Mechanism of Dilutional Anemia in Massive Splenomegaly

By Charles E. Hess, Carlos R. Ayers, William R. Sandusky, Martha A. Carpenter, Richard A. Wetzel, and Daniel N. Mohler

Twenty patients with anemia and massive splenomegaly were studied in order to elucidate the mechanism by which splenomegaly results in plasma volume expansion. In 18 patients, increased plasma volume accounted for most of the anemia. Fourteen patients had an exaggerated renin response to standing, mean 1967 ± 613 (SE) ng angiotensin II/100 ml plasma (p < 0.05). The mean resting forearm blood flow was increased 3.74 ± 0.32 (SE) ml/100 ml forearm tissue (p < 0.001). The venous capacitance was normal, as contrasted to a marked decrease in venous capacitance in patients with anemia of comparable degree without splenomegaly. Cardiac indices were increased in 10 of 11 patients (range 4.1–8.1 liters/min/sq m). In nine of ten patients oxygen consumption was increased (range 147–231 ml/min/sq m). Splenectomy was performed on 14 patients. Splenic blood flow was elevated in four of four patients (range 750–2000 ml/min). Splenic A-V oxygen difference was exaggerated in seven of seven patients and in three of three patients splenic indocyanine-green dye dilution curve failed to show an early peak suggestive of A-V shunting in the spleen. Free portal pressure was elevated in 12 of 12 patients and decreased immediately after splenectomy. The intravascular albumin mass decreased in ten patients, was unchanged in three at 2–4 mo after splenectomy, and was accompanied by a rise in the plasma albumin concentration in nine. These data suggest that a flow-induced portal hypertension with expansion of the portal vascular space is an important early hemodynamic change. This finding, together with a decreased peripheral resistance, probably results in a decrease in effective intravascular volume, resulting in stimulation of the renin-angiotensin-aldosterone system and other renal hemodynamic changes necessary for salt and water retention. Splenectomy usually accomplishes a complete reversal of these abnormalities and correction of the anemia.

An increased rate of destruction of red blood cells by the spleen is a well-recognized cause of anemia associated with splenomegaly. Sequestration of red cells in massively enlarged spleens may also result in a fall in the venous hematocrit.1 In some patients as much as 25% of the total red cell mass may be pooled in massively enlarged spleens.2,3
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BW, body weight; CML, chronic myelocytic leukemia; LRE, leukemia reticuloendotheliosis; MF, myelofibrosis with myeloid metaplasia; S, sarcoidosis; RCM, red cell mass; PV, plasma volume; Pre, before splenectomy; Post, 2-4 mo after splenectomy; Retics, reticulocytes.

* Predicted values obtained from surface area regression equations. The SD for the RCM in adult males is 252 ml, adult females 135 ml, and obese females 200 ml. The SD for the PV in adult males is 357 ml, adult females 241 ml, and obese females 275 ml.

† Mean absolute reticulocyte count in controls is about 6.0 x 10⁶/μl. The mean per cent of reticulocytes in normal adults is reported to be 1.65% ± 0.44% (SD) in males and 2.45% ± 0.82% (SD) in females.

‡ Patient treated with busulfan before and/or after surgery.

§ Massively enlarged spleen (25 cm below left costal margin).

|| Massively enlarged spleen (20 cm below left costal margin).

¶ Moderately enlarged spleen (10 cm below left costal margin).

** Moderately enlarged spleen (10 cm below left costal margin).
In 1958 McFadzean, Todd, and Tsang demonstrated a third factor which may contribute to the anemia of massive splenomegaly; namely, plasma volume expansion leading to a reduced venous hematocrit despite a normal red cell mass. This process was the major factor in the production of anemia in patients with massive cryptogenic splenomegaly. In such patients, splenectomy resulted in a fall in the plasma volume and a rise in the venous hematocrit in the absence of a significant change in the red cell mass. The drop in plasma volume following splenectomy was gradual and usually required 6–8 wk and in some cases up to 24 wk to return to normal.

