Complications

Resistance to Breathing

In discussing the treatment of unconsciousness attention should be drawn to the importance of minimizing the resistance to breathing imposed by the use of such devices as endotracheal tubes and oxygen-therapy apparatus. It is essential that a patient, particularly one whose respiration is depressed, should not be required to make more effort to breathe than is necessary. If such effort is called for the patient becomes physically exhausted, and if the effort required is too great he may be incapable of making it. As a result the lungs are not filled quickly enough and oxygen intake is lowered. In addition, the intrapulmonary negative pressure at the height of inspiration may be greatly increased and the path prepared for pulmonary oedema. With an endotracheal tube, or any other gas pathway through which the patient is made to breathe, the factors which influence resistance are the diameter and length of the instrument and the presence of sharp corners—all being equally important. In any case, the use of endotracheal tubes, invaluable though it is in preventing respiratory obstruction, does not mean that further obstruction cannot occur. Kinking at the back of the pharynx and the passage of a tube into one bronchus are not infrequent and must be watched for.

Pulmonary Oedema

A common complication of the altered mechanics of respiration in the unconscious patient is pulmonary oedema. Most physicians and anaesthetists have had experience of the speed with which moist sounds, and even frothy sputum, appear in the respiratory tract of such a patient. To understand why pulmonary oedema readily appears in these circumstances it is necessary to indicate briefly the normal equilibrium across the alveolar membrane which keeps liquid within the circulatory system. This consists of a balance of forces. On the one hand there is the pressure within the alveoli, falling a little at each inspiration and returning to atmospheric pressure during expiration; on the other side of the membrane is the vascular system. A filtration force of 10 mm. Hg, the systolic pressure, tries to force fluid out into the alveoli, while the osmotic pressure of the blood proteins, of about 20–25 mm. Hg, acts in the reverse direction. When respiratory obstruction is present the intra-alveolar pressure falls unduly at each inspiration, tending to expel fluid. This is further enhanced if the patient has a right heart failure of any degree, leading to a high pulmonary arterial pressure, or has been injudiciously given blood transfusion or saline infusion. If in addition there is a general anoxia, the alveolar cells and the alveolar vessels also become anoxic, their permeability is increased, and a vicious circle created. Suction can clear fluid only from the trachea and main bronchi; it cannot empty the alveoli. Positive-pressure ventilation with an unobstructed airway can reverse this process. Confirmation of this view may be found in the growing practice nowadays of treating the respiratory depression of barbiturate overdose, the respiratory paralysis of poliomyelitis, and also the paralysis induced by curare in cases of tetanus, by means of tracheostomy, positive-pressure ventilation, and frequent suction. In these instances oxygenation is ensured, the respiratory tract kept clear, and pulmonary oedema prevented.

Summary

An outline is given of the main physiological problems common to unconscious patients whatever may be the underlying cause, and in particular those of interest to an anaesthetist.

Treatment resolves itself into ensuring adequate oxygenation by means of a clear airway, with some form of assisted or artificial respiration where indicated. The improved circulation, with fluid loss made good, combines with the improved oxygenation and respiratory

mechanics to prevent the altered dynamics across the alveolar membrane which leads to pulmonary oedema and may prove fatal. Many an unconscious patient who has been adequately treated for the underlying cause dies unnecessarily because these fundamental physiological requirements are not met.

TREATMENT OF LEUKAEMIA AND ALLIED DISORDERS WITH 6-MERCAPTOPURINE

BY

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Within the past ten years a number of chemical agents which produce temporary beneficial effects in leukaemia and allied diseases have been discovered. Their introduction has usually come about in one of three ways: (a) the observation that a compound being investigated for other reasons has a depressant effect on haemopoietic tissues—for example, nitrogen mustard and urethane; (b) the synthesis of compounds related chemically to substances already known to be effective, such as in the case of triethylene melamine, triethylene phosphoramide, and naphthyl-di-2-chlorethylamine (R.48); and (c) the synthesis of analogues of nucleic-acid precursors. It is on the last group that so much attention is now being focused. Undoubtedly the observation by Farber *et al.* (1948) that two folic-acid conjugates, pteroyl-diglutamic acid and pteroyl-triglutamic acid when given to children with acute leukaemia resulted in an acceleration of the leukaemic process gave considerable impetus to research in this particular field. The sequel was the synthesis of the 4-amino analogues of folic acid, aminopterin and amethopterin, which were found to suppress the growth of leukaemic tissue and produce temporary remissions in some children with acute leukaemia (*Proceedings of the Second Conference on Folic Acid Antagonists*, 1952).

