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 com-

plications, 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.

³²P 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 ³²P, 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 ³²P 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*, **i**, 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

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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

routinely in order to ascertain whether the disease had passed into an acute terminal phase.

The initial dosage of mercaptopurine was similar to that employed in the treatment of acute leukaemia—namely, 2.5 mg. per kg. body weight, calculated to the nearest 25 mg. amount. Thus adults received 150 to 200 mg. daily in divided doses of 50 mg. As the leucocyte count fell to normal treatment was either stopped temporarily or reduced until an optimum maintenance dose of between 50 and 150 mg. daily was obtained.

Five patients had received radiotherapy, to which three (Cases 8, 12, and 15) had become resistant, and one had had urethane prior to mercaptopurine. Ten had not previously been treated. All were treated initially in hospital, and thereafter were seen at the out-patient department at intervals of usually a month. Blood studies were made three times weekly during the early stages of treatment and less frequently after satisfactory maintenance therapy had been achieved.

Results of Treatment

The results of treatment are recorded in the accompanying Table. Of the 16 patients at various stages of the disease, including one in the acute terminal phase (Case 8), a response was observed in 15, the other patient (Case 16) dying of a cerebral thrombosis the day after the start of treatment.

Symptomatic Improvement

Only 2 of the 15 patients receiving full courses of treatment failed to show any sustained improvement after mercaptopurine therapy. One (Case 15) had previously been given deep x-ray therapy and had reached a terminal refractory stage. The spleen and liver were reduced in size and the leucocyte count fell from 10,000 to 2,400 per c.mm. Anaemia persisted, however, and there was no subjective improvement. The other patient (Case 14), although showing initial improvement, relapsed rapidly and thereafter required repeated blood transfusions. He had received no previous treatment and was regarded as a therapeutic failure. This patient died six months later after being improved temporarily by radiotherapy.

Objective Improvement

Regression of clinical evidence of the disease was observed in all 15 patients. Cases 3, 4, 6, 12, and 15 had massive splenomegalies, the lower pole of the spleen in each case extending to the pelvic brim. Following treatment, the spleen became impalpable in two (Cases 4 and 6), the tip just palpable in a further two (Cases 3 and 12), while considerable reduction in size was observed in the remaining patient (Case 15). One patient (Case 9), who had previously received radiotherapy and whose spleen had been removed at an earlier date, presented with a huge hepatomegaly associated with pain and discomfort. After mercaptopurine therapy the liver returned to a normal size, the symptoms cleared, and she thereafter remained symptom-free with no clinical evidence of the disease for a further 19 months. Another patient (Case 12) presented with an ulcer on the leg and was found to have a grossly enlarged spleen. The blood picture was typical of chronic myeloid leukaemia. The ulcer healed completely, the spleen regressed in size, and the blood picture improved following treatment with mercaptopurine. This patient previously failed to respond satisfactorily to radiotherapy.

In 11 out of the 15 patients (Cases 1 to 11) clinical improvement was regarded as complete, apart from a slight splenic enlargement in some. These patients returned to normal activities. Case 1, a hospital porter, has not lost a day's work since mercaptopurine therapy was instituted over two and a half years ago. The blood picture has been consistently normal and the only clinical evidence of leukaemia has been an occasionally palpable spleen. Two patients (Cases 2 and 4) have not been away from work for over 18 months, and a boy aged 9 years (Case 3) returned

to school after treatment and continued in good health 20 months later. Five women (Cases 5, 6, 7, 8, and 9), including one (Case 8) in the acute terminal phase, returned to full domestic duties. Remissions have varied in duration, details of which are presented in the Table.

Haematological Changes

Leucocytes

Mercaptopurine led to a fall in the white-cell count in all 15 patients. A delay in response of one to three weeks, comparable to that observed in acute leukaemia, was followed by a rapid fall in the number of leucocytes in the peripheral blood, a normal level being reached within a month of starting treatment. The diminution in leucocytes coincided with a reduction in the size of the spleen and liver, and other objective evidence of the disease. A fall to leucopenic levels has occurred in some instances, and it appears advisable to withdraw temporarily or to reduce the dosage of the drug as the count falls towards normal. When treatment was stopped the leucocyte count continued to fall for a period, but early experience indicated that, if a maintenance dose of mercaptopurine was not given as the count returned to normal, haematological and clinical relapse was likely to occur within a month of stopping treatment (Fountain, 1955). The optimum maintenance dose of mercaptopurine varied from 50 to 150 mg. daily. Occasionally the most satisfactory improvement was observed when the leucocyte count was higher than normal. At these levels (20,000–50,000 per c.mm.) the patients were maintained symptom-free and with good haemoglobin levels. It has been the rule to aim at obtaining the maximum clinical and haematological improvement, and generally when this has been achieved the leucocyte count has returned to between 5,000 and 15,000 per c.mm. On the few occasions when it has remained higher than normal no attempt was made to reduce it further.