Since this report, many investigators have confirmed the role of an expanded plasma volume in the anemia associated with massive splenomegaly of diverse etiology and the gradual fall in plasma volume that occurs subsequent to splenectomy. However, the mechanism of the plasma volume expansion associated with splenomegaly and the gradual fall in plasma volume following splenectomy remains obscure. Pryor has suggested hyperglobulinemia as an etiologic factor in patients with tropical splenomegaly. Although an increase in the total body immunoglobulin pool does lead to plasma volume expansion in hyperimmunized animals and in patients with malignant gammapathies, most patients with massive splenomegaly have no increase in plasma gamma globulin concentration. Prankerd has proposed that the excess plasma volume is contained within the spleen and is in response to the increased anatomical vascular space created by the massively enlarged spleen. However, recent evidence indicates that only 10–30% of the excess plasma volume is contained within the spleen, the major portion being elsewhere. Blendis, Ramboer, and Williams have showed that the portal pressure was elevated in 13 of 20 patients with massively enlarged spleens, and they compared these patients to those with portal hypertension secondary to cirrhosis of the liver in whom plasma volume expansion often exists. Recently Garrett, Goddard, Markly, and Webber have suggested that the marked increase in blood flow through these enlarged spleens has the same hemodynamic effect as an arteriovenous shunt and leads to expansion of the plasma volume.

In the present study, we report hemodynamic, metabolic, and hematologic data on patients with massive splenomegaly before and after splenectomy. Evidence is presented for the development of a flow-induced portal hypertension which expands the anatomic vascular space, leading to a redistribution of blood flow and salt and water retention. Expansion of the extracellular fluid volume may result in a fall in plasma oncotic pressure which, in turn, stimulates hepatic albumin synthesis. The delay in fall of the plasma volume following splenectomy may be due, at least in part, to the time necessary for readjustment of albumin metabolism.

MATERIALS AND METHODS

Patients

Two groups were investigated. Group I consisted of 20 patients with massive splenomegaly and anemia (Table 1) and group II consisted of 12 patients with chronic anemia, but without splenomegaly. All patients received a 110 mEq sodium diet for at least 72 hr prior to study. None of the patients in group I had received transfusions, corticosteroids, or specific chemotherapeutic
agents for at least 4 wk before the time of study. Two patients received busulfan for a period of
14 days prior to surgery in an effort to prevent complications of thrombocytosis following
splenectomy. Patients in group I who had splenectomy were restudied after a period of 2-4 mo;
they were on neither corticosteroids nor other chemotherapeutic agents until the postoperative
studies were obtained.

Splenectomy was performed for one or more of the following reasons: (1) symptomatic anemia
secondary to either an increased rate of red cell destruction by the spleen, splenic pooling of red
cells, or hemodilution; (2) thrombocytopenia with clinically significant bleeding; (3) granulo-
cytopenia with recurrent and/or resistant bacterial infections; (4) symptoms of hypermetabolism
such as marked weight loss, severe sweating, and tachycardia; (5) high output cardiac decomp-
ensation secondary to severe anemia, expansion of the total blood volume, and increased de-
mand on the heart resulting from increased splenic blood flow and hypermetabolism; (6) mecha-

ical compression of the stomach by the spleen resulting in decreased food intake, nausea, and
vomiting; (7) recurrent left upper quadrant pain as a result of splenic infarcts.

Routine Hematologic Studies

Blood collected in disodium EDTA (102 mg EDTA-Na₂ per ml whole blood) was used for the
determination of the PCV (hematocrit, hct), red blood cell (RBC) count, white blood cell (WBC)
count, and platelet count. The PCV was obtained using the microhematocrit method. The
WBC and RBC counts were electronically estimated by the use of the Coulter Counter Model B. Platelets were estimated by use of the Technicon Autocounter. When the platelet count was
below 50,000/cu mm the counts were also determined by phase microscopy. Reticulocytes were
enumerated by use of the new methylene blue stain.

Red Cell Mass (RCM), Red Cell Survival, and Plasma Volume (PV)

The RCM was determined by a modification of the ⁵¹Cr method described by Sterling and
Gray. Following injection of 15 μCi of ⁵¹Cr, venous blood samples were drawn from the
opposite arm at 1, 15, 30, and 60 min.

