probably inhibits the growth of influenza and mumps viruses by some effect on the host cell or on the interaction of host cell and virus. This effect is reversible by removing the amino acid and is brought about in the absence of demonstrable changes in the oxygen consumption, glucose utilization, or growth potential of the tissue. The reversal of the effect of arginine by egg yolk suggests the possibility of interaction with lipids in the cell membrane. The augmenting effect of an alkaline reaction (pH 8.0) is similar to that seen with basic antibacterial substances such as streptomycin and diamidines(7). Synthetic lysine polypeptides have been reported to inhibit the growth of influenza virus(8), but these cause aggregation of virus particles, bacteria and red cells while arginine and lysine apparently have no direct effect either on the infective or hemagglutinating properties of mumps and influenza viruses.

Summary. Arginine, lysine, ornithine, and to a lesser extent some other amino acids retard the growth of influenza and mumps viruses in tissue cultures when added at concentrations of 1 to 10 mg/ml. The virustatic effect of arginine and lysine could not be attributed to toxicity or to direct action of these amino acids on the viruses.

7. Kohn, H. I., *Science,* 1943, v98, 224.

8. Rubini, J. R., Stahmann, M. A., and Rasmussen, A. F., Jr., PROC. SOC. EXP. BIOL. AND MED., 1951, v76, 659.

Received June 22, 1951. P.S.E.B.M., 1951, v77.

Failure of an Ergot Preparation to Shorten Coagulation Time in Hemophilia.* (18830)

FREDERICK S. BIGELOW AND JANE F. DESFORGES. (Introduced by W. B. Castle.)

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

Vodopivec(1) describes a striking acceleration of the clotting of the blood of hemophilics by administration of a mixture of equal parts of 3 hydrogenated ergot alkaloids, namely dihydroergocristine, dihydroergocornine, and dihydroergokryptine. This preparation, known also as Hydergine or CCK-179, was reported to be effective orally in dosage of 1 mg every 3 hours and parenterally after a single injection of 0.6 mg. The clotting time fell to normal 2 to 3 hours after oral, 1 to 2 hours after subcutaneous, and 30 minutes after intravenous administration. The effect persisted for a day after the drug was given orally, and for several hours after parenteral treatment. Although we are ignorant of other observations on the use of ergot derivatives in hemophilia, several papers(2-4) discuss the adrenergic blockade effected by Hydergine and its several components.

Because great clinical interest attaches to any pharmacologic agent able to accelerate coagulation in hemophilia, we have examined the effects of Hydergine† in 4 hemophilics.

Methods. Coagulation time in glass at 37.5°C was determined by the method of Pohle and Taylor(5). One-stage prothrombin levels were measured as described by Rosenfield and Tuft(6), and 2-stage determinations by the method of Ware and See-

* This investigation was aided by a grant from the Blood Grouping Laboratory of Boston, Inc.

1. Vodopivec, M., and Jelavic, N., *Acta Haematol.,* 1950, v3, 247.

2. Rothlin, E., *Bull. de l'Acad. Suisse des Sciences Med.,* 1946, v2, 1.

3. Nickerson, M., *J. Pharm. and Exp. Therap.,* 1949, v95, 27.

4. Kubicek, W. G., Kottke, F. J., Felder, D. A., Laker, D. J., and Visscher, M. D., *Festschrift Für Herrn Prof. E. Rothlin, Basle,* 1948, 295.

† Kindly supplied by Mr. Kenneth Ericson of Sandoz Pharmaceuticals, New York City.

