Hypersplenism in cirrhosis

L. M. BLENDIS
M.B., M.R.C.P.

THE PERIPHERAL blood changes associated with cirrhosis and splenomegaly were first described by Banti in 1894. This is often known as hypersplenism and essentially consists of thrombocytopenia and less frequently neutropenia and anaemia.

Neutropenia

The neutropenia is mild, in the region of 2000–4000 cells/mm³ and was found to be present in forty of eighty patients with subacute or chronic liver disease (Meulengracht & Gormsen, 1948). There was no deviation from the normal differential count. The neutropenia would appear to be a function of portal hypertension and splenomegaly since neutropenia of this order was present in seventeen out of twenty-one patients with extrahepatic portal hypertension (Stathers, Ma & Blackburn, 1968). Occasionally in patients with massive spenomegaly serious neutropenia, that is below 2000 cells/mm³, may be present Welch, (1950). Unfortunately it has been difficult to study neutrophil kinetics except in patients in the terminal stages of their illness (Cronkite *et al.*, 1958; Godwin, Zimmerman & Perry, 1968). The most satisfactory neutrophil isotope label, tritiated thymidine (Cronkite *et al.*, 1959) cannot be used due to the high irradiation dose to individual cells (Robertson & Hughes, 1958).

Thrombocytopenia

In 1929 King found that in 20% of cirrhotic patients the platelet count was decreased although in only two out of fifteen patients were the bleeding and clotting times prolonged. Morlock & Hall (1943) in a survey of eighty consecutive patients with cirrhosis found that 17·5% has a platelet count of less than 100,000/mm³, although in only two patients was the count less than 50,000/mm³. When the patients were divided into two groups, those with and those without gastro-intestinal bleeding, the incidence of thrombocytopenia was 25 and 6%, respectively. In seventeen out of twenty-one patients with extrahepatic portal hypertension already referred to the platelet count ranged from 21,000 to 146,000/mm³ (Stathers *et al.*, 1968).

The mechanism of thrombocytopenia associated with hypersplenism has recently been studied by

Aster (1966) using ⁵¹Cr-labelled platelets. After the injection of the labelled platelets splenic uptake was monitored by means of an external radioactive counter positioned over the spleen, and their disappearance from the circulation assessed by measuring the percentage recovered in a blood sample at 2 hr. Whereas with a normal size spleen there is a 60–70% recovery this may fall to 10–50% in patients with splenomegaly (Fig. 1). This increased
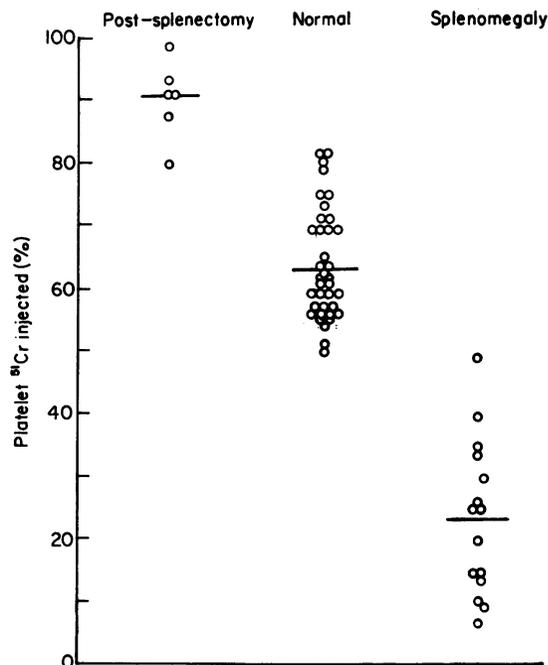

FIG. 1. Recovery in the general circulation of ⁵¹Cr-labelled platelets transfused to asplenic, normal, and splenomegalic subjects. 'Recovery' is the percentage of platelets remaining in the general circulation 2 hr after injection [From Aster (1966) by permission of the Editor of *J. clin. Invest.*]