Red cell survival was also determined by the use of ⁵¹Cr as the tag. The labeling technique
was the same as described for the RCM determination except that a larger dose of ⁵¹Cr (30 μCi)
was used. Serial venous blood samples were withdrawn every other day, three times a week for
a 2-wk period, and counted as in the RCM determination method described above. The plasma
volume was determined by the use of the ¹²⁵I serum albumin method.

Hemodynamic Studies

Patients underwent right heart catheterization under light sedation with phenobarbital. A
No. 6 or No. 7 Lehman catheter was inserted into the right femoral vein using the Seldinger
percutaneous technique. The catheter was advanced through the right heart into the pul-
monary artery wedge position. Appropriate pressures were obtained and recorded on an Elec-
tronics for Medicine DR-8 Recorder as the catheter was withdrawn from this position through
the right cardiac chambers. The Statham strain gauge P23-D was used for all pressure measure-
ments. A 17-gauge 4-inch Jelco IV catheter was inserted into the right femoral artery by the
Seldinger percutaneous technique, and, with the venous catheter in the pulmonary artery, simul-
taneous samples were obtained for determination of oxygen content and blood gases by the stan-
dard methods, while expired air was collected for determination of oxygen consumption for
Fick cardiac output calculations. A dye dilution cardiac output was then obtained in duplicate
with injection of indocyanine green dye into the pulmonary artery while sampling from the femoral
artery using a Gilford densitometer with a Harvard withdrawal pump. Using the pressure
data, as recorded above, and the cardiac outputs, both pulmonary and systemic resistances were
calculated in resistance units. The possibility of any left-to-right shunts was excluded by
negative hydrogen curves in the pulmonary artery. At the conclusion of the procedure, the
catheter and cannula were withdrawn and hemostasis was obtained. The basal oxygen consump-
tion (BMR) was determined by the indirect closed-circuit technique.
Other Studies

Supine forearm blood flow (FABF) and venous volume at 30 mm Hg obstructive pressure (VV30) were measured using the Wood plethysmograph. Peripheral venous renin (PVR) activity was determined by the rat bioassay method. Total serum proteins were measured using a modified Biuret reaction on an autoanalyzer. The albumin fraction was calculated from the serum protein electrophoretic pattern done on cellulose acetate strips.

Serum iron, total iron-binding capacity (TIBC), and percent saturation were determined spectrophotometrically. Serum folate and vitamin B12 levels were determined, respectively, by the Lactobacillus casei bioassay method and the radioisotope dilution method.

Studies Performed at Surgery

All measurements were made while patients were anesthetized endotracheally with a mixture of 30% oxygen and nitrous oxide, reinforced with muscle relaxants when necessary. With a central venous catheter in place, a second catheter was inserted into the splenic vein and advanced into the portal vein. Simultaneous recordings of central venous pressure (CVP) and free portal pressure (FPP) were obtained using the level of the right atrium as the zero point. Samples of splenic arterial and venous blood were obtained and measured for pH and blood gases. In three patients, splenic indocyanine green dye dilution curves were obtained by injection of the dye directly into the splenic artery, while samples were obtained from the splenic vein by the use of a Gilford densitometer with a Harvard withdrawal pump. In four patients, splenic blood flow was measured by the use of an electromagnetic flowmeter.

RESULTS

Clinical

Nineteen of the 20 patients in group I with massive splenomegaly had either a lymphoproliferative or myeloproliferative disorder with involvement of the bone marrow (Table 1). Patient H.T. had sarcoidosis. Sixteen had splenectomy, and 14 were either partially or completely restudied 2-4 mo after surgery. Only one patient (E.P.) expired in the immediate postoperative period (patient had chronic myelocytic leukemia, was in a blast crisis at the time of surgery, and expired on the seventh postoperative day, with progression of the leukemic process and sepsis). Patient H.T. did not return for postsplenectomy evaluation but was much improved clinically. Four patients did not undergo splenectomy; one (N.S.) had CML with massive splenomegaly and responded to busulfan therapy with a marked reduction in spleen size, rise in the hematocrit, and marked clinical improvement. Another (H.C.) had CML in blast crisis with massive splenomegaly at the time of study and expired 3 mo later with sepsis. Patients E.B. and C.H. had only moderate enlargement of the spleen, with little or no increase in PV, and no evidence of increased rate of red cell destruction. In these two patients, the anemia was on the basis of decreased red cell production secondary to involvement of the marrow by the underlying disease process.

