TABLE I.
In Vitro Effect of Various Concentrations of Therapeutic Agents on *Histoplasma capsulatum*.

Concn. mg%		100	50	25	20	10	1	0.1	0.01	0.001	*Control	
Neoarsphenamine		0	+	+	+	+	+	+	+	+	+	
Neostam		+	+	+	+	+	+	+	+	+	+	
Sulfadiazine		+	+	+	+	+	+	+	+	+	+	
Sulfathiazole		+	+	+	+	+	+	+	+	+	+	
Stilbamidine		0	0	0	0	0	+	+	+	+	+	
Concn. units/ml	2500	1250	750	250	125	100	75	50	25	12.5	10	7.5	5	1
Streptomycin	+	+	+	+	+	+	+	+	+	+	+	+	+	
Penicillin											+		+	+

0 No growth.
+ Growth.
* Control tube contained no drug and was always positive.

this was due to the sodium chloride present in the infusion broth, inasmuch as it is known that sodium chloride will produce crystallization of stilbamidine. The cause of the precipitate when neoarsphenamine was used is not known, but is probably related to the colloid-like properties of neoarsphenamine. This factor of precipitation undoubtedly reduced the amount of effective therapeutic agent present. At the time, it was impossible to determine the amount of each agent actually in solution.

Results. The results of these experiments are presented in Table I. On the basis of these experiments, it was found that neoarsphenamine in a concentration of 100 mg%, and stilbamidine in concentrations from 10 to 100 mg%, prevented the growth of *Histoplasma capsulatum*. As previously stated, the actual amount of neoarsphenamine and stilbamidine in solution was less than the tabulated concentrations.

The use of sulfadiazine, sulfathiazole, and neostam as well as streptomycin and penicillin exerted no inhibitory effect in the amounts used.

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Effect of Large Doses of Streptomycin and Influenza Viruses on Chick Embryos.

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(Introduced by V. E. Levine.)

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Search for an effective therapeutic agent against viral infections has been stimulated by the success attained in treating bacterial diseases with sulfonamides and antibiotics. However, since the problem is complicated by the intracellular growth of viruses, it is perhaps not remarkable that the results up to the present time have been almost consistently negative.[1] Recently a small quantity of streptomycin[2,*] became available to us. Because of the effectiveness of this agent against a number of bacteria which have been resistant to previously studied antibiotics and chemotherapeutic drugs, and its low toxicity for the

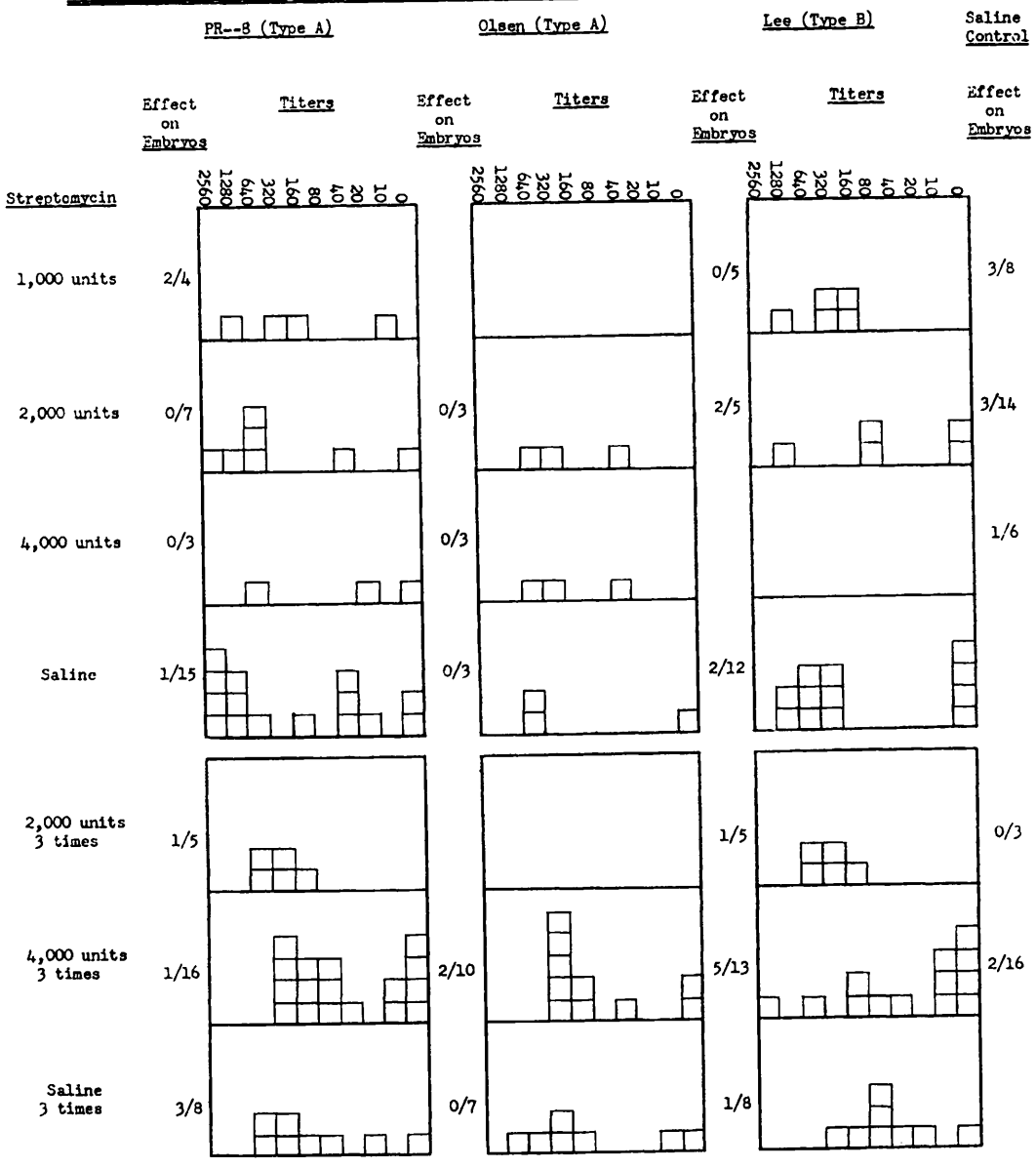
[1] Jones, D., Beaudette, F. R., Geiger, W. B., and Waksman, S. A., *Science*, 1945, **101**, 665.