With the knowledge that folic acid was essential for the synthesis of nucleic acid, antagonists of other nucleic-acid precursors have been prepared and tested for antileukaemic activity. 2:6-Diaminopurine, an analogue of adenine, has been shown (Burchenal, Bendich, *et al.*, 1949; Burchenal, Johnston, *et al.*, 1949) to prolong the survival time of mice with transplanted leukaemia. Burchenal, Karnofsky, *et al.* (1951) reported remissions in five of a series of 25 patients with acute leukaemia treated with this compound. Compounds containing the 2:4-diamino-pyrimidine moiety, including those with antimalarial activity (Falco *et al.*, 1949), were shown to be competitive antagonists of folic acid in the growth of *Lactobacillus casei* (Hitchings *et al.*, 1952), and in animals states indicative of folic-acid deficiency were observed. These findings suggested that such compounds might be effective in acute leukaemia, and it has been shown (Burchenal, 1954) that one such pyrimidine analogue, 2:4-diamino-5(3'4'-dichlorophenyl)-6-methylpyrimidine, produced occasional remissions in children with this disease. Farber, Foley, *et al.* (1953) have shown that a related series of compounds, the dihydrotriazines, have the property of temporarily inhibiting the growth of the leukaemic process in children.

Of the purine and pyrimidine derivatives discovered to date, the most effective in the treatment of leukaemia is the analogue of adenine and hypoxanthine, 6-mercaptopurine (6-MP). This substance, known by the proprietary name "purinethol," has been shown by Burchenal, Murphy, *et al.* (1953) to have produced good clinical and haematological remissions in 15 out of 45 children with acute leukaemia, and in another 10 patients partial remissions and clinical improvement. The same authors described occasional remissions in adult patients with the disease, and encouraging results in patients with chronic myeloid leukaemia.

The present study is based on experience gained in the treatment of 26 patients since June, 1953. Of these, 13 had acute leukaemia, 7 chronic myeloid leukaemia, 2 chronic lymphatic leukaemia, 2 multiple myeloma, 1 mycosis fungoides, and 1 erythroderma secondary to an underlying reticulosis of undetermined type.

PLAN OF TREATMENT

Patients were unselected and none received other forms of chemotherapy previous to, or as a supplement to, treatment with 6-MP. Blood transfusions and antibiotics were prescribed as the need arose. All patients received the initial course in hospital, and clinical and haematological examinations were performed daily or on alternate days. The bone marrow was examined at intervals, generally of two weeks, in cases of acute leukaemia. Patients who improved sufficiently were later followed up in the out-patient department and had blood examinations at weekly or fortnightly intervals.

The dosage of 6-MP was based on that suggested by Burchenal, the initial dose being approximately 2.5 mg. per kg. body weight. Thus a 5-year-old child was started on 50 mg. and an adult on 150–200 mg. per day, measured to the nearest 25 mg. The same dosage scheme was used both for patients with acute and those with chronic leukaemia, and in all instances the daily amount was divided into doses of 25 or 50 mg. given over the 24-hour period.

RESULTS OF TREATMENT

A. Acute Leukaemia

The criteria for a complete remission were strict and consisted of: (a) disappearance of all clinical evidence of disease and return of patient to full activity; (b) return of peripheral blood picture to normal; and (c) return of bone marrow to apparent normality with disappearance of blast cells or reduction to less than 10% of total cell count. A partial remission was said to be present when clinical and haematological improvement was considerable but fell short of the criteria of a complete remission.