Patients in group II with anemia without splenomegaly were studied for comparison to group I patients. The anemia in this group was primarily the result of an absolute decrease in RCM.

Hematocrit, RCM, PV, and TBV Before and After Splenectomy in Group I Patients

The hematocrit rose significantly in 11 of 14 patients within 2-4 mo of splenectomy (Table 1). In two patients the hematocrit did not change following
spleenectomy; one (M.S.) had a marked drop in RCM and PV associated with the progression of her disease, and the other (E.S.) had a marked drop in RCM associated with an increase in PV at the time of restudy and expired 3.5 mo later with massive hepatomegaly. One patient (H.M.) showed a fall in hematocrit postoperatively; this was secondary to a marked drop in RCM with only a moderate drop in PV. He had Philadelphia chromosome-negative CML and at the time of restudy had massive hepatomegaly and was on busulfan therapy. He expired 8 mo after splenectomy in blast crisis.

The initial RCM was within the normal range in 11 of 20 patients, increased in one (H.M.) and decreased in eight (Table I and Fig. 1). Following splenectomy, the RCM did not change significantly in eight, increased in three, and decreased in three. The increase in RCM in three patients following splenectomy was contributed to in one (B.H.) with CLL by transfusions required during and after splenectomy to maintain the hematocrit. The second patient (F.A.) received 2 units of packed red cells at the time of surgery, which contributed in part to the increase in RCM at the time of restudy 8 wk later. In the third patient (C.L.), there was also evidence of hypersplenism preoperatively with a reticulocyte count of 119,000/cu mm (decreasing to 26,000/cu mm after splenectomy) and a red cell half-life of 18.1 days (Table I).

The PV was significantly increased in 19 of 20 patients (Table I and Fig. 1). After splenectomy the PV was decreased significantly in 11 of 14 patients and unchanged in three (Fig. 1). Two patients (J.S. and V.K.) showed only a minimal drop in PV after splenectomy. The rise in hematocrit in these two patients was, in part, the result of removing the site of red cell pooling. Both also had a
slight increase in RCM after splenectomy. In patient J.S. who had a preoperative reticulocyte count of 115,000/cu mm and a red cell half-life of 19.0 days, the increase in RCM after splenectomy was also, in part, the result of increased erythrocyte survival.

The TBV decreased in ten patients and remained unchanged in four (Fig. 1). Also shown in Fig. 1 are blood volume studies on group II patients. The RCM was markedly decreased with a normal or slightly increased PV and a normal or contracted TBV.

The body:venous hematocrit ratio, which reflects the degree of splenic sequestration of red cells, is shown in Fig. 2. The whole body hematocrit is obtained from the independently measured RCM and PV. This ratio has a narrow range in normal controls and is increased in the presence of splenomegaly, the degree depending on the volume of red cells sequestered in the spleen. This ratio was increased in 14 of 20 patients, normal in 5, and decreased in 1. After splenectomy the ratio dropped significantly in 11 and increased in 2.

Hemodynamic and Metabolic Studies in Group I Patients

These studies are presented in Table 2. The cardiac index (CI) was elevated in 10 of 11 patients. No values were obtained postoperatively. The blood pressure (BP), mean blood pressure (MBP), pulse pressure (PP), and peripheral resistance (PR) were calculated from data obtained at right heart catheterization
Table 2. Hemodynamic and Metabolic Studies Before and After Splenectomy

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Normal values ± 0.7 ± 15.7/7.4 ± 8.7 ± 4.0 ± 12.4 ± 17

CI, cardiac index; BP, arterial blood pressure—in those patients who had cardiac catheterization studies the values were obtained by means of an intraarterial strain gauge; MBP, mean arterial blood pressure; PR, peripheral resistance; PP, pulse pressure; Conc, concentration; TIP, total intravascular pool; Pre, before splenectomy; Post, 2–4 mo after splenectomy.

