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Effect of Acute Liver Damage on Ac-Globulin Activity of Plasma.*

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Normal plasma has been shown to contain a factor, Ac-globulin, which is a highly active accelerator of blood clotting.[1-3] It acts by catalyzing the interaction of prothrombin, thromboplastin and calcium with the resultant formation of thrombin. The hemorrhagic disease, parahemophilia, recently reported to occur in the human being,[4] is the result of a deficiency of this factor. Ac-globulin is differentiated from prothrombin in that it is precipitated from aqueous solutions at a higher pH, is more readily destroyed by heating, and is less soluble in concentrated ammonium sulfate solutions.[3,5] It is measured quantitatively[5] by an adaptation of the 2-stage method of prothrombin determination and may be detected in normal dog plasma in dilutions up to 350,000.

In acute liver damage, such as that produced by the administration of chloroform, there is a marked decrease in plasma prothrombin and fibrinogen.[6,7] In this paper we report that acute liver damage produced by chloroform also lowers plasma Ac-globulin.

Experimental. Quantitative estimation of Ac-globulin was achieved by an adaptation of the 2-stage prothrombin assay procedure. Details of the method are reported elsewhere.[5] In essence the method consists of comparing the rates of activation of prothrombin with thromboplastin and calcium ions in the presence of known and unknown amounts of Ac-globulin. The prothrombin, thromboplastin and calcium are kept constant. When prothrombin is activated in this manner under standard conditions the rate of thrombin formation is directly proportional to Ac-globulin concentration. Thrombin is measured by adding fibrinogen at intervals and noting the clotting time.

Three adult male dogs weighing 13 to 19 kg were observed for a period of 2 weeks and judged to be healthy on the basis of normal rectal temperature, maintenance of weight and food intake, alertness and activity. They were fasted for 36-72 hours and then given moderately deep chloroform inhalation anaesthesia varying in length of time from 1½ to 3 hours. Plasma Ac-globulin, coagulation time (Lee-White), hematocrit and icterus index were determined at intervals before and after chloroform administration. Prothrombin was determined by the 2-stage method of Warner, Brinkhous and Smith,[6,8] as modified by Ware and Seegers.[5] The modification consists only of supplying Ac-globulin when necessary. Heparin was used as the anticoagulant for blood specimens taken from one dog and 3.5% sodium citrate for those taken from the other 2 dogs.

Results. For 4 to 6 days following the administration of chloroform, the dogs showed lethargy, anorexia, and a low-grade temperature increase. The establishment of liver damage was shown by the development of an icteric color to the plasma first becoming noticeable 24-48 hours after the anaesthesia, and by the development of hypoprothrombinemia. At no time, however, did the animals show clinical jaundice or clay-colored stools.

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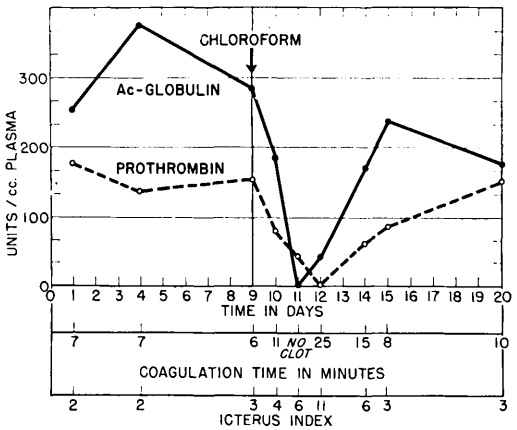

FIG. 1.

The effect of acute liver damage (chloroform intoxication) on the plasma Ac-globulin concentration of the dog.

The onset of the plasma jaundice and the peak of the icterus index rise were not associated with a drop in the hematocrit. All of the dogs survived.

The duration of chloroform administration, from 1½ to 3 hours, appeared to have no marked influence on the resulting changes in Ac-globulin and prothrombin concentrations. The values shown in Fig. 1 for the dog anesthetized for a period of 3 hours are representative for the group. Within 24 to 48 hours after anaesthesia, the plasma Ac-globulin decreased precipitously in all dogs from initial values of 100 to 370 units per cc to low values of 1 to 3 units per cc. Prothrombin also decreased to low levels but did so somewhat later, within 48 to 72 hours after anaesthesia. Ac-globulin returned to normal values in approximately 6 days, while prothrombin returned more slowly, reaching normal values in about 10 days. Significantly increased coagulation time, hematoma formation and excessive bleeding from venipuncture wounds were encountered 2 days after anaesthesia; the dog receiving 3 hours of anaesthesia, in addition, showed continuation of the bleeding tendency through the third day. Fibrinogen was absent in this dog 2 days after anaesthesia as shown by the failure of blood samples to clot following the addition of a very active preparation of thrombin.

Discussion. These experiments indicate that the hemorrhagic tendency occurring in cases of acute liver damage is attributable not only to decreased prothrombin and fibrinogen concentration[6,7] but also to decreased plasma Ac-globulin. The data suggest further that plasma Ac-globulin is formed in the liver.

Summary. Acute hepatic damage in the dog, caused by chloroform intoxication, is followed by a pronounced and rapid decrease in plasma Ac-globulin concentration. This decrease is accompanied by a parallel decrease in plasma prothrombin concentration. Ac-globulin returns to normal values more quickly than does prothrombin.