Of 13 patients, seven responded to treatment. Five (two children and one adult with acute lymphoblastic leukaemia, and two adults with acute myeloblastic and acute monocytic leukaemia respectively) developed a complete clinical and haematological remission lasting from seven weeks to seven months. One patient, a child aged 3½ years, relapsed after remission lasting three months, but further treatment resulted in a second remission of four months' duration. Resistance to therapy has been observed following relapse, and in only one case has 6-MP been effective a second time. One adult and one child showed temporary, partial clinical and haematological improvement, while six patients (three adults and three children) failed to respond to treatment, four dying within the first week.

Illustrative Cases

CASE 1: ACUTE LYMPHOBLASTIC LEUKAEMIA.—A boy aged 3½ years was admitted to the General Infirmary at Leeds on June 20, 1953. Five weeks previously mumps had been diagnosed, and he then got rapidly worse. He lost appetite and pain in the legs prevented him from walking. Increased pallor was noticed and the temperature was at times raised.

On admission he was anaemic, and there were enlarged lymph nodes in the cervical, axillary, and inguinal regions, also numerous small scalp tumours. The skin, throat, and mouth appeared healthy; the liver and spleen were not palpable. There was no pyrexia.

Blood studies supported a diagnosis of acute lymphoblastic leukaemia. On June 26 blood findings were: Hb, 6 g. per 100 ml.; R.B.C., 1,900,000 per c.mm.; reticulocytes, 1.9%; platelets, 60,000 per c.mm.; W.B.C., 4,800 per c.mm. (blast cells 17%, lymphocytes 83%). The tibial bone marrow was highly cellular and replaced by lymphoid cells, of which 56% were primitive cells with the characteristics of lymphoblasts, while the rest were more or less mature lymphocytes. Packed red cells were immediately transfused, raising the haemoglobin level to 13.5 g. On the same day 6-MP therapy, 50 mg. by mouth daily for nine days, was started. On July 5 this was increased to 75 mg. daily for five days, and during the next two days a further 75 mg. was given. 6-MP was stopped on July 11, after a total of 0.9 g. had been given. During treatment the child's condition remained good, pain in the legs was moderate, and he was afebrile. On July 14 the lymph nodes and scalp tumours were impalpable, and the white cell count had fallen to 850 per c.mm. and the haemoglobin to 9.6 g. Leucopenia persisted for three weeks and was followed by haematological remission.

On August 1 the leucocyte count was 4,000 (polymorphs 55%, lymphocytes 45%) and the platelet count 169,000 per c.mm. Blast cells in the tibial bone marrow had decreased to 6.4%; lymphocytes were 17.2%, myeloid cells 46.4%, and erythroid cells 30.0%, and the marrow was less cellular. The presence of erythroid elements was reflected in the rising haemoglobin level and red cell count, which on August 5 were 12.2 g. per 100 ml. and 4,000,000 per c.mm. respectively.

The patient was discharged on August 11. Physical examination revealed no abnormality, his appetite was good, and he regained full activity. Full clinical and haematological remission continued for three months, when relapse occurred. He was readmitted to hospital, and a second course of treatment with 6-MP for seven weeks again led to a complete remission lasting four months, during which a daily maintenance dose of 25 mg. 6-MP was prescribed. He had now become resistant to 6-MP, and A.C.T.H. was substituted. Although he has since been persistently leukaemic, his clinical condition has been fairly good. He has now survived over a year since the disease was diagnosed.

CASE 2: MONOCYTIC LEUKAEMIA (NAEGELI TYPE).—A 44-year-old baker was admitted to St. James's Hospital, Leeds, on June 9, 1953, with a four-weeks history of lumbar pain and of sweating and dyspnoea on exertion. Examination showed widespread ecchymoses, and two small skin tumours in the xiphisternal region. Sacral oedema was present; the liver was palpable 6 cm., and the spleen 5 cm., below the costal margin. The temperature was normal; no other physical abnormalities were found. A chest radiograph was normal. Biopsy showed the skin tumours to be due to leukaemic infiltration. The blood count on June 11 was: Hb, 8.5 g.; R.B.C., 2,800,000 per c.mm.; reticulocytes, 1%; platelets, 66,000 per c.mm.; W.B.C., 6,800 per c.mm. (blast cells 11%, myelocytes 11%, neutrophils 30%, eosinophils 11%, basophils 1%, lymphocytes 22%, monocytes 14%). The sternal bone marrow showed: blast cells, 59%; myeloid cells, 12%, erythroid cells, 8.5%; lymphocytes, 15%; other cell types, 5.5%. Megakaryocytes were scanty. Many of the primitive blast cells were monocytoid, the appearance suggesting a Naegeli-type monocytic leukaemia.

