DIAGNOSIS AND TREATMENT OF THE BUDD-CHIARI SYNDROME IN POLYCYTHAEMIA VERA

BY

O. FitzGERALD, M.D., M.Sc.
Visiting Physician, St. Vincent's Hospital; Lecturer in Therapeutics, University College, Dublin

P. FitzGERALD, M.D., M.Ch., M.Sc.
Visiting Surgeon, St. Vincent's Hospital; Associate Professor of Surgery, University College, Dublin

D. CANTWELL, M.D., M.R.C.P.I.
University Medical Tutor, St. Vincent's Hospital

AND

J. A. MEHIGAN, M.Ch., B.Sc., F.R.C.S.I.
University Surgical Tutor, St. Vincent's Hospital

The Budd–Chiari syndrome is a disease entity which follows occlusion of the hepatic veins. Originally described by Budd in 1845 and subsequently by Chiari in 1899, it had been recorded in 116 cases up to 1952. Later reports have referred to involvement of the inferior vena cava in addition to the hepatic veins. The aetiological factors are numerous (Palmer, 1954).

Thrombotic complications being relatively frequent in polycythaemia vera, it is not surprising that the syndrome should have been recorded in that condition. Nevertheless, Sohval (1938) states that the hepatic veins are the rarest thrombotic site in polycythaemia—the first case having been described by Oppenheimer in 1929, and not more than 10 cases had been reported up to 1938.

A case is reported which presented the features of the chronic phase of the syndrome as described by Budd and by Chiari, due to hepatic-vein thrombosis in polycythaemia vera.

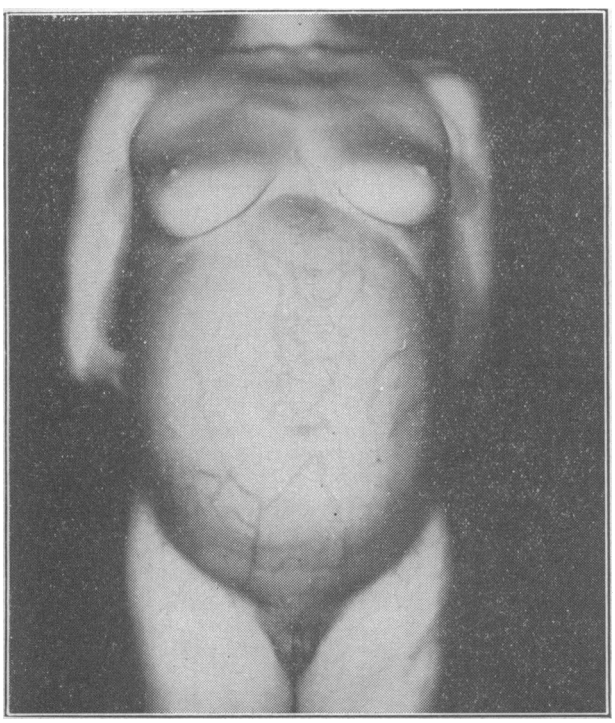

FIG. 1.—Infra-red photograph showing abnormal venous pattern. Note also external genitalia.

Case Report

A woman aged 22 was admitted to St. Vincent's Hospital in December, 1954. She was an only child and there was no family history of polycythaemia or of any significant illness. Her present history of polycythaemia dated from five years before admission, when she complained of severe pain in the back and in the region of the left shoulder. She had a haematemesis at that time and was admitted to her local hospital, where she was told she had liver trouble. Subsequently she developed marked varicosities in her lower limbs and also generalized dependent oedema. She visited her practitioner again with a view to treatment of the varicose veins, and he referred her for further investigation to Mr. Dermot Kennedy, of Cashel, who subsequently referred her to one of us.

On examination she was found to be an undersized but well-nourished girl with a cyanotic hue. She had marked varicosities in the lower limbs but none in the abdominal wall. She had had amenorrhoea for two years, and the external genitalia were somewhat hypertrophied (see Fig. 1). The cardiovascular and respiratory systems were normal. The abdomen was greatly distended. The liver was enlarged three to four finger-breadths and its surface was firm but not tender. The spleen was also greatly enlarged. There was no ascites. Other systems were normal.

