

brum in the absence of an adequate supply of this amino acid indicates clearly that lysine is a dietary essential for the human subject.

The single experiment performed on a female subject (Fig. 2) also shows the prompt development of a negative nitrogen balance on withdrawal of lysine and the return to nitrogen equilibrium when lysine was restored. It may be noted, however, that on one occasion during the deficiency period the negative nitrogen balance virtually disappeared. This point coincided with the onset of menstruation. We are inclined to attribute this brief period of nitrogen equilibrium to a decrease in the metabolic requirements associated with menstruation, a phenomenon described by Benedict and others.³ The menstrual period in our subject was characterized by an unusually scanty flow and by the complete absence of symptoms of premenstrual distress—swelling of the breasts, headache and gain in weight—which the subject usually experienced. This finding is of interest in view of the known influence of a lysine-deficient diet in suppressing the estrous cycle in animals.⁴

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Clotting Action of Rabbit-Clotting Globulin.

R. M. BIRD, B. MCSWAIN, G. L. KAUER, JR., AND FRANK GLENN.
(Introduced by P. Reznikoff.)

From the Departments of Medicine and Surgery, New York Hospital, and Cornell University Medical College.

Parfentjev¹ has shown that a "pseudoglobulin" fraction derived from rabbit plasma acts as a powerful blood coagulant. Taylor and

³ Pearson, P. B., *Am. J. Physiol.*, 1937, **118**, 786.

⁴ Benedict, F. B., and Finn, M. D., *Am. J. Physiol.*, 1928, **86**, 59.

¹ Parfentjev, A., *Am. J. Med. Sc.*, 1941, **202**, 578.

his coworkers^{2, 3} have reported on its *in vitro* action and its local hemostatic effect on cutaneous and oral bleeding surfaces. This report covers a study of the *in vitro* and *in vivo* action of "rabbit-clotting globulin."*

The clotting properties of the stock globulin solution were tested on oxalated and heparinized normal dog blood, on fibrinogen solution, on oxalated 1% prothrombin dog blood, and on blood containing adrenalin. In all instances the globulin exhibited powerful thrombic activity. Oxalated blood was clotted more rapidly than heparinized blood. Neither low prothrombin nor adrenalin inhibited the speed of coagulation. Quantitatively our globulin was not as potent a coagulant as the material reported on by the previous observers.²

Twenty-two dogs were used to study the effects of globulin administered intravenously. The injection of 0.03 cc or more per kg resulted in the appearance of toxic signs, and 0.3 cc or more per kg was invariably lethal. Doses smaller than 0.3 cc/kg occasionally resulted in death and the severity of toxic signs varied with individual animals. Two of 3 animals were protected from lethal intravenous injection of globulin by the subcutaneous administration of adrenalin. A significant reduction in the clotting time followed the intravenous injection of 0.01 cc to 0.05 cc of globulin per kg. When larger quantities were injected slowly there resulted initially a fall in the clotting time followed by a prolongation. No constant variation in the dog's prothrombin or fibrinogen blood levels accompanied a fall in the clotting time, but one or both of these decreased with a negative phase of coagulation. Thus the intravenous administration of globulin resulted in a positive or negative phase, or both, depending on the amount and rapidity of the injection.

Globulin introduced by stomach tube caused a fall in the clotting time. The graph illustrates the effect on clotting time, prothrombin and fibrinogen of 1 cc of globulin per kg given orally to a dog. Seven dogs were given globulin orally in doses from 1 cc to 4 cc per kg. In no animal did the fasting stomach contents contain free HCl. A fall in the clotting time was observed in every instance. Hypoprothrombinemia to 60% resulted in 3 dogs which received 2 cc or more per kg. Fibrinogen was never altered significantly. In no animal were toxic signs observed. *In vitro*, gastric juice containing 10° free HCl

² Taylor, F. H. L., Lozner, Eugene L., Adams, Margaret A., *Am. J. Med. Sc.*, 1941, **202**, 585.

³ Lozner, Eugene L., MacDonald, Harriet, Finland, Maxwell, and Taylor, F. H., *Am. J. Med. Sc.*, 1941, **202**, 593.

* "Rabbit-clotting globulin" was supplied by Lederle Laboratories.

RABBIT-CLOTTING GLOBULIN

EFFECT OF ADMINISTRATION OF R. C. G.
BY
STOMACH TUBE

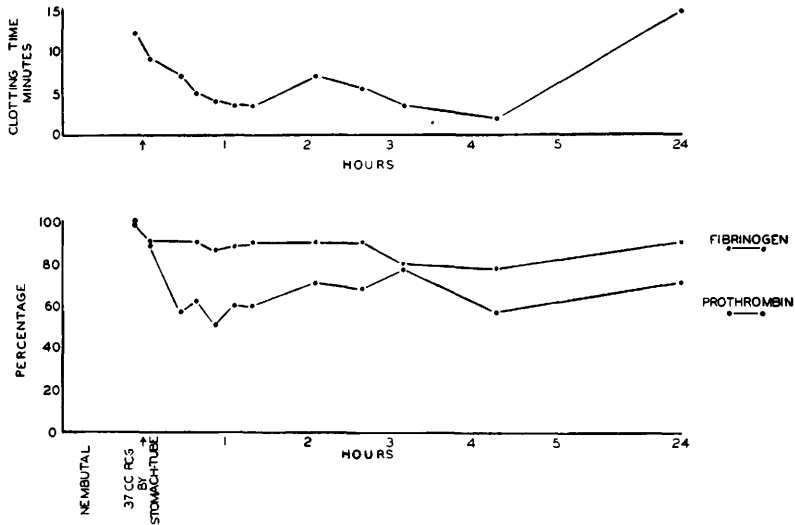


FIG. 1.

or N/10 HCl itself completely abolished the clotting action of the globulin even in high dilutions of the acid. Rectal instillation and subcutaneous or intramuscular injections were less effective in reducing the clotting time.

Local application to various cutaneous and visceral bleeding surfaces resulted in prompt hemostasis only in areas of capillary bleeding. Experimental pulmonary emboli were easily produced by release of the clot formed by injection of globulin into a temporarily ligated section of the inferior vena cava.

Eight patients with gastrointestinal hemorrhage or hemophilia have been given globulin by mouth with either cessation of bleeding or reduction in clotting time, or both, in 4 cases. This study is being continued.