5. Pohle, F. J., and Taylor, F. H. L., *J. Clin. Invest.,* 1937, v16, 741.

gers(7). Serum prothrombin was measured on serum separated one hour after clotting and incubated at 37.5°C for 24 hours, using barium sulfate plasma as diluent. Labile factor was determined in plasma by the method of Stefanini(8). The recalcification time of oxalated plasma was performed according to Quick(9), with the modification of adjusting the pH to 7.35 by equilibrating the sample with a gas mixture of 5% carbon dioxide and 95% oxygen before recalcifying. Fibrinolytic activity was tested by observation of fibrin clots formed by addition of 0.2 ml each of 0.02 M $CaCl_2$, Difco thromboplastin, and of oxalated plasma to 5 ml of imidazole-buffered saline (pH 7.25). Lysis within 24 hours at 37.5°C was considered abnormal. Proteolytic activity was also measured after the method of Tagnon(10), using bovine fibrinogen tagged with radio-active iodine as substrate.

The 4 hemophilics were well established as to diagnosis and had been frequently treated at this hospital for the usual sequels of the disease. They were normotensive, and reduction of the coagulation time of their blood promptly followed the addition of normal blood *in vitro* or *in vivo*. One patient, Case 1, has frequently been hospitalized by hemophilic arthropathy, while the others, Cases 2, 3, and 4, were admitted to the metabolic ward for the purpose of this study. Before Hydergine administration one or more base-line determinations of pulse and blood pressure were made and the coagulation tests were performed. Case 1 received Hydergine 1 mg orally every 4 hours for 3 days, followed by 1 mg orally every 3 hours for 1 day, and finally 0.5 mg intravenously. Cases 2 and 3 each received 0.6 mg intravenously once. Case 4 was given 1.2 mg intravenously once. The coagulation tests were performed daily during

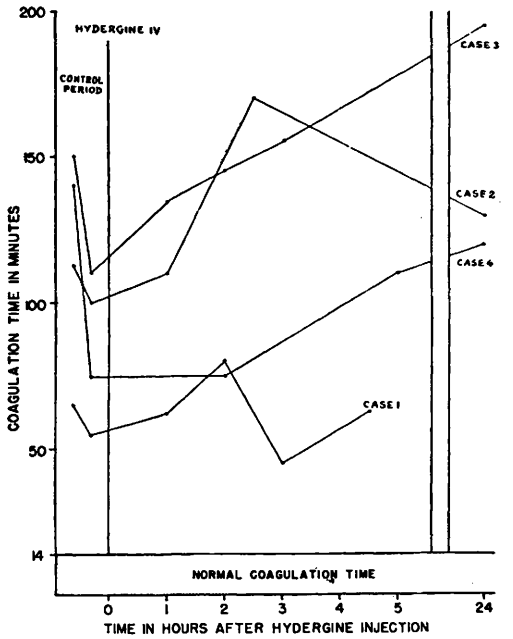

FIG. 1. Coagulation time in 4 hemophilics following intravenous administration of Hydergine. Case 1 received 0.5 mg; cases 2 and 3 received 0.6 mg; case 4 received 1.2 mg.

the period of oral treatment. Following the intravenous administration they were repeated at approximately hourly intervals for 3 hours, and again at 24 hours.

Results. In Case 1 during oral treatment a decline in clotting time from 69 to 40 minutes occurred. However, this was probably insignificant as there was no shortening of clotting time in any of the 4 patients following intravenous Hydergine (Fig. 1). Of the 3 patients receiving 0.5 or 0.6 mg intravenously, the recalcification times (Fig. 2) decreased slightly in 2 at the first hour after injection, while there was no change in the third patient. In Case 4, who received 1.2 mg intravenously, there was a more marked decrease in the recalcification time, which was found to be 135 seconds 2 hours after administration of the drug. Thereafter the value fluctuated from 270 seconds at 5 hours to 135 seconds at 24 hours. The one-stage prothrombin level was not significantly altered in any patient after intravenous Hydergine; the two-stage prothrombin content declined slightly at the second hour after injection in the 2 patients in

