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Received May 26, 1953. P.S.E.B.M., 1954, v85.

An Hemostatic Defect Associated with Dextran Infusion. (20798)

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(Introduced by Victor M. Sborov.)

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Dextran, a glucose polymer of high molecular weight, has been developed as a plasma expander(1). During the course of studies at Walter Reed Army Hospital on the metabolic effects of dextran, 2 patients developed a bleeding tendency. One patient, after receiving 6000 ml of 6% dextran over a 6-day period developed repeated epistaxis and bled from a duodenal ulcer. The second patient, after receiving 14000 ml of 6% dextran over a period of 14 days, bled for more than 30 minutes from an incised sebaceous cyst. The bleeding time and prothrombin time were prolonged in both cases. Detailed studies were initiated to determine whether the administration of dextran provoked an hemostatic defect.

Methods. Six lots of commercially available dextran from 4 manufacturers were tested. Studies were done on normal young adult subjects who received intravenously varying amounts of 6% dextran. Bleeding time was measured following a stab incision with a Bard-Parker No. 11 blade through the dependent ear lobe. Prothrombin activity was measured by the one-stage Quick method; the clotting time was done in siliconized glassware. Plasma coagulation factors V and VII (labile and stable factors), prothrombin consumption, platelet count, clot retraction, antithrombin titer, and plasma dextran levels were determined(2,3). The subjects in these studies were divided into 3 groups.

Results. The first group of 11 patients received 1000 to 1500 ml of dextran daily until the bleeding time was prolonged to greater than 10 minutes. The total amount of dextran required to prolong the bleeding time varied from 1500 ml given in a single infusion to 6500 ml given over a period of 5 days. Determinations were carried out at least 4 times before each study and at 3-hour intervals for 9 to 12 hours after infusion. The bleeding time exceeded 12 minutes in 4 subjects and 30 minutes in 7 subjects. The prolonged bleeding times were usually not present immediately after infusion, but were maximal 3 to 9 hours after completion of the last infusion. With one exception the bleeding time returned to normal in 24 hours. Concomittant with the increased bleeding time, progressive diminution of prothrombin activity was noted with each repeated infusion of dextran in all subjects. The maximum depression of activity after infusion varied from 75-50% of normal. This depression of prothrombin activity was partially corrected by the addition of factors V and VII. Fig. 1 depicts the typical changes observed.

The clotting time was never abnormal, even when the bleeding time exceeded 30 minutes. Platelet counts were not below 150000/cu mm

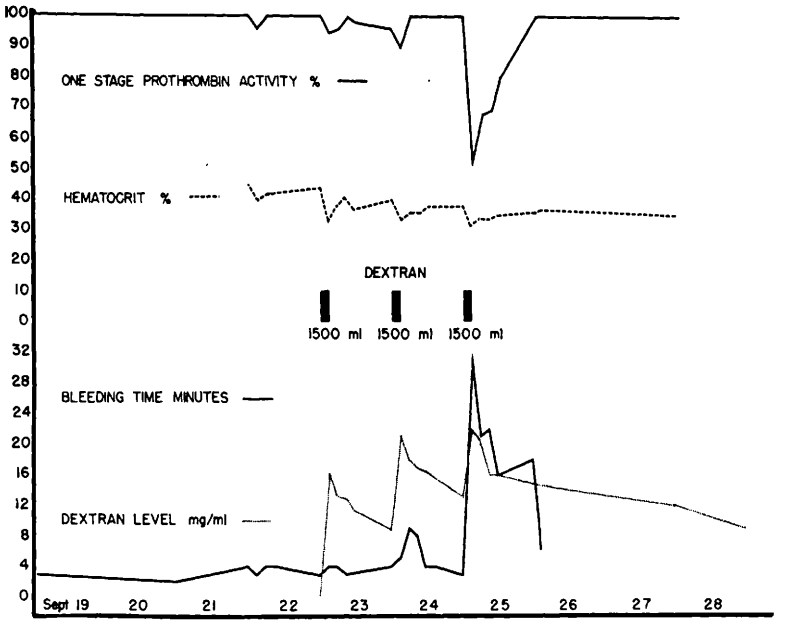

FIG. 1. Typical changes with dextran infusion observed in one subject.