The proportion of immature granular cells in the peripheral blood was observed to diminish as the leucocyte count fell, and in several cases prolonged disappearance of immature cells from the peripheral blood was noted.

Haemoglobin and Platelets

One of the essential criteria of an effective therapeutic agent for chronic myeloid leukaemia is its ability to produce a rise in the haemoglobin level. In the present series definite improvement in erythropoiesis and haemoglobin synthesis followed treatment with mercaptopurine in 12 patients. In one (Case 2) the initial haemoglobin level was within normal limits and was maintained at a normal level following treatment. In two further patients (Cases 14 and 15) no improvement occurred.

The rate of rise of haemoglobin varied. In seven patients not receiving blood transfusions prior to mercaptopurine therapy the increase averaged 3.2 g. during the first two months of treatment. In all, the maximum haemoglobin level was not reached until three to five months after the beginning of treatment.

Another essential property is that the therapeutic agent should not prevent normal platelet development. With the present dosage scheme, serious thrombocytopenia has not yet been observed to follow mercaptopurine therapy. A definite increase following treatment was observed in one patient (Case 3), the platelets rising from 25,000 per c.mm. to within normal limits. However, with the knowledge that excessive dosage with mercaptopurine may lead to marrow hypoplasia (Burchenal *et al.*, 1953) overdosage must be guarded against. The blood picture should be checked at regular intervals, for thrombocytopenia remains a potential hazard of mercaptopurine therapy.

Comment

Several agents are now available for the management of patients with chronic myeloid leukaemia. Most physicians still favour radiotherapy, including radioactive phosphorus,

as the treatment of choice in the early stages of the disease. An increasing interest in chemotherapy during the past ten years has, however, led to important developments in this field, and, although no chemical agent has yet been shown to be more effective than radiotherapy, several have been discovered which result in prolonged clinical and haematological improvement. On account of its freedom from side-effects busulphan ("myleran"; 1:4-dimethanesulphonyloxybutane) has probably proved the most satisfactory to date (Galton, 1953; Galton and Till, 1955; Blackburn *et al.*, 1956).

Experience with mercaptopurine is still limited, but the present study suggests that it will also be a useful therapeutic agent for the palliative treatment of chronic myeloid leukaemia. By the use of daily maintenance therapy prolonged remissions may be obtained. No toxic side-effects have been observed and dangerous thrombocytopenia has not occurred. Like all other chemotherapeutic compounds, including busulphan, overdosage must be guarded against on account of the possible danger of bone-marrow depression. Regular attendance as out-patients for blood examination is essential, and in the present series it has been the custom to see all out-patients at monthly intervals once a satisfactory stabilizing dose of mercaptopurine has been obtained. The early case, as would be expected, is probably the most amenable to treatment, although one patient in the acute terminal phase (Case 8) had a complete clinical

and haematological remission lasting six months following mercaptopurine therapy, while another (Case 12), after responding unfavourably to radiotherapy, was maintained in satisfactory health, with improvement in the blood picture, for nine and a half months.

Whether maintenance therapy may lead to early drug resistance, as suggested by Galton and Till (1955) as a possible disadvantage of this form of treatment, is doubtful. A longer period of follow-up, together with a comparison of survival time with those treated with radiotherapy, should help to elucidate this problem.

At the present stage, the ability of mercaptopurine to produce prolonged remissions, together with its low toxicity and ability occasionally to produce remissions in the acute terminal phase of the disease, suggests it will hold a place in the ever-growing therapeutic armamentarium for the management of patients with chronic myeloid leukaemia.

Summary

An account is given of the treatment with mercaptopurine (6-MP) of 16 patients with chronic myeloid leukaemia.