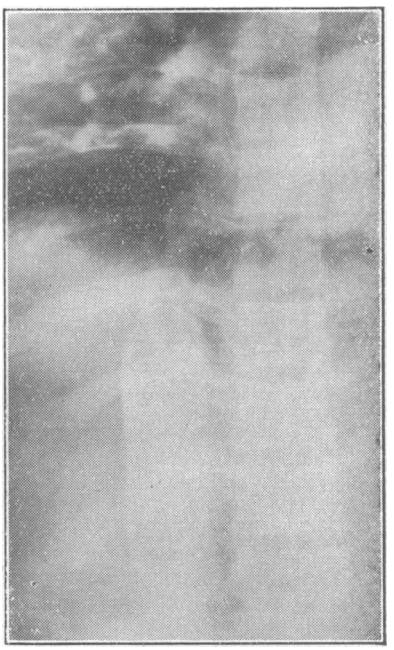

FIG. 2.—Venogram of the inferior vena cava showing coning of recanalized vena cava.

Laboratory Investigations. — On admission her haemogram showed 8,700,000 red cells/c.mm. (174% of normal), average diameter 7.5 μ; haemoglobin, 16.6 g./100 ml. (101%); colour index, 0.57; haematocrit, 63%; M.C.H.C., 26%; M.C.V., 72 cubic microns. There were 6,400 leucocytes (within normal limits) and 500,000 platelets per c.mm. Liver-function tests were as follows: total protein, 7 g./100 ml.—albumin 4.75 g., globulin 2.25 g. (electrophoresis showed slight increase in the gammaglobulin fraction); direct van den Bergh, negative (total bilirubin, 1.75 mg./100 ml.); alkaline phosphatase, 26 K.-A. units; prothrombin time, 36 seconds, or 25% of normal (following administration of 30 mg. of vitamin K for three days the reading was 28 seconds, or 45% of normal); bromsulphthalein test (45 minutes; 5 mg./kg.) showed a retention of 70%. The Wassermann reaction was negative, and fibrinogen estimation, E.S.R., blood sugar, serum cholesterol and calcium, and urinary 17-ketosteroids were all normal. Infra-red photography displayed dilated veins on the anterior abdominal wall (Fig. 1). E.C.G. was normal.

X-ray examination showed the lungs and cardiac shadow to be within normal limits, and screening produced no evidence of constrictive pericarditis. A barium swallow disclosed oesophageal varices. A venogram of inferior vena cava showed "coning" below the diaphragm (Fig. 2). A dilated azygos vein was suspected, but intracostal venography, with the technique described by Tori (1954), was not successful.

Laparotomy was performed with a view to liver biopsy and portal venography. This confirmed the diagnosis of portal hypertension, and the venogram showed intrahepatic obstruction (Fig. 3). Liver biopsy was reported as follows: Sections show only a portion of one portal tract containing a bile duct. The liver cells appear normal; apart from a few cells showing fine vacuolation, a normal finding in biopsy material. There is no evidence of inflammation or of fibrosis. No hepatic veins are included in the specimen.

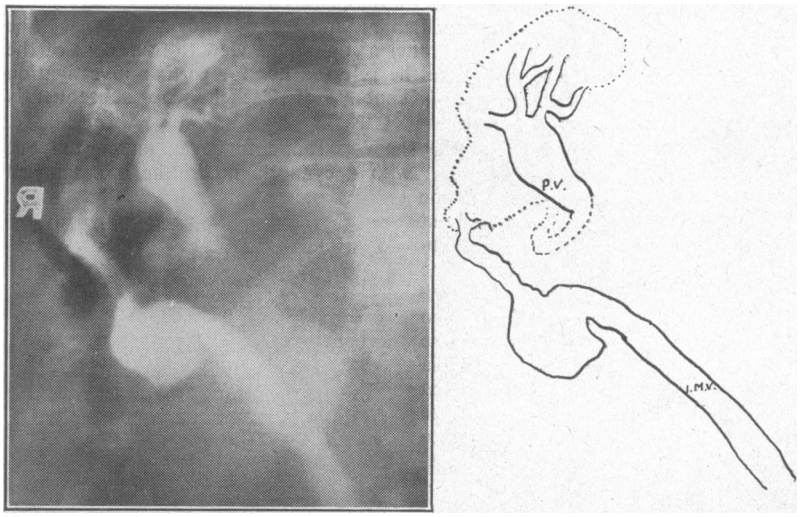

FIG. 3.—Interior mesenteric venogram showing intrahepatic portal obstruction with grossly distended veins. P.V.=Portal vein. I.M.V.=Inferior mesenteric vein.