disappearance of labelled platelets from the circulation is due to sequestration within the enlarged counter. Infusion of noradrenaline caused splenic contraction and discharge of platelets from the splenic pool with a marked rise in the peripheral platelet count. Penny, Rozenberg & Firkin (1966)
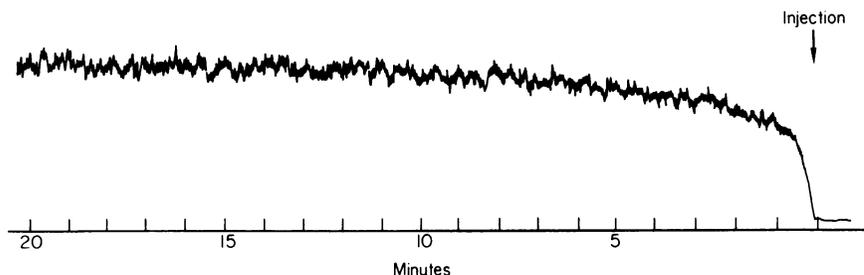
Fig. 2. ^{51}Cr red cell radiosplenogram. A typical tracing from a patient with idiopathic splenomegaly [From Pryor (1967) by permission of the Editor of *Quart. J. Med.*]

have shown that these splenic platelets are morphologically and functionally identical to circulating platelets. Therefore, the thrombocytopenia of hypersplenism may be due to trapping of platelets within a splenic pool without any change in the total platelet mass, life span or production rate of the platelets.

Anaemia

Anaemia in cirrhotic patients may be due to many factors apart from hypersplenism. These include chronic blood loss from the gastro-intestinal tract and dietary deficiencies, such as folic acid, associated with chronic alcoholism (Kimber *et al.,* 1965). The association of cirrhosis and haemolysis was first demonstrated by Chaplin & Mollison (1953) using the Ashby technique. In five patients red cell survival was reduced to between 25 and 55 days. The exact mechanism is uncertain and both intrinsic and extrinsic factors are probably involved. The possibility of an intrinsic defect in the red blood cell was suggested by Pitcher & Williams (1963) by demonstrating that red cells from cirrhotic patients still had a reduced survival in 'normal subjects' and by the finding of low levels of reduced glutathione in the red cell in the majority of patients studied. This is known to be the mechanism in patients with certain types of drug-induced haemolytic anaemias (Beutler, 1957) but Pitcher & Williams (1963) were not able to show a correlation between this defect and the degree of haemolysis.

The presence of an extrinsic haemolytic mechanism was suggested by Jandl (1955) who showed that the survival of normal red cells in cirrhotic patients was reduced. A true acquired autoimmune haemolytic anaemia, however, is extremely rare in cirrhosis. Jones and his co-workers (1955) failed to demonstrate antibodies in any of their cirrhotic patients with a diminished red cell survival, i.e. antibodies are rarely the cause of the extrinsic defect. The sequestration of red cells by the enlarged spleen may be one extrinsic mechanism. This was demonstrated by Motulsky and co-workers (1958) in patients with blood dyscrasia and by Pryor (1967) in patients with tropical splenomegaly. Using

an external radioactive counter over the spleen a marked delay in reaching a plateau recording was seen due to the presence of a slow-mixing red cell pool (Fig. 2). This finding was confirmed by Toghill (1964) who showed that producing splenic contraction by intravenous noradrenaline infusion resulted in a diminution of the red cell pool with subsequent rise in the packed cell volume. In contrast to platelet sequestration, pooling of red cells within the spleen results in damage to the red cell membrane and a shortening of their life span (Prankerd, 1963). However, this phenomenon has been more difficult to demonstrate in cirrhotic patients.

The other major cause of anaemia in cirrhosis due to hyperspenism is an enlarged plasma volume causing haemodilution. Using ^{125}I-labelled human serum albumin we have measured the plasma volume of thirty-four cirrhotic patients and 70·6% had an enlarged plasma volume, that is greater than 50 ml/kg body weight (Fig. 3). In other studies this figure has varied from 11% (Boivin, Hartmann & Fauvert, 1961) to 80% (McFadzean & Todd, 1967). Some doubt has been expressed as to whether markers dependent on the distribution of albumin are true indicators of the volume of plasma in cirrhotic patients (Peters, 1948). Lieberman & Reynolds (1967) have shown, however, that leakage of labelled albumin into the lymphatics, the suggested source of the error with this method, resulted in a maximum activity of only 0·8% of that of plasma.