Treatment with 6-MP, 100 mg. daily by mouth for seven days, was begun on June 15. On June 22 the patient had severe dyspnoea owing to a large left-sided pleural effusion, and 2 pints (1.1 litres) of haemorrhagic fluid was removed. The dose was then increased to 200 mg. daily. Whole blood was transfused on the fifth day of treatment, raising the haemoglobin level to 10.5 g. No clinical or haematological change occurred during the first three weeks of treatment. On July 8 the patient felt much better, the lumbar pain had disappeared, and his appetite improved. The size of the liver

and spleen had not changed, however, and a large pleural effusion was still present. The haemoglobin level had fallen and more whole blood was transfused. The leucocyte count was 4,200 and the platelet count 85,000 per c.mm. The leucocyte count continued to fall, and treatment was stopped on July 14, when leucocytes numbered 1,200 per c.mm.; a total dose of 5.3 g. of 6-MP had been given. He was now symptom-free; the liver was impalpable, and the lower pole of the spleen could be felt only on deep inspiration. The remaining skin tumour had disappeared, but fluid was present in the left pleural cavity and a further 2 pints was removed on July 13. On July 14 the sternal bone marrow was hypocellular and blast cells had decreased to 10%.

The platelet count three days after stopping treatment rose to 192,000 per c.mm., and thereafter remained normal. Leucopenia persisted for two weeks, the leucocyte count then rising to normal. On July 29 findings on physical examination were normal and the blood picture was as follows: Hb, 11.5 g.; R.B.C., 3,800,000 per c.mm.; reticulocytes, 1%; platelets, 250,000 per c.mm.; W.B.C., 5,700 per c.mm. (neutrophils 78%, eosinophils 2%, lymphocytes 16%, monocytes 4%). The sternal bone marrow was still hypocellular, but the differential count was much improved: blast cells, 3.6%; myeloid cells, 47.6%; erythroid cells, 16.4%; lymphocytes, 13.6%; degenerate cells, 18.8%.

The patient was discharged on August 1 without maintenance therapy. For seven weeks after cessation of treatment he was symptom-free and carried out normal activities. A chest radiograph one week after discharge was normal. In early September relapse occurred and treatment with 6-MP was restarted. The disease was now, however, completely refractory to therapy and the patient died on October 8, 1953. A graphic record of the patient's progress is shown in Fig. 1.

CASE 3: ALEUKAEMIC LYMPHATIC LEUKAEMIA.—A 62-year-old housewife was admitted to the General Infirmary at Leeds on July 23, 1953, with a ten-weeks history of increasing pallor, lassitude, loss of appetite, and dyspnoea on exertion. Temperature 100.4° F. (38° C.). She was anaemic, with large lymph nodes in axillae and groins. The liver was palpable 5 cm., and the spleen 12 cm., below the costal margin. Slight sacral oedema and crepitations at both lung bases were detected. There were no other physical abnormalities. Blood findings were: Hb, 7.8 g.; R.B.C., 2,800,000 per c.mm.; platelets, 119,000 per c.mm.; W.B.C., 1,900 per c.mm. (polymorphs 36%, monocytes 2%, lymphocytes 62%). A percentage of the lymphocytes had nucleoli. Sternal bone marrow was moderately cellular; 66.4% of cells were of the lymphoid series, about half being lymphoblasts. The rest were equally divided between the myeloid and erythroid series. The picture was that of aleukaemic lymphatic leukaemia.