6. Rosenfield, R. E., and Tuft, H. S., *Am. J. Clin. Path.*, 1947, v17, 405.

7. Ware, A. G., and Seegers, W. H., *Am. J. Clin. Path.*, 1949, v19, 471.

8. Stefanini, M., *Am. J. Clin. Path.*, 1950, v20, 233.

9. Quick, A. J., *Am. J. Med. Sc.*, 1941, v201, 469.

10. Shulman, N. R., and Tagnon, H. J., *J. Biol. Chem.*, 1950, v186, 69.

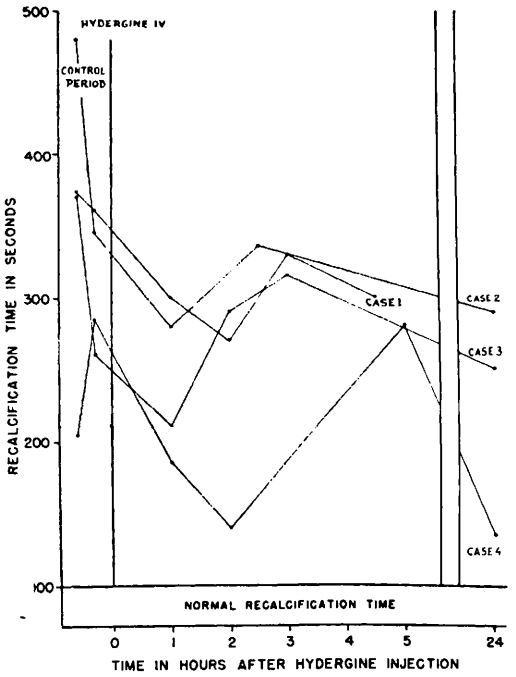

FIG. 2. Recalcification time in 4 hemophilics following intravenous administration of Hydergine. Case 1 received 0.5 mg; cases 2 and 3 received 0.6 mg; case 4 received 1.2 mg.

whom it was determined. Of the 3 patients receiving the intravenous dose of 0.5 or 0.6 mg the serum prothrombin decreased moderately in 2, though never to levels below 50%, while it was unchanged in the third. In the fourth patient, who received 1.2 mg intravenously, it changed from an original value of 60% to a final value of 20%. The decline was gradual and did not correlate with the variations in recalcification time. Lysis of the diluted plasma clot occurred in a single specimen taken after 24 hours of oral treatment in Case 1 and in specimens from Case 4 at 2 and at 5 hours after the 1.2 mg injection. In the patients receiving 0.6 mg intravenously, none of numerous clots dissolved. Using fibrinogen tagged with radioactive iodine as a substrate, samples of plasma from Cases 2, 3, and 4 showed no increase in lysis after Hydergine administration. Plasma labile factor was insignificantly altered in any patient in the first 5 hours after injection. Only the patient who was given 1.2 mg of Hydergine intravenously experienced unpleasant symptoms. These consisted of nausea and vomiting shortly after injection, severe nasal congestion, and frontal headache which lasted about 6 hours. Alterations in pulse and blood pressure were not remarkable in any patient.

Summary and conclusions. Three hemophilics were treated with Hydergine according to a regimen reported to effect a marked reduction of clotting time. A fourth patient received twice the amount of drug stated by Vodopivec to be effective upon intravenous administration. No important acceleration of coagulation was noted. Only in the patient who received an excessive dose and became ill were there any impressive changes. These consisted of a transient decrease in recalcification time and a gradual decline in serum prothrombin, as well as fibrinolysis *in vitro*. Since the Hydergine used in this study is believed to be identical to that administered by Vodopivec, we are unable to explain our inability to confirm his findings.

The authors are indebted to Miss Helen Corrigan and Mrs. William Stephan for technical assistance.

Received June 22, 1951. P.S.E.B.M., 1951, v77.

Effect of Starvation on Phagocytosis *in vivo*.* (18831)

A. KUNA,† B. BLATTBERG, AND J. REIMAN. (Introduced by R. Chambers.)
From the Veterans Administration Hospital, Staten Island, N. Y.

Phagocytosis has long been known to bear

* Sponsored by Veterans Administration and published with the approval of Chief, Medical Director. Statements and conclusions published by the authors are a result of their own study and do not necessarily reflect opinion or policy of Veterans Administration.

† Present address, Veterans Administration Hospital, Northport, L. I.