

Effect of Aureomycin on Heparin Concentration and Clotting Time of Human Blood.* (18236)

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While Macht and Farkas(1) reported that aureomycin increased the coagulability of blood, other investigators found no evidence for this following the administration of the drug(2,3). The mechanism of an effect of aureomycin on coagulability may be a reaction between the aureomycin and the naturally occurring heparin. Experiments demonstrating that aureomycin does lower the concentration of heparin in human plasma and serum and also increases the coagulability of blood are presented in this report. Increasing amounts of aureomycin were added to normal serum and plasma in the following manner: Aureomycin† (5 μ g to 8 mg) was diluted with about 1 cc of 0.9% NaCl, adjusted to pH 7.3 with 0.1 N-HCl, brought to a volume of 2 cc with 0.9% NaCl and added to 10 cc of clear normal serum or plasma. The mixture was centrifuged for 15 minutes at 1600 times gravity and -2°C . The supernatant was analyzed for heparin‡ by the method of Jacques, Monkhouse, and Stewart(4) with slight modifications to be described in a subsequent report(5).

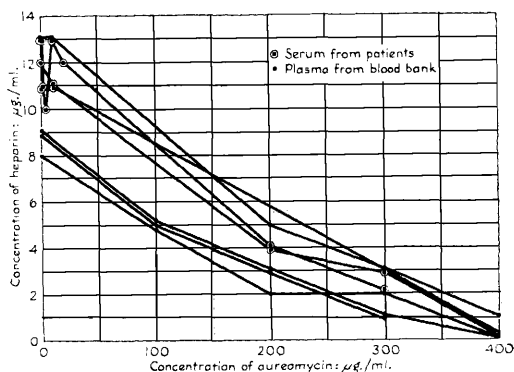


FIG. 1.

Effect of aureomycin on the concentration of heparin in human serum and plasma.

The effect of aureomycin on blood coagulability was investigated by determinations of the coagulation times of 11 patients just before and just after infusions of aureomycin. The coagulation times were done by the same technician using the 3 tube method of Lee and White. After a control coagulation time, 0.5 g of aureomycin dissolved in 500 cc of 0.9% NaCl was administered intravenously. When the infusion was finished the coagulation time of blood drawn from a vein in the opposite arm was determined.

As increasing amounts of aureomycin were added to the serum and plasma *in vitro*, the amount of heparin decreased (Fig. 1). In the presence of 100 to 200 μ g aureomycin/cc serum the concentration of heparin was approximately halved. Less than 20 μ g aureomycin/cc did not appear to have a significant effect on the concentration of heparin as measured by the method used.

The blood of 10 of the 11 patients clotted more rapidly after an infusion of 0.5 g of aureomycin dissolved in 0.9% NaCl (Table I). In one patient there was no change in the coagulation time. There was no instance in which the coagulation time was increased after the infusion of aureomycin.

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1. Macht, D. I., and Farkas, R., *Science*, 1949, v110, 305.

2. Harned, B. K., Cunningham, R. W., Clark, M. C., Cosgrove, R., Hine, C. H., McCauly, W. J., Stokey, E., Vessey, R. E., Yuda, N., SubbaRow, Y., *Ann. N. Y. Acad. Sci.*, 1949, v51, 182.

3. Ross, S., Burke, F. G., Rice, C. C., Schoenback, E. S., Bischoff, H., Washington, J. A., *Clin. Proc. Child. Hosp.*, 1948, v4, 315.

† Kindly supplied by Lederle Laboratories.

‡ Heparin of Hynson, Westcott and Dunning, Inc., used for standards.

4. Jacques, L. B., Monkhouse, F. C., Stewart, M., *J. Physiol.*, 1949, v109, 41.

5. Ochs, M., M. S. Thesis in Physiological Chemistry, University of Minnesota, in preparation.

TABLE I. Effect of Aureomycin Given by the Intravenous Route on Coagulation Time.

Patient No.	Clotting time (min.)		
	Before aureomycin	After aureomycin	Diff.
1*	30	19.5	—10.5
2	21	15	— 6
3	19	17	— 2
4	19	17.5	— 1.5
5	17	13	— 4
6	22	15.5	— 6.5
7	23	19.5	— 3.5
8	23	21	— 2
9	26	23	— 3
10	23	23	0
11	16	12	— 4

* Convalescing from infectious hepatitis.

The data presented is in accord with Macht and Farkas' finding(1) that in certain instances aureomycin increases the coagulability of the blood. The present results suggest that this increased coagulability is due to an anti-heparin effect of aureomycin. The observation of Miller *et al.* that certain antibiotics including aureomycin reduce mortality from x-radiation(6) and the finding of Allen *et al.* that shortly after x-radiation a heparin-like substance appears in the plasma of dogs (7), suggest the possibility that protection

6. Miller, C. P., and Hammond, C. W., *Science*, 1950, v111, 719.

by certain antibiotics against the effects of radiation may be mediated, at least in part, through an anti-heparin effect. Whether or not this phenomenon is responsible for an increased incidence of thrombosis following the use of antibiotics, which has been suggested by some observers and denied by others(8), should be investigated further. It is worthy of note that both streptomycin and penicillin have been shown to increase the coagulability of blood(9-11).

Summary. Addition of aureomycin to human plasma *in vitro* produces a significant decrease in the heparin concentration. Aureomycin administered by the intravenous route lowered the coagulation time of the blood of 10 of 11 patients.

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7. Allen, J. G., Sanderson, M., Milham, M., Kirschon, A., Jacobson, L. O., *J. Exp. Med.*, 1948, v87, 71.

8. Long, P. H., *J. Am. Med. Assn.*, 1950, v142, 49.

9. Moldavsky, L. F., Hasselbrock, W. B., Cateno, C., *Science*, 1945, v102, 38.

10. Macht, D. I., *Science*, 1947, v105, 313.

11. Macht, D. I., *Arch. Int. of Pharmacodyn.*, 1947, v74, 399.

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Effects of X-irradiation on Passively Transferred Antibody.* (18237)

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Although much work has been done in an attempt to elucidate the mechanisms involved in antibody production and the factors which influence active immunity, very little is known about the mechanism of antibody destruction. Heidelberger *et al.*(1) have demonstrated that dietary amino acids containing isotopic nitro-

gen (N 15) are incorporated into actively produced antibody in similar quantities to their incorporation into the plasma proteins, and that the rate of disappearance from the 2 proteins is similar. Passively transferred homologous antiserum showed no uptake of the dietary isotopic nitrogen and was therefore considered anabolically inert.

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1. Heidelberger, M., Treffers, H. P., Schoenheimer, R., Ratner, S., and Rittenberg, D., *J. Biol. Chem.*, 1942, v144, 555.