Packed red cells were transfused on July 26, and treatment with 6-MP, 200 mg. daily, was begun on August 7. On August 17 she felt better and her appetite improved. No change was seen on physical examination, but four days later the liver, spleen, and lymph nodes began to get smaller. Dosage was reduced to 100 mg. daily on August 24, and discontinued seven days later, a total of 4.2 g. having been given. Now the spleen was impalpable and the liver edge could be felt only on deep inspiration. A few small, fleshy lymph nodes remained in the axillae. Physical examination was otherwise negative, temperature was normal, and the patient symptom-free.

Unlike in the first two cases, no significant reduction in white cell count followed treatment, and at no stage did it

fall below the initial figure. Improved distribution of leucocytes in the peripheral blood was, however, seen within ten days of the start of therapy. The haemoglobin level rose steadily, but there was little increase in platelets. At the end of treatment blood findings were: Hb, 11.2 g.; R.B.C., 3,700,000 per c.mm.; platelets, 100,000 per c.mm.; W.B.C., 3,100 per c.mm. (polymorphs 65%). The bone marrow was less cellular; few lymphoblasts (1.2%) were seen, and 33.6% of the cells were lymphocytes. Erythropoiesis was active and normoblastic, 34.0% of the cells being of this series, and the rest developing granulocytes.

The patient was discharged on September 5 feeling well. When seen ten days later improvement was maintained. The haemoglobin had risen to 12 g. and the platelet count to 275,000 per c.mm. She remained well, with a normal peripheral and bone-marrow blood picture, for seven months, being fully active and living a normal life. Maintenance therapy was not given during the remission, and since relapse in April, 1954, the disease has been refractory to further treatment with 6-MP.

CASE 4.—A man aged 41 was admitted to the General Infirmary at Leeds on April 7, 1954, with widespread purpura, epistaxis, and a large left pleural effusion. The liver and spleen were not enlarged. The blood picture was typical of acute myeloblastic leukaemia, with a total leucocyte count of 129,000 per c.mm., the majority blast cells. As he was very ill an attempt was made to induce an early response to 6-MP by a large initial dose (1 g. over the 24 hours) on April 8, followed by 200 mg. daily thereafter. The leucocyte count fell to 4,800 per c.mm. in four days with much clinical improvement. Treatment was stopped on April 14, when the leucocyte count was 2,000 per c.mm. Improvement continued, the pleural effusion cleared without paracentesis, and the enlarged lymph nodes receded. On May 1 blood findings were Hb, 12.2 g.; W.B.C., 5,400 per c.mm. (polymorphs 65%, lymphocytes 34%, monocytes 1%); platelets, 450,000 per c.mm. Sternal bone marrow: blast cells, 3.2%; myeloid cells, 43.4%; lymphocytes, 12%; erythroid cells, 39.2%; other cell types, 2.2%.

He was discharged on May 8 on a daily maintenance dose of 100 mg. of 6-MP. The remission has now lasted two months.

B. Chronic Myeloid Leukaemia

Of seven patients at different stages of the disease, including one in the acute phase, a varying response was observed in six; the other patient died of cerebral thrombosis a week after starting treatment. Improvement was

FIG. 1.

assessed on subjective, objective, and haematological changes following treatment.

Subjective improvement—increase in well-being, activity, appetite, and weight—was observed in four cases. Two others showed little subjective improvement, but there were a reduction in size of spleen and a fall in leucocyte count.

Objective improvement—diminution in size of spleen, lymph nodes, etc.—was observed in five cases. In only one case did the spleen fail to regress after prolonged treatment.

The leucocyte count fell in all six cases. In two cases erythropoiesis improved, but in another two no rise in haemoglobin level or red cell count occurred. Two patients had no significant anaemia.