[2] Schatz, A., Bugie, E., and Waksman, S. A., PROC. SOC. EXP. BIOL. AND MED., 1944, **55**, 66.

* The streptomycin was supplied by Merck and Company through the courtesy of Dr. D. F. Robertson. It consisted of remnants of lots No. 199, 209, 212.

CHART I

Inability of Streptomycin to Prevent Infection of Embryonated Chick Eggs with Influenza Strains



Legend: Numerator----embryos dead after 48 hrs.
Denominator--embryos inoculated.
□----------one embryo, location indicates agglutination titer of allantoic fluid after 48 hrs.

chick embryo,[3] a laboratory trial against viruses which would grow in the chick embryo seemed warranted.

Method of Study. The allantoic cavities of 11- to 13-day-old embryonated chicken eggs were inoculated with various strains of influenza combined with varying amounts of streptomycin. The PR-8 and Olsen strains were used as representative of Type A and the Lee strain as an example of Type B

[3] Jones, D., Metzger, J. J., Schatz, A., and Waksman, S. A., *Science*, 1944, **100**, 103.

influenza.† Each embryo received an original total inoculum of 0.15 cc; of this 0.05 cc was a 1:1000 dilution of infected allantoic fluid, and 0.10 cc was either saline or the antibiotic reconstituted and diluted with sufficient saline to give the desired concentration. The virus and streptomycin were mixed immediately before inoculation. In those instances where more than one "dose" of streptomycin was given, the subsequent injections were made in 0.15 cc quantities within the first 24 hours. In the interim, the shellholes were sealed with a small tent of Scotch tape. The eggs were incubated at 36° to 37°C for 48 hours. After this period the allantoic fluids were collected and their hemagglutinating titers for chicken red cells were determined.[4]

† The influenza strains were furnished by Dr. M. D. Eaton.

[4] Florman, A. L., and Crawford, J. P., *Am. J. Med. Sci.*, 1944, **208**, 494.

Results of Study. The results of several experiments are summarized in Chart I.‡ From this it is apparent that:

1. A total of 12,000 units given over a period of 24 hours failed to make any significant difference in the multiplication in the chick embryo of the PR-8, Olsen, and Lee strains of influenza. This represents a total dosage of approximately 200,000 units per kilo of egg weight per 24 hours. It may be contrasted with the 150 and 300 units of streptomycin which protect chick embryos against *Shigella Gallinarum* and *Brucella abortus* infections.[3]

2. Despite the very large amounts of streptomycin administered in these experiments there was no evidence of any lethal effect on the developing embryo. The low toxicity of this new agent is noteworthy.

‡ The chart was prepared by Cpl. Fred W. Trader and photographed by the U.S.A. Signal Corps.

15213 P

Protection of Mice Against Lethal Action of Gonococcal Endotoxin by Penicillin.*

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We have reported[1] that large subcutaneous doses of penicillin repeatedly administered exert a considerable degree of protection against the toxicity of sterile meningococcal endotoxin as measured by its lethal action in mice and rabbits. Neter[2] claimed that penicillin mixed with tetanus toxin did not protect mice from death. According to Ercoli, Lewis, and Moench[3] large doses of penicillin neutralized diphtheria toxin *in vitro*, but had no effect in guinea pigs on the lethal action of incompletely neutralized diphtheria toxin. Little other investigation has been directed toward the effect of penicillin on the action of toxic bacterial substances. Carpenter and his co-workers[4,5,6] reported detoxification by sulfanilamide and sulfapyridine of the "toxins" of gonococcus and other bacteria.

The crude endotoxin used in these experiments was prepared from 5 strains of gonococcus grown for 18 hours on an agar medium[7]

* Aided by a grant from the John and Mary R. Markle Foundation.

[1] Boor, Alden K., and Miller, C. Phillip, *Science*, 1945, **102**, 427.

[2] Neter, Erwin, *J. Inf. Dis.*, 1945, **76**, 20.

[3] Ercoli, N., Lewis, M. N., and Moench, Lucille J., *J. Pharm. Exp. Ther.*, 1945, **84**, 120.

[4] Carpenter, C. M., Hawley, P. L., and Barbour, G. M., *Science*, 1938, **88**, 530.

[5] Barbour, Gerald M., and Carpenter, Charles M., Am. Assn. Adv. Sci., Pub. No. 11, 1939, 114.

[6] Carpenter, Charles M., and Barbour, Gerald M., PROC. SOC. EXP. BIOL. AND MED., 1939, **41**, 354.

[7] Boor, Alden K., PROC. SOC. EXP. BIOL. AND MED., 1942, **50**, 22.