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Spleen Transplantation in Classical Hemophilia

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Recent evidence has indicated that the spleen may be partly responsible for synthesis or storage of antihemophilic factor (Factor VIII) in dogs (1) and in man (2). Transplantation of the spleen into dogs with congenital deficiency of Factor VIII has been shown to result in increased circulating levels of this clotting factor for prolonged periods (3). Spleen transplantation in man has been done without significant morbidity due to the procedure itself or graft versus host reaction (4,5). Therefore, it seemed reasonable to attempt allogenic grafting of a spleen into a patient with severe Factor VIII deficiency.

Case Report

Q.N., a 16-year-old boy with hemophilia A (Factor VIII, AHF deficiency), had been observed at the University of Colorado Medical Center from the age of 17 months. His past medical history revealed difficulty with persistent oozing from the circumcision site in the neonatal period, easy bruising, excessive bleeding from minor lacerations, and the development of a large hematoma of the scalp at 11 months

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of age which lead to the diagnosis of severe hemophilia. Representative coagulation studies showed: bleeding time (Ivy), 3½ min; Lee-White clotting time, > 30 min; clot retraction, good; one-stage prothrombin time, 12.6 sec (normal—12 sec); partial thromboplastin time (PTT), 127.5 sec (normal—38 sec); Factor I, 493 mg; Factor II, 80%; Factor V, 80%; Factor VIII, 0%; Factor IX, 64%; Factor X, 60%; Factor XI, 75%. Using the thromboplastin generation test and the PTT inhibitor test no AHF inhibitor or antibody had ever been demonstrated. The family history was negative for bleeding disorders. However, the patient's mother was shown to be a hemophilia carrier with repeated Factor VIII assays that ranged from 26% to 38% of normal.

During the 14-year period that the patient was observed at this institution he required 41 hospital admissions for treatment of hemarthroses involving almost all of the major joints, recurrent hemorrhages into major muscle groups, bleeding from open lacerations, and retroperitoneal hemorrhages. In addition, he had innumerable out-patient visits and 24-hour emergency room admissions for control of hemorrhage. A team approach in an attempt to help solve the patient's multiple problems was undertaken by representatives from the Departments of Hematology, Orthopedics, Physical Medicine, Psychiatry, and Social Service, but the patient's physical and emotional debilitation continued despite combined and persistent efforts.

On 31 January 1968, the patient was admitted to Colorado General Hospital for an elective splenic homotransplantation with the father as the donor. The only donor-recipient mismatch in the HLA (6) antigen system was in the Terasaki Group 3. Routine preoperative clotting studies performed on the father were normal.

Two days prior to surgery the patient was given a "test" infusion of 1911 units of glycine-precipitated AHF (Hyland) and serial PTT's and Factor VIII assays were done. All Factor VIII assays were done in duplicate by the method of Pool (7). These assays were confirmed by the PTT assay of Proctor and Rapaport (8). The initial level of 27% Factor VIII fell to 2% in 30 hr. During the same period administration of heterologous antilymphocyte globulin (ALG) and azathioprine (Imuran®) was begun (9).

Based on the results of the previously determined decay rate of exogenously administered AHF, 3782 units of glycine-precipitated AHF were administered to the patient 2 hr prior to operation on 3 February 1968. Splenic transplantation was completed in 5 hr. The donor spleen was transplanted to the right extraperitoneal space of

the recipient by a previously described technique (4). The ischemic time from donor removal to revascularization by the recipient was 60 min. After completion of the anastomoses it was necessary to readjust the position of the spleen many times due to kinking of either the anastomosed splenic artery or vein. An additional 1800 units of glycine-precipitated AHF was infused 2 hr after surgery was begun. The patient tolerated the operation well. Blood loss was estimated to be 50 ml.

