Observations on the Anemia of Cryptogenetic Splenomegaly
II. Expansion of the Plasma Volume

By A. J. S. McFadzean, David Todd and K. C. Tsang

In the preceding communication it has been shown that although splenectomy for cryptogenetic splenomegaly removes all evidence of excessive hemolysis and results in a significant increase in the hemoglobin level and in the erythrocyte count, nevertheless significant anemia persists. The purpose of this communication is to report observations which indicate that expansion of plasma volume plays a significant part in the production of anemia prior to splenectomy and is possibly alone responsible for the anemia which persists following splenectomy.

Material and Methods

Observations were made on 57 patients with cryptogenetic splenomegaly. The clinical and laboratory findings together with the appearances on aspiration liver biopsy permitted their division into one group of 40 with cirrhosis of the liver and another of 17 in which the changes in the liver were of less severe degree. None of these patients had a history of significant bleeding and, we would emphasize, none had clinically detectable anasarca at the time of investigation. Observations were also made on 28 patients who, suffering from cryptogenetic splenomegaly, had been splenectomized not less than nine months before. Also investigated were certain additional patients who are more appropriately described later.

Conventional methods were employed to enumerate red cells and to determine hemoglobin and the hematocrit. Plasma volume was estimated by the T-1824 dye method described by Crooke and Morris. Employing the correction factor for trapped plasma reported by Barnes, Loutit and Reeve, the total red cell volume was calculated from the plasma volume and venous hematocrit assuming the ratio of body hematocrit: venous hematocrit to be 0.92.

Unless explicitly stated otherwise, all differences described were significant statistically.

Results

The results, expressed as the means and their standard deviations, in both groups are set out in table 1. Figures 1 and 2 present graphically the plasma volume and red cell mass in each patient of both groups. It will be seen from table 1 that in both groups of patients in whom the spleen had not been removed the plasma volume was increased. Consideration of figures 1 and 2 shows that this increase was invariably present although varying widely in degree. The mean red cell volume did not differ significantly from that of the normal controls. Figures 1 and 2 show that it was reduced in 22, within normal limits in 31, and in four it was above the normal limits.

In both splenectomized groups a significant degree of anemia persisted. In each group the total red cell volume was greater than that before splenec-
Fig. 1.—The red cell mass and plasma volume in patients with cryptogenetic splenomegaly not associated with cirrhosis of the liver. In the splenectomized group the operation had been performed not less than 9 months before. Pre- and postsplenectomy findings in the same patients are connected.

tomy. While in each group the mean total red cell volume was greater than that in normal controls this was significant only in the group without cirrhosis of the liver. Consideration of figures 1 and 2 shows that in 17 of the 28 patients the red cell volume was within normal limits and in the remaining 11 it was above normal. The plasma volume in each group was lower than in the corresponding nonsplenectomized group, but remained higher than in the normal. Figures 1 and 2 show that in all save one of the splenectomized patients the plasma volume was increased. In the exception it was within normal limits.

In order further to investigate the adjustment in plasma volume which occurred following splenectomy, 22 patients, 12 of whom had cirrhosis of the liver, were investigated both before and one month after splenectomy. The
Table 1.—Certain Data in Patients With Cryptogenetic Splenomegaly Including Patients Splenectomized 9 or More Months Before

<table>
<thead>
<tr>
<th>Subject</th>
<th>No.</th>
<th>Age (years)</th>
<th>Weight (Kg.)</th>
<th>Size of Spleen (em.)</th>
<th>Hgb (Gm. per 100 ml.)</th>
<th>RBC (mill. per cu. mm.)</th>
<th>H'crit (%)</th>
<th>Blood Volume (ml. per Kg.)</th>
<th>Plasma Volume (ml. per Kg.)</th>
<th>Red Cell Volume (ml. per Kg.)</th>
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<tr>
<td>Normal Controls</td>
<td>12</td>
<td>25.6±7.0</td>
<td>60.5±7.6</td>
<td>—</td>
<td>15.1±0.6</td>
<td>5.08±0.49</td>
<td>45.5±3.1</td>
<td>83.0±5.9</td>
<td>45.2±3.4</td>
<td>36.2±2.7</td>
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<tr>
<td>Cryptogenic Splenomegaly without Cirrhosis</td>
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<tr>
<td>A</td>
<td>17</td>
<td>29.8±9.6</td>
<td>45.2±11.4</td>
<td>15±3</td>
<td>8.8±1.03</td>
<td>3.11±0.5</td>
<td>27.5±8.6</td>
<td>120.6±18.5</td>
<td>88.5±14.1</td>
<td>32.1±7.1</td>
</tr>
<tr>
<td>B</td>
<td>18.8±5.1 months after Splenectomy</td>
<td>10</td>
<td>24.6±9.8</td>
<td>52.8±4.2</td>
<td>13.8±1.03</td>
<td>4.62±0.39</td>
<td>42.1±0.7</td>
<td>101.5±8.6</td>
<td>59.8±5.3</td>
<td>41.6±4.3</td>
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<tr>
<td>P Value</td>
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<tr>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.1&gt;0.05</td>
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<tr>
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<td>&lt;0.001</td>
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<tr>
<td>A</td>
<td>40</td>
<td>38.8±9.0</td>
<td>51.0±4.2</td>
<td>8±4</td>
<td>10.6±1.77</td>
<td>3.69±0.52</td>
<td>32.8±5.1</td>
<td>109.0±5.5</td>
<td>75.5±18.0</td>
<td>38.5±5.3</td>
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<tr>
<td>B</td>
<td>20.2±7.2 months after Splenectomy</td>
<td>18</td>
<td>36.2±8.9</td>
<td>54.9±7.3</td>
<td>13.0±1.0</td>
<td>4.32±0.37</td>
<td>39.9±3.2</td>
<td>104.5±8.9</td>
<td>64.8±6.5</td>
<td>39.4±5.5</td>
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<tr>
<td>P Value</td>
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<tr>
<td>A v. Controls</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td>&lt;0.1&gt;0.05</td>
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<td>&lt;0.001</td>
<td>&lt;0.1&gt;0.05</td>
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<td>A v. B</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.1&gt;0.05</td>
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</table>
results are set out in table 2. It will be seen that in the group with cirrhosis of the liver no significant effect was exerted by splenectomy within a period of one month, whereas in the group without cirrhosis of the liver there was a fall in plasma volume and a rise in red cell volume.