It was decided to treat the polycythaemia first, and accordingly the patient was transferred to St. Luke's Hospital under Dr. O. Chance; she was there given 5 millicuries of ^{32}P, resulting in a much improved blood picture after six weeks: red blood cells, 3,600,000 (72% of normal); haemoglobin, 11.6 g./100 ml. (73%); colour index, 1; haematocrit, 37%; M.C.H.C., 31%; leucocytes, 1,280 (normal distribution) and platelets, 116 per c.mm. Liver-function tests also showed improvement, particularly the bromsulphthalein, which now gave 15% retention.

At this stage it was apparent that the polycythaemia had been adequately controlled but that further problems still existed. These were portal hypertension and the possibility that the hypersplenism secondary to it would affect the peripheral blood picture.

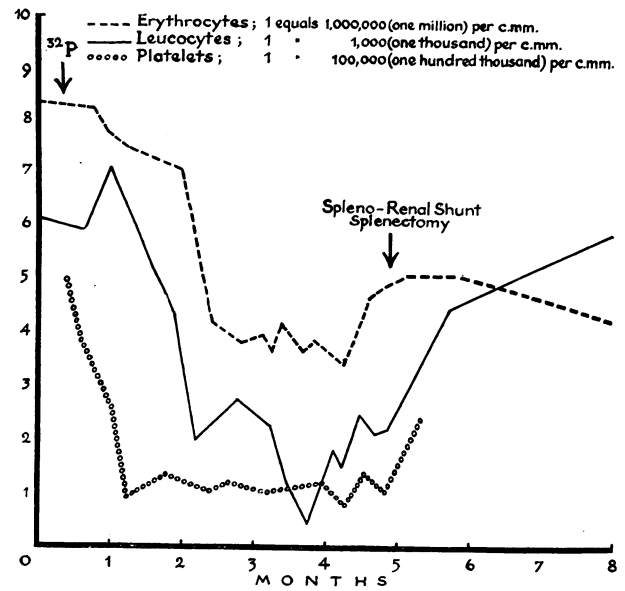

FIG. 4.—Effect of ^{32}P and operation on erythrocytes, leucocytes, and platelets.

Accordingly a splenectomy with spleno-renal shunt was performed on May 27, 1955, through an anterior midline incision. There was no ascites. The liver was nodular and moderately enlarged. The spleen was also enlarged and adherent to the diaphragm and abdominal wall posteriorly. The splenic vein was distended and thickened at the portal end. There was, however, no perivenous (portal) fibrosis. An area of thickening or calcification was felt on the right side of the inferior vena cava behind the liver.

The spleen was isolated and removed. The left renal vein was exposed and an end-to-side spleno-renal anastomosis was carried out. The post-operative course was uneventful. The patient was on a low-protein diet for 48 hours before and for four days after operation, and was given a broad-spectrum antibiotic as prophylaxis against neurological sequelae.

The histological report on the *spleen* was as follows: "Sections show some atrophy of the Malpighian corpuscles, marked fibrosis of the pulp, numerous haemorrhages, and many siderotic nodules giving a strongly positive reaction for iron. This is typical of well-marked portal hypertension. Sections from splenic vein show several thrombi in various stages of organization."

Post-operative Investigations.—Red blood cells, 5,000,000 (100% of normal), average diameter 6.9 μ; haemoglobin, 13.12 g. (82% of normal); colour index, 0.82; haematocrit 43%; M.C.H.C., 26%; M.C.V., 72 cubic microns; leucocyte count, 4,480 per c.mm. (distribution within normal limits); platelets, 265,000 per c.mm. The albumin/globulin ratio was 3:2.5 (total protein 5.5 g. per ml.); thymol turbidity, 2.5 units; prothrombin time was 80% of normal. Bromsulphthalein test was not repeated, as a sensitivity test was strongly positive. The blood picture changes during treatment are illustrated graphically in Fig. 4.