*Mean ± SD from Barratt-Boyes and Wood.  
†Mean ± SD from Baldwin, Courand, and Richards.

or, in those patients not undergoing right heart catheterization, from an average of at least three recordings of supine forearm BP measured by use of a sphygmomanometer. When not measured at right heart catheterization, the mean right atrial pressure was taken as 4 mm Hg. The PP tended to be wide, particularly in those patients who had measurements of arterial pressure made by use of the intraarterial Statham strain gauge. The PR was significantly decreased in 10 of the 11 patients who had right heart catheterization performed.

Basal oxygen consumption before and after splenectomy are also shown in Table 2. Nine of 11 patients had a significant increase in oxygen consumption that decreased in five of five patients studied after splenectomy. In patient C.H. whose oxygen consumption was normal, the spleen was only moderately enlarged.

Effect of Splenectomy on Plasma Proteins in Group I Patients

The total intravascular albumin mass decreased in 10 of 14 patients and was associated with an increase or no significant change in the serum concentration in 11 patients (Table 2).
Table 3. Studies Performed During Surgery

<table>
<thead>
<tr>
<th>Subject</th>
<th>FPP (mm Hg)</th>
<th>Splenic A-V O₂ Diff. (mm Hg)</th>
<th>SBF (ml/min)</th>
<th>STT (sec)</th>
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<td>9.2</td>
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</table>

Normal values 5.9–9.6* 100–300†

FPP, free portal pressure; A-V O₂ Diff., arteriovenous oxygen difference; SBF, splenic blood flow; STT, splenic transit time; Pre, before splenectomy; Post, 2–4 mo after splenectomy.

* From Sedgwick and Poulantzas.47
† From Blendis et al.48

Studies Performed During Surgery in Group I Patients

These studies are presented in Table 3. The FPP was elevated in 12 of 12 patients and dropped significantly immediately after clamping the splenic artery in eight of ten patients who had postsplenectomy measurements. The pressure returned to normal in only four patients, the normal range for FPP measurements at laparotomy being 5.9–9.6 mm Hg.47 The splenic A-V oxygen difference expressed in millimeters of Hg was either normal or increased in seven of seven patients. The splenic blood flow was markedly increased in all four patients in whom it was measured; values ranged from 750–2200 ml/min. Splenic indocyanine green dye dilution curves in three of three patients failed to show an early peak suggestive of A-V shunting; the splenic transit time was very prolonged.

Peripheral Vein Renin (PVR) Activity

The mean PVR activity in group I patients is shown in Fig. 3. The mean values in seven anemic patients without splenomegaly and in 15 normal subjects are also presented. The mean supine and upright values in group I patients are significantly increased over normal controls (p < 0.05 and p < 0.02, respectively). After splenectomy, the mean upright PVR activity is significantly decreased from preoperative values (p < 0.05). The mean upright PVR activity value in group I patients is also significantly increased above the mean supine value before splenectomy (p < 0.01). After splenectomy, this difference is no longer present. The mean upright PVR activity in group II patients (anemia
without splenomegaly) is significantly increased above the mean value of 15 normal controls ($p < 0.05$). However, the supine PVR activity in group II patients is not significantly different from the mean value of 15 normal controls.

**Forearm Blood Flow (FABF) and Venous Tone (VV30)**

The mean FABF and VV30 for group I patients, group II patients (anemia without splenomegaly), and 15 normal subjects are compared in Fig. 4. The mean FABF in group I patients is significantly increased above the normal mean ($p < 0.01$) and tended to decrease postsplenectomy. In anemia without splenomegaly, the mean FABF is not significantly different from the normal mean.

The mean value for VV30 in group I patients is not significantly different from
the normal mean. However, the mean value for $V_{V,30}$ in group II patients is significantly decreased when compared to the mean in normal subjects and the mean of group I patients ($p < 0.02$). Thus, the venoconstriction that occurs in anemia without splenomegaly does not occur with dilutional anemia of comparable degree secondary to massive splenomegaly.