The plasma volume was determined after a further interval of four months in eight of the above patients, four of whom had cirrhosis of the liver. The results are shown in table 3. It will be seen that the fall in plasma volume between one and five months after splenectomy was either equal to (2 cases) or greater than (6 cases) that encountered one month after splenectomy.

In order to determine the influence of recent massive gastrointestinal bleeding, patients with cirrhosis of the liver and history of such bleeding within the previous two months were investigated. Two of these patients were re-
<table>
<thead>
<tr>
<th>Subjects</th>
<th>No.</th>
<th>Size of Spleen (cm.)</th>
<th>Blood transfused at operation (pinia)</th>
<th>Weight (kg.)</th>
<th>H’crit (%)</th>
<th>Hgb (Gm. per 100 ml.)</th>
<th>RBC (mill. per cu.mm.)</th>
<th>Blood Volume (ml. per Kg.)</th>
<th>Plasma Volume (ml. per Kg.)</th>
<th>Red Cell Volume (ml. per Kg.)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Cryptogenic Splenomegaly</td>
<td>15</td>
<td>±2</td>
<td>±1.4</td>
<td>±5.9</td>
<td>±3.1</td>
<td>±1.53</td>
<td>±0.45</td>
<td>±15.5</td>
<td>±14.9</td>
<td>±11.5</td>
<td>±6.0</td>
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<tr>
<td>Cryptogenic Splenomegaly</td>
<td>12</td>
<td>±4</td>
<td>±1.1</td>
<td>±9.4</td>
<td>±5.3</td>
<td>±2.0</td>
<td>±0.69</td>
<td>±18.8</td>
<td>±21.9</td>
<td>±9.1</td>
<td>±4.4</td>
</tr>
</tbody>
</table>

No significant differences
ANEMIA OF CRYPTOGENETIC SPLENOMEGALY. II.

529

BEFORE SPLENECTOMY
O AFTER SPLENECTOMY

$60
$40
$20
$0

Fig. 3.—The red cell mass and plasma volume in patients with cryptogenic splenomegaly with cirrhosis of the liver with a history of recent massive gastrointestinal hemorrhage.

Table 3.—The Plasma Volume in Patients With Cryptogenic Splenomegaly Before and 1 and 5 Months After Splenectomy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Plasma Volume (ml. per Kg.)</th>
<th>Before Splenectomy</th>
<th>After Splenectomy</th>
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<tr>
<td></td>
<td></td>
<td>1 month</td>
<td>5 months</td>
</tr>
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<td>Cryptogenetic</td>
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<td>94</td>
<td>89</td>
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<tr>
<td>Splenomegaly</td>
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<td>88</td>
<td>82</td>
</tr>
<tr>
<td>without</td>
<td></td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
<td>103</td>
<td>76</td>
</tr>
<tr>
<td>Cryptogenetic</td>
<td></td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td></td>
<td>107</td>
<td>88</td>
</tr>
<tr>
<td>with</td>
<td></td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
<td>75</td>
<td>73</td>
</tr>
</tbody>
</table>
investigated six months after splenectomy. The results are shown in figure 3. It will be seen that all eight patients showed an increase in plasma volume and a decrease in total red cell volume. In the two patients investigated six months after splenectomy the total red cell volume had risen to within normal limits and the plasma volume had fallen, although it remained higher than normal.