The clinical position seven months after operation was as follows: The abdominal distension had decreased and the varicosities in the leg were apparent only in the erect position. There had been no further haematemesis, although oesophageal varices were still present. The liver was still enlarged (+2) and the abdominal wall collaterals previously visible after infra-red photography were absent. The liver-function tests showed a moderate improvement and the blood picture remained normal.

Discussion

The Budd-Chiari syndrome appears most commonly in young adults, and the number of correct ante-mortem diagnoses is small. Amongst the reported causes of the syndrome are trauma, pregnancy, peritonitis, carcinoma of the gall-bladder, malignant growth in the inferior vena cava, thrombophlebitis of the inferior vena cava, actinomycosis, hepatoma, hepatic abscess secondary to Pick's disease, sickle-cell anaemia, and polycythaemia vera.

The clinical picture varies, depending on the extent and rapidity of the onset of the vascular occlusion. There may be a sudden extensive occlusion, giving an acute type of picture with sudden pain in the right hypochondrium, back, and shoulders, muscle guarding, and hepatic tenderness. Not infrequently death occurs in hepatic coma. The chronic type, associated with hepato-splenomegaly, varies in the clinical picture according to the rapidity of occlusion, the degree of recanalization, and the presence of collateral circulation which occurs subsequently.

The presenting symptoms will also vary, depending on whether both the hepatic veins and the inferior vena cava are involved, and on the degree of recanalization. With major involvement of the vena cava these will be varicose veins and dependent oedema. In addition, symptoms of portal hypertension are evident in all chronic forms of the syndrome.

The clinical picture may have to be considered in the differential diagnosis of such conditions as hepatic cirrhosis, hypersplenism, constrictive pericarditis, portal vein thrombosis, splenic vein thrombosis, and the Banti syndrome. Radiology, particularly venography, both portal and vena caval, is a further aid to diagnosis. It is noteworthy that both ascites and jaundice are unusual findings in these cases.

The collateral flow is via the lumbar azygos, hemiazygos, and vertebral and oesophageal veins. The extent of the collateral blood drainage will depend on the extent of the thromboses and the degree of recanalization of major veins.

Assessment of hepatic function will show varying degrees of improvement, depending on the degree of venous occlusion and periportal fibrosis present. At necropsy varying histological pictures have been disclosed, depending on the length of time that the condition has been in existence. There may be congestion, central necrosis with atrophy, fibrosis, and a compensatory hypertrophy as occurs in many liver diseases. Two other types of hepatic involvement in polycythaemia vera, apart from that due to this syndrome, have been reported. The first, described by Mosse (1914), is hepatic cirrhosis; the second, hepatic enlargement due to chronic hyperaemia.

Up to a short time ago the diagnosis of the Budd-Chiari syndrome was only of academic importance, but in recent years there have been many advances in medical and surgical therapy which may benefit these cases. In the acute stage the place of anticoagulants in those cases believed to be due to a pure thrombotic venous lesion has yet to be established. In the chronic stage the problem is of a different character. The hepatic veins are relatively inaccessible, but no doubt we will soon see the surgeon interested in vascular diseases making a direct approach to this area. At present, however, the most satisfactory procedure is one that endeavours to meet the portal hypertension which ultimately ensues in these cases, and which indeed gives rise to these symptoms which bring the patient under medical care. Here assessment must be made of liver function, by biochemistry and biopsy, and of the degree of portal hypertension by the presence of oesophageal varices and direct or indirect portal venography followed by a vena-caval venogram. These investigations should precede such surgical measures as porto-caval or spleno-renal shunts. Catheterization and venography of hepatic veins has also been used in the condition (Brink and Botha, 1955).

Surgical intervention has, to date, had a high mortality. Thompson (1947) states that of nine patients operated on eight died, but no details are given of the procedures which were carried out.

Jonas and Lawrence (1954), however, have reported a case in detail—that of a 19-year-old patient who presented with the syndrome (chronic). In this, following a vena-caval venogram which showed coning below the diaphragm and collateral vessels, a direct approach was made on the inferior vena cava through the chest. But the patient, who had manifest evidence of portal hypertension, died shortly after the operation. They concluded that recourse to surgery should be avoided in type B—that is, chronic forms of the syndrome. We feel that this is not so.