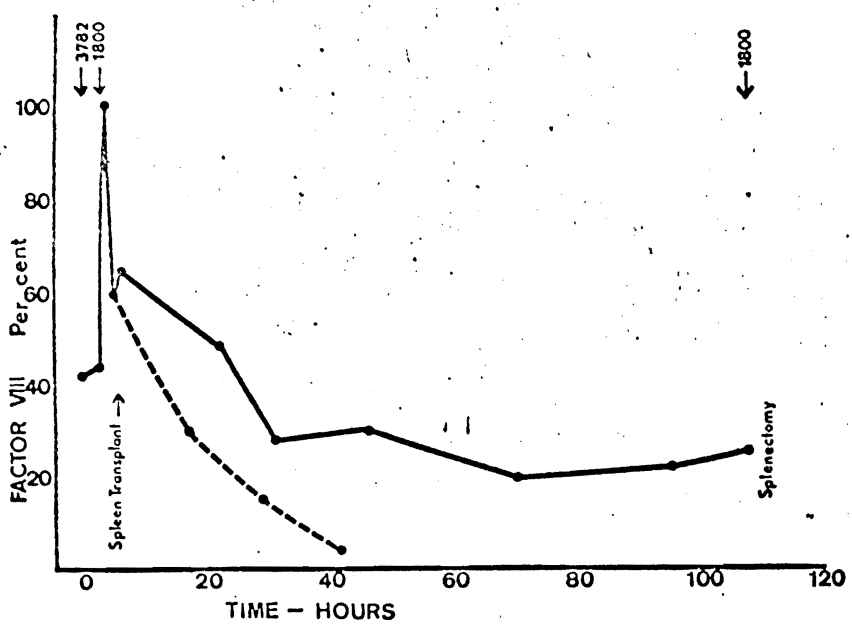

Fig. 1. The numbers at the top of the graph refer to units of Factor VIII given to the patient. A unit of Factor VIII is that activity contained in the equivalent of 1 ml of fresh normal plasma. The dotted line represents an estimate of decay of exogenous Factor VIII.

The recipient was followed up by routine laboratory studies plus daily PTT and Factor VIII assays (Fig. 1). Medications were limited to intravenous fluids, antibiotics, ALG, azathioprine and prednisone. No further Factor VIII was administered. Ambulation was begun on the 4th postoperative day. In the evening of 7 February 1968 the patient began to complain of exquisite pain over the right iliac fossa in the area of the incision. Because of concern over possible bleeding, the patient was given 1800 units of AHF cryoprecipitate. Symptoms persisted and the patient was taken to the operating room for exploration. At surgery approximately 2 liters of fresh blood was found

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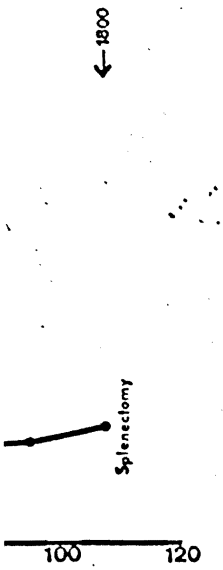

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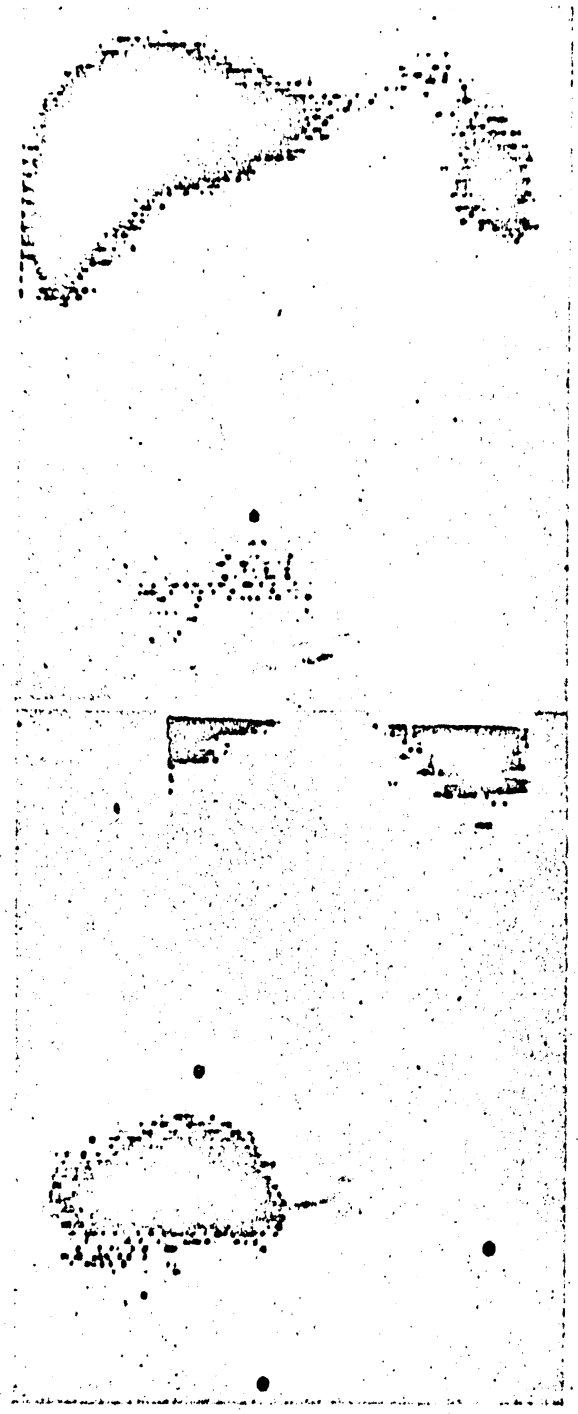