The initial recommended dose in adults is 150 to 200 mg. daily, followed by a daily maintenance dose of 50 to 150 mg. On this regime remissions of up to two

Details of Cases

Case No.	Age and Sex	Before Treatment with 6-MP				Dose of 6-MP (g.)	Six Months after Start of Treatment with 6-MP				Clinical Course from Start of Treatment
		Clinical Condition	Hb (g. per 100 ml.)	W.B.C. $\times 10^3$ (per c.mm.)	Previous Treatment		Clinical Condition	Hb (g. per 100 ml.)	W.B.C. $\times 10^3$ (per c.mm.)	Duration of Remission (Months)	
1	49 M	Fair. Spleen 8 cm. below costal margin	9.0	128	Nil	4.4 0.05-0.1	Good; working. Spleen 1 cm. below costal margin	13.6	10.5	30+	Good health
2	25 M	Good. Spleen 2 cm. below costal margin	14.5	75	Radiotherapy	3.5 0.05-0.1	Good; working. Spleen 1 cm. below costal margin	10.0	12.8	18+	" "
3	9 M	Poor. Weight loss; dyspnoea. Spleen to pelvis	6.9	300	Nil	5.75 0.05	Good; at school. Spleen 1 cm. below costal margin	13.0	7.0	20+	Good health. Platelets rose from 25,000 per c.mm. to normal
4	18 M	Fair. Spleen to pelvis	10.4	259	"	4.4 0.05-0.1	Good; working. Spleen not palpable	14.8	12.6	20+	Good health
5	42 F	Poor. Severe bronchitis. Spleen 12 cm. below costal margin	11.8	96	Urethane	3.05 0.05-0.1	Well for 6 months. Pain in chest	12.3	12.4	6	Died of respiratory infection
6	34 F	Poor. Haematemesis. Spleen to pelvis	4.9	204	Nil	2.9 0.05-0.1	Good. Spleen not palpable	13.6	6.3	12+	Good health
7	62 F	Poor. Abdominal pain. Haematuria. Spleen 4 cm. above pubis	8.3	275	"	5.15 0.05-0.1	Good. Fully active	14.6	11.2	12+	" "
8	56 F	Poor. Acute phase. Spleen 15 cm. below costal margin	8.2	152	Radiotherapy	4.1 0.05	Relapsing	12.3	27.3	6	Died 1 month after relapse
9	58 F	Fair. Abdominal pain. Liver 12 cm. below costal margin	12.0	128	Splenectomy. Radiotherapy	5.1 0.05-0.1	Good. Liver not palpable	13.6	24.1	19	Died following tuberculous infection
10	55 M	Good. Spleen 10 cm. below costal margin	10.9	58	Nil	3.85 0.05-0.15	Good. Spleen not palpable	14.2	9.6	10+	Good health
11	32 M	Good. Spleen to umbilicus	11.5	262	"	4.6 0.1-0.15	Good. Spleen not palpable. Working	14.6	22.4	8+	" "
12	49 M	Poor. Spleen to pelvis. Ulcer on leg. Poor response to radiotherapy	3.2	198	Radiotherapy	2.4 0.05-0.15	Good. Spleen 1 cm. below costal margin. Ulcer healed. Light work	12.2	40.8	9½	No response to busulphan terminally
13	48 F	Poor. Mitral stenosis. Heart failure. Spleen 5 cm. below costal margin	7.4	202	Nil	3.4 0.05-0.1	Fair. Relapsing	11.8	64.0	5	Died in acute phase 2 months after relapse
14	48 M	Fair. Spleen 2 cm. below costal margin. Liver to umbilicus	7.5	364	"	4.8 0.1-0.15	—	—	—	—	Poor response. Persistent anaemia. Temporarily improved by radiotherapy. Died 6 months later
15	58 F	Poor. Heart failure. Spleen to pubis. Liver 6 cm. below costal margin	7.7	10	Radiotherapy	2.4 —	—	—	—	—	Poor response. Terminal stage. Persistent anaemia. Died 3 months later
16	69 M	Poor. Heart failure. Spleen at umbilicus. Liver 15 cm. below costal margin	10.5	198	Nil	0.2 —	—	—	—	—	Died before treatment effective

and a half years have been observed. The patient in the early stages of the disease is likely to respond better to treatment, but of three patients (Cases 8, 12, and 15) who had become refractory to radiotherapy, two, including one in the acute terminal stage (Case 8), were benefited by mercaptopurine.

No unpleasant side-effects have been observed, and evidence of serious bone-marrow depression has not followed prolonged dosage with mercaptopurine. The need for regular blood examination is, however, stressed.

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ADDENDUM.—The patient in Case 6 has since died following admission to hospital with widespread haemorrhage. There was leucopenia and thrombocytopenia, and marrow depression secondary to mercaptopurine therapy seemed the likely explanation.