Norris (1956) suggests an alternative approach. He describes a case in which ligation of the hepatic artery was carried out. We feel that an operative venous shunt (porto-caval or spleno-renal) is a more logical measure, as the danger to life is from oesophageal varices, not from hepatic congestion. Such a shunt also encourages the possibility of recirculation through the vertebral and azygos veins.

Surgery has been made safer in these cases owing to better understanding of hepatic function and metabolism. Recent work has shown that a low-protein diet before and after the operation period plus a broad-spectrum antibiotic has reduced the possibility of liver failure and coma, which may otherwise ensue.

There are many factors worthy of comment regarding polycythaemia vera itself. It may occur in young adults, and its natural history is usually prolonged. Vascular complications, which are usually thrombotic, occur particularly in the first decade. Leukaemia and myelosclerosis occur in the second decade particularly. Furthermore, anaemia may arise from haemolysis.

^{32}P has been used extensively in treatment, sometimes combined with venesection in severe cases. The results of therapy are encouraging; remissions lasting up to a year are reported. Though leukaemia and myelosclerosis may occur after radiation, the incidence of these complications, which is about 8% after ^{32}P, is not increased as compared with cases not treated by this means. However, the incidence of vascular complications falls from a 50% rate in the untreated to about 5% in the treated cases.

Summary

A case of the Budd-Chiari syndrome occurring in polycythaemia vera is described. The relevant literature is briefly reviewed. The value of radiology in the investigation of this syndrome is stressed. Treatment of the primary haematological condition with ^{32}P was carried out. Subsequently a spleno-renal shunt and splenectomy were performed. The patient appears to be much improved.

We are grateful to Mr. D. Kennedy, Dr. O. Chance, Dr. L. O'Connell, and Dr. T. D. O'Farrell for their co-operation. We are also indebted to the departments of radiology and of pathology, St. Vincent's Hospital, and the department of photography, Dr. Steevens' Hospital, for assistance in investigating the case.

ADDENDUM.—The patient has just returned to hospital (July, 1956) and is in very good health, not complaining of any serious symptoms. She still has oesophageal varices, probably carrying collateral blood return. Prothrombin content is now normal, although the liver is still somewhat enlarged.

REFERENCES

Brink, A. J., and Botha, D. (1955). *Brit. J. Radiol.*, **28**, 330.
Budd, G. (1845). *Diseases of the Liver*, p. 147. J. Churchill, London.
Chiari, M. (1899). *Beitr. path. Anat.*, **26**, 1.
Jonas, E. G., and Lawrence, I. H. (1954). *Brit. J. Surg.*, **41**, 628.
Mosse, M. (1914). *Z. klin. Med.*, **79**, 431.
Norris, T. St. M. (1956). *Lancet*, **1**, 232.
Oppenheimer, B. S. (1929). *Trans. Ass. Amer. Phys.*, **44**, 338.
Palmer, E. D. (1954). *Ann. intern. Med.*, **41**, 261
Sohval, A. R. (1938). *Arch. intern. Med.*, **62**, 925.
Thompson, R. B. (1947). Ibid., **80**, 602.
Tori, G. (1954). *Brit. J. Radiol.*, **27**, 16.

TREATMENT OF CHRONIC MYELOID LEUKAEMIA WITH MERCAPTOPURINE

BY

JAMES R. FOUNTAIN, M.D., M.R.C.P.Ed.
Medical Tutor, Department of Medicine, the General Infirmary at Leeds

In previous reports (Burchenal *et al.*, 1953; Fountain, 1954, 1955) the effectiveness of mercaptopurine (6-MP; "puri-nethol") as a therapeutic agent in acute leukaemia has been assessed. Preliminary observations suggested that it might also hold a place in the treatment of chronic myeloid leukaemia and that by the use of maintenance therapy prolonged remissions might occur (Fountain, 1955). This paper presents my experience of treating 16 unselected patients with chronic myeloid leukaemia during the past two and a half years.

Materials and Method

The diagnosis of chronic myeloid leukaemia was based on examination of the peripheral blood. In patients with advanced disease bone-marrow studies were carried out