Fig. 2. Spleen scan on patient done one day post-transplant. Fair uptake is seen over the donor spleen.

Fig. 3. Spleen scan on patient done 2 hr prior to second laparotomy. Good uptake is seen over the donor spleen.

in the iliac fossa along with several large clots. The transplanted spleen was found to be markedly swollen with three lacerations. Splenectomy was performed and the blood loss was replaced. Postoperatively the patient's clotting deficiency was kept corrected with 2000-4000 units of either glycine-precipitated AHF or AHF cryoprecipitate intravenously every 12 hr for 14 days. Factor VIII levels were maintained between 25 and 60%. No additional problems were encountered and he was discharged on 27 February 1968 with complete healing of the incision. Since that time he has had four additional hospital admissions for treatment of hemarthroses of his shoulder.

Spleen scans with technetium sulfide done on 4 February 1968 (one day postoperatively) and on 7 February 1968 (2 hr prior to second laparotomy) are shown in Fig. 2 and 3.

Pathologic examination of the ruptured donor spleen revealed small lymphoid nodules; the stromal tissue contained increased numbers of lymphocytes, histiocytes, and reticulum cells. Many of the lymphocytes had the appearance of lymphoblasts or "transformed" lymphocytes.

Comments

As shown in Fig. 1, our patient maintained levels of at least 20% Factor VIII for four days, long after the effects of intraoperative therapy should have been dissipated. It is impossible to say whether the Factor VIII was newly synthesized or slowly released from storage in the donor spleen; however, if this level could have been maintained it would have transformed the patient into a very mild hemophiliac.

The reasons for the rupture of the donor spleen and subsequent termination of this investigation remain unclear. Mechanical factors from the abnormal position of the organ, swelling or increased friability due to rejection, or trauma from too early ambulation of the patient could each have played a part.

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DISCUSSION

R. B. Epstein summarized the data of the group at the University of Washington on transplantation of liver, spleen, and bone marrow to hemophilic dogs. Their best result was with a transplanted normal liver into a hemophilic dog; the animal maintained normal Factor VIII levels for six months. When a hemophilic liver was transplanted into a normal dog, the plasma Factor VIII level was 50% for two months, even after splenectomy. In splenic transplants only an equivocal use in Factor VIII occurred. Normal bone marrow transplanted to a lethally irradiated hemophilic dog who survived for 34 days caused no rise in Factor VIII.

R. Desai reported on human splenic cell suspensions or homogenates being administered to hemophiliacs, with a subsequent rise in Factor VIII.

In regard to splenic transplants or infusates, it was pointed out by others that splenic transplants do not do well unless the recipient animal is first splenectomized.

N. R. Shulman remarked that in two groups of normal animals where one group was hepatectomized and one group, in addition, splenectomized, there was no difference in the rate of loss of Factor VIII—the half-life being approximately 13 hr in both groups.

H. S. Sise pointed out the experiences of the French boarding schools for hemophiliacs and of Dr. Strauss in Boston that mortality in hemophilic boys receiving modern treatment is extremely low. In view of this, the use of any operative procedure in clinical experimentation with a significant mortality rate should be thoroughly explored to determine if it has real relevance.

PART IV

Moderators
P. DIDISHEIM *and*