McFadzean & Todd (1967) found that expansion of plasma volume could be related to the degree of splenic enlargement although Kimber and his co-workers (1965) found no association with splenomegaly. Our results so far support the view that enlargement of the spleen is associated with increase in plasma volume (Blendis, Toghill & Williams, 1968). However, the presence of portal hypertension has also been implicated by the finding of a correlation with the wedged hepatic vein pressure (Lieberman & Reynolds, 1967) and by an approximate relationship with the presence of portal venous collaterals with their increased vascular capacity (Eisenberg, 1956).
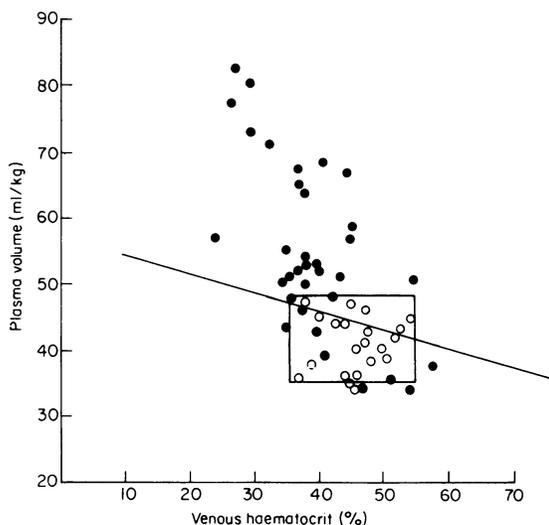
FIG. 3. To show the incidence of an expanded plasma volume in patients with cirrhosis. The rectangle represents the limits of the normal range; the range for venous haematocrit is taken from Dacie & Lewis (1963) and that for plasma volume is taken from Gibson & Evans (1937). The continuous line is from published information and is that given by Mollison (1967). ●, Cirrhosis; ○, controls.

Indications for splenectomy

Since the effects of hypersplenism in cirrhosis are usually mild, splenectomy is seldom indicated. The serious degree of neutropenia seen in the hypersplenism of Felty's syndrome is extremely rare in cirrhosis. Although splenectomy will cause a remission in the neutropenia it will not alter the ultimate prognosis in these patients (Poinso *et al.*, 1958). Thrombocytopenia in cirrhosis rarely presents an haemorrhagic hazard. However severe thrombocytopenia in cirrhosis, with purpura, has been reported and in these cases splenectomy brought about a complete remission (Morlock & Hall, 1943). The haemolysis of hypersplenism or the dilutional effect of an expanded plasma volume are rarely serious enough to warrant splenectomy. When this was performed the red cell mass increased due to correction of haemolysis and although the plasma volume decreased it remained elevated in twelve out of fourteen patients (McFadzean & Todd, 1967).

Splenectomy should be performed in association with a splenorenal shunt if there is evidence of portal hypertension, since the propagation of thrombus within the splenic vein into the hepatic portal vein, which happens not infrequently, will render future shunt operations impossible. The problem of an increased risk of infection after splenectomy that occurs in children (Eraklis *et al.*, 1967) is not present to such an extent in adults.

References

ASTER, R.H. (1966) Pooling of platelets in the spleen: role in the pathogenesis of 'hypersplenic' thrombocytopenia. *J. clin. Invest.* **45**, 645.

BANTI, G. (1894) La splénomegalie avec cirrhose du foie. *Sem. méd. Paris.* **14**, 318.

BEUTLER, E. (1957) The glutathione instability of drug-sensitive red cells. *J. Lab. clin. Med.* **49**, 84.

BLENDIS, L.M., TOGHILL, P.J. & WILLIAMS, R. (1968) Effect of splenomegaly on the plasma volume. *Proc. 3rd Meeting European Ass. for the Study of the Liver.*

BOIVIN, P., HARTMANN, L. & FAUVERT, R. (1961). L'anémie des cirrhoses. Fréquence et mechanisme. *Nouv. Rév. franç. Hémat.* **1**, 3.

CHAPLIN, H. & MOLLISON, P.L. (1953). Red cell life-span in nephritis and hepatic cirrhosis. *Clin. Sci.* **12**, 351.

CRONKITE, E.P., FLIEDNER, T.M., RUBINI, J.R., BOND, V.P. & HUGHES, W.L. (1958) Dynamics of proliferating cell systems of man studied with tritiated thymidine. *J. clin. Invest.* **37**, 887.

CRONKITE, E.P., BOND, V.P., FLIEDNER, T.M. & RUBINI, J.R. (1959) The use of tritiated thymidine in the study of DNA synthesis and cell turnover in hemopoetic tissues. *Lab. Invest.* **8**, 263.