**Discussion**

The evidence presented indicates that following splenectomy, which has been shown to remove all evidence of excessive hemolysis, the total volume of red cells becomes normal or greater than normal. The position prior to splenectomy is more difficult to assess. Although the technic employed to determine the total red cell volume is generally considered valid, the observations of Hope and Verel, among others, question the constancy of the ratio of body hematocrit to venous hematocrit. The direct measurement of the red cell volume has shown that this ratio is increased in patients with splenomegaly. The results here reported indicate that prior to splenectomy the mean red cell volume is not significantly different from normal and that it rises significantly following splenectomy. We are aware of the necessity of confirming our results by the direct determination of the red cell volume employing Cr-tagged red cells, a technic not available to us at present.

It has been shown that splenectomy results in a reduction in plasma volume which, however, remains significantly greater than normal. It would seem therefore that splenectomy exerts its beneficial effect upon the anemia not only by removing excessive hemolysis, but also by reducing an expanded plasma volume. Since the total red cell volume is normal or greater than normal following splenectomy, it is tempting to suggest that hypervolemia alone is responsible for the anemia which persists following this operation. This, however, may not be the sole explanation, for hyperplasia of the erythroid series in the marrow persists in a significant number of cases.

It remains to be determined how far other splenomegalies of pathogenesis distinct from that of cryptogenic splenomegaly produce an increase in plasma volume. We have found it to occur in association with the splenomegaly of leishmaniasis, schistosomiasis and quartan malaria. In cirrhosis of the liver in temperate climate, presumably of pathogenesis distinct from that of the cirrhosis associated with cryptogenic splenomegaly, expansion of the plasma volume has been reported. Also employing the T-1824 technic Perera, Hiller, Huffman and Levey and Bateman, Shorr and Elgvin found it to be uniformly present. Hyde, Berlin, Parsons, Lawrence and Port employing P32-tagged red cells, failed to find the increase consistent, and Eisenberg using Cr-tagged red cells, reported similar findings.

Perera considered that the hypervolemia encountered in cirrhosis of the liver was the passive consequence of an expanded vascular bed. Eisenberg subscribed to this view and reported a correlation between the presence of esophageal varices and hypervolemia. We have found no such correlation in our series of patients with cirrhosis of the liver. While it is admitted that in the group without cirrhosis of the liver there is marked dilatation of the
splenic vein and development of retroperitoneal collaterals, it is difficult to
believe that these could be responsible for the increase in blood volume
encountered. Equally difficult to accept is the proposition that the slow re-
duction in plasma volume following splenectomy is due to slow closure of
collateral channels. The phenomenon is under investigation and further dis-
cussion here would be conjectural.

**Summary**

In cryptogenetic splenomegaly, although there is consistently a significant
reduction in hemoglobin concentration and in the red cell count, the total
red cell volume may be reduced, normal or increased.

Following splenectomy the total red cell volume is either within normal
limits or is increased, yet significant anemia persists.

Before splenectomy a significant increase in plasma volume is consistently
present. Following splenectomy the plasma volume falls, but it remains sig-
nificantly greater than normal. It would appear that the greater the plasma
volume before splenectomy the greater is the fall following splenectomy.
This fall in plasma volume is not a prompt response to splenectomy, for the
fall which occurs one month after splenectomy is equalled or exceeded by
that occurring in the succeeding four months.

It is concluded that an expanded plasma volume before splenectomy con-
tributes with the hemolysis previously reported to the development of the
anemia encountered in cryptogenetic splenomegaly. Expansion of the plasma
volume at least contributes to the anemia which persists following splenectomy.

**Summario in Interlingua**

In splenomegalia cryptogenetic, il es possibile que le volumine del
erthrocytos total es reducite o normal o augmentate, ben que il ha uni-
formemente un reduction significative del concentration de hemoglobina e
del numeration erythrocytic.

Post splenectomia, le volumine erythrocytic total pote trovar se intra limites
normal o illo pote esser augmentate, durante que grados significative de
anemia persiste.

Ante le splenectomia un augmento significative del volumine de plasma
es uniformemente presente. Post le splenectomia le volumine de plasma
descende sed illo remane significativamente supra le norma. Il pare que
quanto plus grande le volumine de plasma es ante le splenectomia, tanto plus
grande es le descendita de illo post le splenectomia. Iste reduction del
volumine de plasma non es un prompte responsa al splenectomia. De facto,
le grado de reduction occurrente un mense post le splenectomia es equalate o
excedite per le grado de reduction que occurre durante le sequente quatro
menses.

Es concludite que un expandite volumine de plasma ante le splenectomia
contribue, insimul con le previemente reportate hemolys, al disveloppamento
del anemia que es incontrate in splenomegalia cryptogenetic. Expansion del
volumine de plasma age al minus como contributor al anemia que persiste
post le splenectomia.
REFERENCES


Observations on the Anemia of Cryptogenetic Splenomegaly II. Expansion of the Plasma Volume

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