Other Hematologic Studies in Group I Patients

The presplenectomy WBC and platelet counts reflect not only the underlying disease process but also the effect of splenomegaly on these values. The circulating platelet count often drops to very low levels with massive splenomegaly, and the decrease is the result primarily of sequestration of platelets in the spleen and not of an increased rate of destruction by the spleen. In all of 14 patients studied after splenectomy, the platelet count increased (Table 1). The WBC also tended to increase after splenectomy (Table 1); the degree depended on the underlying disease process and upon whether or not the patient received busulfan therapy before splenectomy to prevent postoperative thrombocytosis, as patients F.A. and H.M. did.

DISCUSSION

The fully developed “big spleen syndrome” is characterized by an expanded anatomical vascular space, expanded plasma and total blood volume, anemia, hypermetabolism, high cardiac output, a wide pulse pressure, decreased peripheral resistance, and probably an increased rate of synthesis of albumin (Fig. 5). The anemia that often accompanies massive splenomegaly may be the result of several mechanisms. In 14 of 20 patients in this study a low RCM was a factor in the decreased venous hematocrit (Table 1 and Fig. 1). Hyperhemol-
ysis was a contributing factor in only 4 of these 14 patients (M.S., J.S., C.L., and H.M.). Evidence suggested that the low RCM in the other patients was the result of decreased red cell production secondary to involvement of the bone marrow by the primary disease process. When the underlying disease does not compromise bone marrow reserve as is the case of "tropical splenomegaly" the RCM is often increased in the presence of a low venous hct and normal red cell survival.2,3

Another less well known cause of a decreased venous hematocrit in patients with splenomegaly is sequestration of erythrocytes within the spleen.4,5 The number of red cells that may be trapped varies greatly not only with the size of the spleen, but also with the underlying disease process, and may exceed 25% of the total RCM in massively enlarged spleens.4,5,9,10 The volume sequestered in the spleen can be calculated from the body:venous hematocrit ratio and agrees closely with the values determined by direct isotopic methods.2 The body:venous hematocrit ratio has a narrow range with a mean of 0.87 ± 0.06 (± SD) in normal males and 0.90 ± 0.06 (± SD) in normal females and in patients with anemia over a wide hematocrit range if splenomegaly is not present.4,5 The ratio was greater than 1.00 in 11 of 20 patients in this study, and, after splenectomy, the ratio decreased in 11 of 13 patients (Fig. 2). In 4 of 11 patients showing a decrease postoperatively, values less than 1.00 were observed before splenectomy. The contribution of splenic red cell pooling to the lowered venous hematocrit was considerable in patients V.S., J.S., V.K., N.S., J.B., M.B., E.S., M.S., C.H., and E.B. (Fig. 2).

In 18 of 20 patients in this study, however, the most important factor in the decreased venous hematocrit was expansion of the PV with dilution of the circulating RCM, a result that agrees with those of other investigators.1,6,52 In addition, other data strongly suggest that one of the factors responsible for the PV expansion is flow-induced portal hypertension (Fig. 5). This concept is supported by the observation that portal venous pressure returns to normal in most cases following clamping of the splenic artery (Table 3). Increased portal blood flow secondary to splenic arteriovenous fistulae33,35 and massive splenomegaly56,57 is a well-recognized cause of portal hypertension. Splenectomy, ligation of the splenic artery, or closure of the fistula results in a fall in portal venous pressure.35,53 A fall in portal venous pressure also occurs with splenectomy or splenic artery ligation in patients with portal hypertension secondary to intrinsic liver disease;35,51,62 the degree of fall depends on the size of the spleen and the magnitude of the increase in splenic arterial blood flow.