DACIE, J.V. & LEWIS, S.M. (1963) *Practical Haematology*, 3rd edn. Churchill, London.

EISENBERG, S. (1956) Blood volume in patients with Laennec's cirrhosis of the liver as determined by radioactive chromium tagged red cells. *Amer. J. Med.* **20**, 189.

ERAKLIS, A.J., KEVY, S.V., DIAMOND, L.M. & CROSS, R.E. (1967) Hazard of overwhelming infection after splenectomy in childhood. *New Engl. J. Med.* **276**, 1225.

GIBSON, J.G. & EVANS, W.A. (1937) Clinical studies of the blood volume. *J. clin. Invest.* **16**, 317.

GODWIN, H.A., ZIMMERMAN, T.S. & PERRY, S. (1968) Peripheral leucocyte kinetic studies of acute leukaemia in relapse and remission and chronic myelocytic leukaemia in blastic crisis. *Blood*, **31**, 686.

JANDL, J.H. (1955) The anaemia of liver disease: observations on its mechanism. *J. clin. Invest.* **34**, 390.

JONES, P.N., WEINSTEIN, I.M., ETTINGER, R.H. & CAPPS, R.B. (1955) Decreased red cell survival associated with liver disease. *Arch. intern. Med.* **95**, 93.

KIMBER, C., DELLER, D.J., IBBOTSON, R.N. & LANDER, H. (1965) The mechanism of anaemia in chronic liver disease. *Quart. J. Med.* **34**, 33.

KING, R.B. (1929) The blood picture in portal cirrhosis of the liver. *New Engl. J. Med.* **200**, 482.

LIEBERMANN, F.L. & REYNOLDS, T.B. (1967) Plasma volume in cirrhosis of the liver: its relation to portal hypertension, ascites and renal failure. *J. clin. Invest.* **46**, 1297.

McFADZEAN, A.J.S. & TODD, D. (1967) The blood volume in post-necrotic cirrhosis of the liver with splenomegaly. *Clin. Sci.* **32**, 329.

MEULENGRACHT, E. & GORMSEN, H. (1948) Blood and bone marrow changes in infective subacute and chronic atrophy of the liver. *Blood*, **3**, 1416.

MOLLISON, P.L. (1967) *Blood Transfusion in Clinical Medicine*, 4th edn. Blackwell Scientific Publications, Oxford.

MORLOCK, C.G. & HALL, B.E. (1943) Association of cirrhosis, thrombopenia and haemorrhagic tendency. *Arch. intern. Med.* **72**, 69.

MOTULSKY, A.G., CASSERD, F., GIBLETT, E.R., BROUN, G.O. & FINCH, C.A. (1958) Anaemia and the spleen. *New Engl. J. Med.* **259**, 1164.

PENNY, R., ROZENBERG, M.C. & FIRKIN, B.G. (1966) The splenic platelet pool. *Blood*, **27**, 1.

PETERS, J.P. (1948) The role of sodium in the production of oedema. *New Engl. J. Med.* **239**, 353.

L. M. Blendis

PITCHER, C.S. & WILLIAMS, R. (1963) Reduced red cell survival in jaundice and its relation to abnormal glutathione metabolism. *Clin. Sci.* **24**, 239.

POINSO, R., HAWTHORN, E., BONDIL, J.N., MARRIQ, P. & BASSILANA, R. (1958) Outcome of neutropenic splenomegaly. *Sem. hôp. (Paris),* **34**, 2284.

PRANKERD, T.A.J. (1963) The spleen and anaemia. *Brit. med. J.* **2**, 517.

PRYOR, D.S. (1967) The mechanism of anaemia in tropical splenomegaly. *Quart. J. Med.* N.S. **36**, 337.

ROBERTSON, J.S. & HUGHES, W.L. (1958) Intra-nuclear irradiation with tritium-labelled thymidine. *Trans. First Nat. Conf. Biophys.*

STATHERS, G.M., MA, M.H. & BLACKBURN, C.R.B. (1968) Extrahepatic portal hypertension: the clinical evaluation investigation and results of treatment of 28 patients. *Aust. Ann. Med.* **17**, 12.

TOGHILL, P.J. (1964) Red-cell pooling in enlarged spleens. *Brit. J. Haemat.* **10**, 347.

WELCH, C.S. (1950) Portal hypertension. *New Engl. J. Med.* **243**, 598.