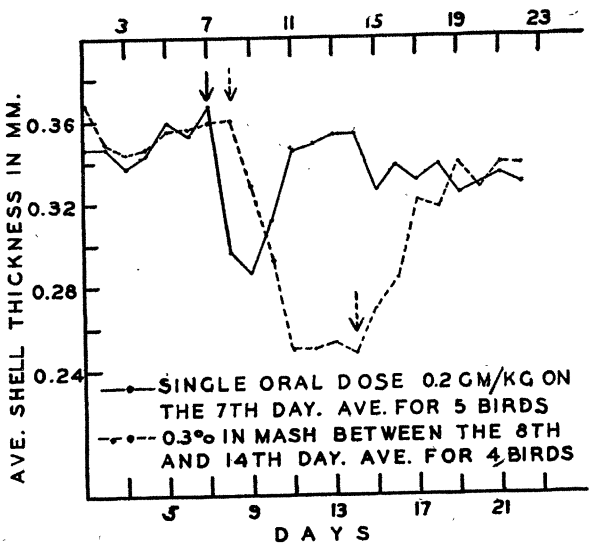

FIG. 1. Effect of sulfapyridine on shell thickness in the domestic fowl.

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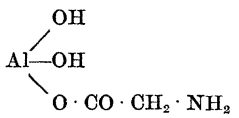
ORAL PENICILLIN WITH BASIC ALUMINUM AMINOACETATE

RECENTLY in this laboratory[1] a new antacid, basic aluminum aminoacetate, was synthesized and studied pharmacologically and clinically. The structure proposed for the compound is



Having established the value of the compound as a rapidly active antacid with high buffer capacity, the thought of using it to protect penicillin from destruction by gastric acid occurred to us. Libby[2] has shown that effective concentrations of penicillin may be obtained in dog's serum after the oral administration of the drug suspended in oil.

Penicillin was acidified with artificial gastric juice[3] and other samples were treated with gastric juice buffered with basic aluminum aminoacetate to pH 4 to 4.5. The activity of each sample of penicillin was determined by the agar cup against staphylococcus aureus as compared with the untreated drug by the method of Abraham[4] *et al.* Gastric juice destroyed completely the activity of the drug. The penicillin treated with gastric juice buffered with the antacid was from 50 to 70 per cent. as active as the untreated penicillin.

Twelve individuals were given 100,000 units of penicillin mixed with 3 grams of basic aluminum aminoacetate, suspended in 100 to 150 cc of water. The mixture was administered in the morning on a fasting stomach. Blood samples were taken 2, 3, 5 and 7 hours after administration and in these serum levels of penicillin were determined by the method of Rake and Jones.[5]

Wide variations were found in the rates of absorption and/or excretion. Effective levels were obtained soon after ingestion and the presence of the drug in the serum, in some cases, could be detected 7 hours after ingestion. Table 1 gives average serum concentrations with respect to time in these 12 individuals.

TABLE 1

SERUM LEVELS OF PENICILLIN
Oxford units per 100 cc serum

Time after ingestion	2 hrs.	3 hrs.	5 hrs.	7 hrs.
Units	39	68	37	17

By the Abraham[4] method penicillin was shown also to be present in the urine 2 hours after ingestion.

SUMMARY

This method appears to be suitable for the oral administration of penicillin. Basic aluminum amino-

[7] R. Benesch, M. R. A. Chance and L. E. Glynn, *Nature*, 155: 204, 1945.

[1] J. C. Krantz, Jr., D. V. Kibler and F. K. Bell, *Jour. Pharmacol. and Exp. Therap.*, 82: 247, 1944.

[2] R. L. Libby, SCIENCE, 101: 178, 1945.

[3] J. C. Krantz, Jr., and A. A. Silver, *Annal. Int. Med.*, 4: 441, 1931.

[4] E. P. Abraham *et al.*, *Lancet*, 2: 177, 1941.

[5] G. Rake and H. Jones, *Proc. Soc. Exp. Biol. and Med.*, 52: 136, 1943.