Illustrative Cases

CASE 5.—A 49-year-old man had been well up to the day preceding his admission to the General Infirmary at Leeds on September 25, 1953, when he had a sudden attack of left abdominal pain with vomiting. He had a history of perforated peptic ulcer in 1945 and of partial gastrectomy in 1949. He was a pale, thin man, in obvious pain, and vomited repeatedly during examination. A large, rubbery, mobile lymph node was felt in the left axilla, and the spleen was palpable 8 cm. below the left costal margin. No other clinical abnormalities were found. Blood findings indicated chronic myeloid leukaemia and were as follows: Hb, 9.0 g.; R.B.C., 3,300,000 per c.mm.; reticulocytes, 2%; platelets, 300,000 per c.mm.; W.B.C., 128,000 per c.mm. (myelocytes 2%, metamyelocytes 17%, neutrophils 79%, eosinophils 1%, lymphocytes 1%). An occasional nucleated red cell was seen in the peripheral blood film. The sternal bone marrow was hypercellular with a marked preponderance of granular cells.

Treatment with 6-MP was begun on September 28. Within 48 hours of admission the abdominal pain and vomiting ceased, but tenderness of the left upper abdomen persisted for a week. The blood picture was unaltered until October 21, when the leucocyte count fell to 60,000 per c.mm. Two days later it was 44,000 per c.mm., and treatment was stopped, a total dose of 4.4 g. having been given. The spleen, which during the first three weeks had enlarged, became smaller. The patient was discharged on October 28, his progress being regularly followed. His condition remained satisfactory, with a rise in haemoglobin to 11.2 g., and he returned to work the following month. On November 30 the spleen was much larger and the leucocyte count had risen to 56,000 per c.mm. Treatment with 6-MP was restarted in a dose of 100 mg. daily, and after three weeks clinical and haematological improvement was again observed.

In view of previous experience and that of others a maintenance dose of 6-MP seemed necessary if a satisfactory clinical and haematological state was to continue for any length of time, therefore a dosage of 100 mg. and 50 mg. on alternate days was prescribed. On this the patient has remained well, the spleen and lymph nodes have been impalpable and leucocytes and haemoglobin have been kept at normal levels for six months, during which time he has been fully active and doing a normal day's work.

CASE 6.—In a spinster aged 58 chronic myeloid leukaemia was diagnosed in March, 1952. She had no treatment during the following year, but owing to splenic enlargement and discomfort a splenectomy was performed in April, 1953. Deep x-ray therapy was then given with temporary improvement. On December 4, 1953, she was admitted to the General Infirmary at Leeds complaining of tiredness, loss of appetite, abdominal pain and distension, and swollen ankles. The liver was enlarged 12 cm. below the right costal margin, and small discrete lymph nodes were felt in the axillae and inguinal regions. Anaemia was not clinically evident. Blood examination revealed: Hb, 12.0 g.; R.B.C., 3,700,000 per c.mm.; platelets, 210,000 per c.mm.; W.B.C., 128,000 per c.mm. (myelocytes 3%, metamyelocytes 12%, neutrophils 84%, lymphocytes 1%).

Treatment with 6-MP, 200 mg. daily, was begun on December 5, but there was a delay of nine days before it took effect. After 12 days the leucocyte count had fallen to 39,600 per c.mm., the patient felt better, and the liver was smaller, being palpable 6 cm. below the right costal margin. Treatment was now stopped, a total of 2.6 g. having been given, and she was discharged with instructions to attend for follow-up. No further improvement occurred during the following week, and treatment with 6-MP was restarted in a dose of 100 mg. daily. On December 30 she felt much better and had gained 7 lb. (3.175 kg.) in weight. The liver was, however, still 6 cm. below the right costal margin, and the leucocyte count had risen to 91,200 per c.mm. Increasing the dose to 150 mg. resulted in a fall in leucocyte count to 15,400 by January 11, when the liver edge was just palpable and she was symptom-free; haemoglobin was 13.5 g. and platelets 250,000 per c.mm.

This patient has been maintained on a daily dose of 50 or 100 mg. of 6-MP for six months, during which time she has been symptom-free and fully active. No objective signs of disease have reappeared and the blood picture has remained satisfactory. The patient's progress is shown graphically in Fig. 2.