(normal 200000 to 300000) in any patient. Prothrombin consumption was normal, and no circulating antithrombin was demonstrable. Clot retraction was normal. The fibrinogen level decreased from 400-500 mg % to 200-300 mg % at the end of the infusion; it returned to normal within 24 hours and was not significantly depressed when the bleeding time was maximal. Serial blood volume determinations using Cr^{51} tagged red blood cells(4) carried out on 3 patients receiving dextran daily showed that the maximum plasma volume expansion occurred immediately after the infusion and progressively declined thereafter.

After 1000 ml or more of dextran had been administered urinalyses showed the presence of renal epithelial cells, hyaline casts, and occasionally red cell casts and oval fat bodies in the sediment. The changes persisted throughout the period of administration and for 2-3 days thereafter. There was no proteinuria. The creatinine clearance and phenolsulfonphthalein excretion tests were normal throughout.

The second group of 15 subjects received a single infusion of 500 ml of 6% dextran. Bleeding time and prothrombin activity were determined before, immediately after, and at 3, 6, and 9 hours following infusion. Minimal depression of prothrombin activity to 85% of normal occurred in 3 of these subjects following infusion. Two of these subjects showed an increase in bleeding time from 3 and 4 minutes to 8 and 9 minutes respectively.

The third group of 50 subjects received a single infusion of 1000 ml of dextran. Bleeding times were determined before, immediately after, and at 3, 6, and 9 hours after infusion. Fourteen of the 50 developed bleeding times greater than 10 minutes within 9 hours following the infusion. Six hours following the infusion the bleeding time was greater than 30 minutes in one subject and greater than 3 hours in 2 other subjects. One of the latter had a bleeding time of 11 minutes 24 hours after the infusion. The remaining subjects had bleeding times well within the normal range 24 hours after the infusion. Table I summarizes the results in the 3 groups.

Two patients with chronic hepatitis were given 1000 ml of dextran daily for 10 days. Bleeding times and prothrombin times were done daily. The first of these patients showed a change of bleeding time from 3 to 24 minutes and a depression of prothrombin activity from 50-30% of normal. These values were

TABLE I. Relationship of Total Amount Dextran Infused to Prolonged Bleeding Time.

Cum dose of dextran	Days of infusion	Total No. subjects	Subjects with bleeding times >10′
500	1	15	0
1000	1	57	14
1500	1	8	2
2000	2	4	1
2500	2	4	2
3000	2	5	2
3500	3	2	1
4000	3	1	1
4500	4	2	1
5000	4	2	1
6500	5	1	1

prolonged for several days following the last dextran infusion. The second patient showed a change of bleeding time from 4-14 minutes and a depression of prothrombin activity from 95% to 35% of normal. In this patient the bleeding time was normal in 24 hours, while the prothrombin activity returned to normal in 4 days.

Discussion. It is generally accepted that the bleeding time is not usually prolonged unless the prothrombin activity is less than 10% of normal. Since the depression of prothrombin activity observed here is not of this magnitude, it is felt that the prothrombin deficiency cannot explain the increase in bleeding time. Because the maximal increase of plasma volume does not coincide with the prolongation of bleeding time, it would appear that the phenomenon is not correlated with intravascular volume changes. The defect may be related to abnormalities of hemostasis at the site of injury.

It should be emphasized that, excepting the patients with hepatitis, the present study has been carried out on normal subjects, in contrast to an army sponsored clinical trial of dextran in surgical patients and battle casualties, wherein some 4000 units of dextran were given to 2000 individuals with no report of hemorrhagic disease(5). In the present study the subjects were not under severe stress and were normovolemic prior to infusion. These differences in the recipients may prove important in determining the clinical significance of the phenomenon.

Summary. An hitherto undescribed hemostatic defect has been observed in normal subjects after infusion of dextran. This defect was characterized principally by a prolonged bleeding time. It was possible to produce this defect in all subjects in whom sufficient dextran was infused. The amount of 6% dextran required to produce this defect varied from 1000 to 6500 ml. Changes in plasma coagulation factors were minor and not sufficient to cause a prolonged bleeding time. The clinical significance of the hemostatic defect requires investigation.

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Received November 9, 1953. P.S.E.B.M., 1954, v85.