REFERENCES

- Blackburn, E. K., King, G. M., and Swan, H. T. (1956). *British Medical Journal*, 1, 835.
 Burchenal, J. H., Murphy, M. L., Ellison, R. R., Sykes, M. P., Tan, T. C., Leone, L. A., Karnofsky, D. A., Craver, L. F., Dargeon, H. W., and Rhoads, C. P. (1953). *Blood*, 8, 965.
 Fountain, J. R. (1954). *N.Y. Acad. Sci.*, 60, 439.
 — (1955). *British Medical Journal*, 1, 1119.
 Galton, D. A. G. (1953). *Lancet*, 1, 208.
 — and Till, M. (1955). *Ibid.*, 1, 425.

ADRENAL VIRILISM TREATED WITH STEROIDS

BY

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Congenital adrenocortical hyperplasia is manifested as pseudohermaphroditism in females and macrogenitosomia praecox in males, both conditions being due to excess of adrenal androgens and being associated with increased urinary excretion of 17-ketosteroids. If the adrenal disturbance arises after the fourth month of foetal life, by which time the external genitalia have developed, the result in the female is virilism, characterized by hirsutism and hypertrophy of the clitoris. Wilkins and his colleagues (1950, 1951, 1952a, 1952b), the first to treat the condition with cortisone, observed a prompt fall in the 17-ketosteroid excretion and a striking improvement in the clinical features. These changes are due to the inhibitory effect of cortisone on the secretion of corticotrophin, which is responsible for the hyperplasia and the excessive production of adrenal androgens (Bartter *et al.*, 1951). The effects of long-term cortisone treatment of congenital adrenocortical hyperplasia have been described (Wilkins *et al.*, 1952a, 1952b; Goldberg, 1954), but there are few reports of such treat-

ment in patients in whom virilism developed later in life. Bishop *et al.* (1952), Hubble (1952), and Bastenie *et al.* (1953) have described cases treated for a short time with cortisone.

Segaloff *et al.* (1955), taking advantage of the very slow absorption of hydrocortisone acetate when injected intramuscularly, described the beneficial effects of this preparation in adrenal virilism when injected as infrequently as once a week or even once a fortnight.

More recently Δ^1 unsaturated forms of both cortisone and hydrocortisone, known as prednisone and prednisolone respectively, have been produced. They are much more active than the parent steroids but have little or no effect on the blood electrolytes. Kupperman *et al.* (1955) compared the effect of oral cortisone and prednisone in the treatment of adrenal virilism and concluded that prednisone is the steroid of choice, since they found that it was three to four times more active than cortisone and did not induce sodium retention.

The following four cases of virilism due to adrenocortical hyperplasia are reported with particular reference to the effects of treatment with cortisone, hydrocortisone acetate, prednisone, and prednisolone.

Case 1

The patient was a boy aged 3½ years. Excessive growth of the penis and the appearance of pubic hair were observed when he was aged 2. On examination his height was 3 ft. 6 in. (106.6 cm.) and weight 3 st. 3 lb. (19 kg.). The penis was enlarged and there was scanty pubic hair (Fig. 1); both testes were in the scrotum and were of normal size. Radiological examination of the skeleton showed a bone age of 11 years. Radiological examination of the pituitary fossa and tomograms of the adrenal regions were normal. Serum sodium and potassium were normal. The daily 17-ketosteroid excretion over a period of ten days ranged from 11.9 to 25.6 mg. per 24 hours (mean: 17.5 mg.). The intramuscular injection of 100 mg. of cortisone acetate on three alternate days caused the 17-ketosteroid excretion to fall to 1.5 mg. per 24 hours, thereby suggesting the presence of adrenocortical hyperplasia rather than a tumour.

FIG. 1.—Showing hypertrophy of penis and slight pubic hair in Case 1.

Treatment.—In September, 1954, treatment with cortisone was started in doses of 25 mg. by mouth three times daily. With this dosage the 17-ketosteroid excretion was maintained at 1 to 3 mg. per 24 hours, but it rose to 7.2 mg. when the dose was reduced to 25 mg. twice daily. In January, 1956, the 17-ketosteroid excretion was 2.9 mg. per 24 hours, the patient having received cortisone, 25 mg. three times daily, continuously for the previous eighteen months without any toxic effects.

Results.—During the period of treatment the height increased by 4 in. (10 cm.); the penis remained the same size and the pubic hair partly disappeared.