CASE 7.—A 56-year-old housewife was admitted to St. James's Hospital, Leeds, on December 18, 1953, with a seven-years history of myeloid leukaemia treated by several courses of deep x-ray therapy, the last in October, 1953. Her main complaints were repeated vomiting, a dragging sensation in the left abdomen, loss of weight, sweating, and epistaxis. The spleen was firm and tender and extended to 15 cm. below the left costal margin, and the liver was palpable 2 cm. below the right costal margin. Blood examination showed the following: Hb, 8.2 g.; R.B.C., 2,300,000 per c.mm.; platelets, 225,000 per c.mm.; W.B.C., 152,000 per c.mm. (blast cells 8.5%, myelocytes 25.5%, metamyelocytes 8.0%, polymorphs 35.8%, lymphocytes 17.5%, monocytes 2%). Sternal bone marrow was hypercellular, with blast cells 74.0%, myeloid cells 21.6%, erythroid cells 3.2%, lymphocytes 0.8%, and other cells 0.4%. The findings were characteristic of the acute terminal phase of chronic myeloid leukaemia.

Treatment with 6-MP, 200 mg. daily, was started on December 18, and on December 23 blood was transfused,

FIG. 2.

raising the haemoglobin level to 11.3 g. per 100 ml. The leucocyte count fell after three days' treatment, and by two weeks had reached 13,000 per c.mm.; the patient felt stronger, vomiting and sweating had ceased, the liver was impalpable, and the spleen 9 cm. below the left costal margin. The dose of 6-MP was reduced to 100 mg. daily on January 2, and this was continued until January 14, when treatment was stopped, a total of 4.1 g. having been given in 27 days. By now the leucocyte count had fallen to 300 per c.mm., and the haemoglobin to 7.5 g., and the spleen was just palpable. More blood was transfused on January 22, and this raised the haemoglobin level to 11.7 g. The bone-marrow picture was also much improved: blast cells, 8.5%; myeloid cells, 47.5%; erythroid cells, 18.5%; lymphocytes, 24%; other cells, 1.5%. She was now well enough to get up, and although the leucopenia persisted for a month no complications resulted. The haemoglobin level was maintained without further blood transfusion, and clinical examination failed to reveal any of the usual findings of leukaemia. On February 2 she was discharged, and when next seen two weeks later she was symptom-free and doing a full day's domestic duties. Blood examination showed: Hb, 12.0 g.; R.B.C., 4,000,000 per c.mm.; platelets, 200,000 per c.mm.; W.B.C., 4,400 per c.mm. (polymorphs 80%, lymphocytes 20%). She was put on a daily maintenance dose of 50 mg. of 6-MP, and remained in good health for four and half months after completing the initial course of treatment. Relapse then occurred, and the disease was found to be resistant to further treatment with 6-MP. She died on June 26, 1954.

C. Chronic Lymphatic Leukaemia

Two patients (aged 73 and 56 years) with chronic lymphatic leukaemia showed no clinical or haematological evidence of improvement after one month's treatment with 6-MP.

D. Miscellaneous Group

Two patients with multiple myeloma, and one with erythroderma considered to be due to a reticulosis of undetermined type, failed to benefit from a month's treatment with 6-MP. One patient with mycosis fungoides appeared to be temporarily improved.

TOXICITY

An important property of 6-MP is its low toxicity. Apart from depressing bone-marrow function it has not resulted in any definite toxic side-effects in the present series. Burchenal has stated (Burchenal, Murphy, *et al.*, 1953) that gastro-intestinal symptoms may occur; but, whereas there has been vomiting in some of the cases now reported, on no occasion was it definitely attributable to the drug, nor did it necessitate interrupting treatment. Ulceration of the mouth, which is so common after treatment with aminopterin or amethopterin, was not observed. Severe thrombocytopenia attributable to 6-MP occurred in only one case—of multiple myeloma—but on no occasion was there haemorrhage. Haemorrhage due to overdosage with 6-MP has, however, been described by Burchenal and his co-workers, and must always be considered as a possible complication. Leucopenia is expected to follow treatment of acute leukaemia, and should not give rise to undue anxiety. No evidence was seen of megaloblastic erythropoiesis, which is an occasional sequel of anti-folic-acid treatment.