With the gradual increase in portal venous pressure, expansion of the anatomical portal vascular space probably occurs. This change could lead to portal venous pooling of blood, activation of the renin–angiotensin–aldosterone system, and other renal mechanisms that result in salt and water retention and expansion of the extracellular fluid and plasma volume.63 Another factor contributing to salt and water retention is the decrease in systemic peripheral resistance which is due, at least in part, to the hypermetabolic state that often accompanies massive splenomegaly. The increased FABF suggests that this decrease in peripheral resistance may be due to cutaneous vasodilatation
stimulated by the increased heat production (Fig. 4). Most of the increase in oxygen consumption is accounted for by a marked increase in splenic blood flow accompanied by normal or increased A-V oxygen differences across the spleen (Table 3). The increased cardiac index also contributes to the increased oxygen consumption.

With expansion of extracellular fluid and plasma volume, dilution of plasma albumin concentration might occur and result in a decrease in the colloid osmotic pressure. A fall in colloid osmotic pressure stimulates hepatic albumin synthesis. In 10 of 14 patients in this study (Table 2), a drop in the intravascular albumin mass was found 2-4 mo after splenectomy. In nine patients, this fall in the intravascular albumin pool was accompanied by an actual increase in the plasma albumin concentration (Table 2). The delay of 2-4 mo for the PV to return to normal after splenectomy may be due, in part, to the time required to catabolize the increased mass of albumin and to the time necessary for readjustment of the increased albumin synthetic rate present before splenectomy. The drop in the intravascular albumin mass after splenectomy assumes more significance if one considers the narrow range of fluctuation, over many years, in the total plasma albumin pool of healthy subjects. Other factors such as the time required for readjustment of the volume regulatory mechanism following splenectomy are probably also important in the delayed fall in PV.

The concept of the central role of flow-induced portal hypertension in the pathogenesis of plasma volume expansion is given added support by the finding of many investigators that plasma volume expansion with dilutional anemia is often seen in patients with portal hypertension secondary to intrinsic liver disease. Portacaval shunting often produces a significant drop in PV. Lending further support to the importance of expanded anatomical vascular space are studies in women in the last trimester of pregnancy. At or near term, the PV may increase as much as 1300 ml with a lesser increase in the RCM. The mechanism is again thought to be due in part to an increase in the anatomic vascular space (a result of placental growth) and subsequent expansion of the PV and RCM.

Arteriovenous shunting in spleens has been proposed as the mechanism for PV expansion in massive splenomegaly. Although PV expansion does occur with major arteriovenous shunts, we were unable to demonstrate an early peak in the splenic indocyanine-green dye dilution curves measured at surgery in three patients and concluded that there was no major shunting in the spleen itself. In addition, the A-V oxygen difference across the spleen was normal or often markedly increased, a finding not compatible with major shunting.

The finding of normal or only minimally elevated PV and a contracted TBV in patients with varying degrees of anemia without splenomegaly (Fig. 1) supports the concept that anemia does not play a primary role in the development of PV expansion in the presence of massive splenomegaly.

Most of the hematologic, hemodynamic, and metabolic abnormalities in patients with massive splenomegaly improve with splenectomy. In patients with tropical splenomegaly and primary splenic hyperplasia with no liver or bone marrow disease, the PV almost always returns to normal after splenectomy, but this decrease may require up to 6 mo. Failure of the PV to return
to normal in some patients in this study may be due to residual portal hypertension secondary to liver involvement by the underlying disease process, a low RCM at the time of restudy, and a persistent increase in albumin synthesis. Although the portal pressure fell significantly immediately following splenectomy, most of the post-splenectomy values remained above normal (Table 3). Residual portal hypertension and a low RCM probably were contributing factors in the elevated PV in three patients (M.S., E.S., and H.M.), all of whom had marked hepatomegaly and a very low RCM at the time of restudy. In patients J.S., C.L., and F.A., who had marked hepatomegaly and a normal RCM at the time of restudy, residual portal hypertension alone was probably a factor. Patients E.L., J.B., V.K., and M.B. had only a minimal elevation of the PV at the time of restudy.

ACKNOWLEDGMENT

The authors are grateful to Elizabeth Ortt and Curtis Morton for their highly competent technical assistance, to Susan Worthington for secretarial help, and to Dr. T. C. Bithell, Dr. M. S. Wheby, Dr. J. T. Carpenter, Jr., and Dr. B. S. Leavell for their constructive comments and encouragement and for reviewing the manuscript.

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