DISCUSSION

A study of the results obtained in this limited series supports the finding of Burchenal and others that 6-MP may produce temporary remissions in a percentage of cases of acute leukaemia and modify the course of chronic myeloid leukaemia. Chronic lymphatic leukaemia, however, appears to be unaffected by it.

Until a much larger number of patients have been treated no definite information can be obtained as to age group and morphological type of acute leukaemia likely to be most responsive to treatment with 6-MP. All that can be

said is that adults as well as children have had remissions following treatment, and that remissions have been noted in the lymphoblastic, myeloblastic, and myelo-monocytic types of acute leukaemia. Thus 6-MP may be more versatile in its action than aminopterin and amethopterin, which are generally accepted as ineffective in adults and most effective in acute lymphoblastic leukaemia. As with other chemotherapeutic agents used in the management of acute leukaemia (Fountain, 1954), the remissions in patients who respond are only temporary, and, although a second response may occur, the disease gradually becomes resistant to further treatment.

A delay of 7 to 28 days was usual before the drug took effect, which suggests that four patients who died within the first week of treatment had received an inadequate therapeutic trial. In two cases a fall in leucocyte count with clinical improvement occurred, however, within a few days of starting treatment. One patient (Case 7), in the acute terminal phase of chronic myeloid leukaemia, received a routine course of treatment. The other (Case 4) had an extremely acute form of myeloblastic leukaemia with considerable haemorrhagic manifestations. In the hope that the rate of action of the drug would be increased an initial "loading" dose of 1 g. in the first 24 hours was given. Dramatic clinical and haematological improvement followed within the next four days. Although its value remains to be proved—another patient failed to respond rapidly to large doses—such a dosage scheme seems worth trying, as it is obvious that with such a disease as acute leukaemia the rapidity of action of the therapeutic agent is of prime importance. It may be of interest that both patients who responded rapidly to 6-MP had a high initial leucocyte count (over 100,000 per c.mm.), the predominant cell in each case being the primitive blast cell.

Whether patients who experience a complete remission should receive a daily maintenance dose of 6-MP remains to be answered, but from the limited data in this series it seems likely that maintenance therapy may not greatly prolong the remission. Continuous therapy seems essential in chronic myeloid leukaemia if the beneficial effect of the drug is to be maintained, for it has been my experience that in its absence clinical and haematological relapse may follow within a month of stopping treatment.

CONCLUSION

It has been shown that a new compound, 6-mercaptopurine, allied to the folic-acid analogues has been discovered with which dramatic remissions may be obtained in a percentage of cases of acute leukaemia. Unlike aminopterin and amethopterin, 6-MP has a low toxicity and can be used with little danger of added discomfort to the patient—an important consideration in the management of cases of leukaemia. That the remissions are only temporary suggests that the value of 6-MP as a research compound will at present outweigh its clinical usefulness. However, with the knowledge that aminopterin and amethopterin, A.C.T.H. and cortisone, and 6-MP may all produce clinical and haematological remissions in acute leukaemia, it seems desirable to give patients the advantage of such chemotherapy. Symptomatic relief may be obtained, and by sequential use these drugs may offer several months of useful life.

Although more patients with chronic myeloid leukaemia must be treated before the ultimate value of 6-MP is known, initial observations suggest that it will have its place in the management of this disease. The experience of Burchenal and his colleagues that 6-MP benefited two patients in the acute terminal phase of the disease has been supported by a case in this series, and it may be that one of its main uses in chronic myeloid leukaemia will be in the later acute stage of the disease.

SUMMARY

A purine antagonist, 6-mercaptopurine, has been shown to produce complete clinical and haematological

remissions in five out of thirteen patients, of various ages, with acute leukaemia, and partial remissions in two others. The remissions were only temporary, and resistance to further therapy with 6-MP eventually resulted.

Six patients with chronic myeloid leukaemia showed a varying response. One patient in the acute terminal phase had a remission lasting four and a half months.

Two patients with chronic lymphatic leukaemia, two with multiple myeloma, and one with reticulosis of the skin did not respond, while one patient with mycosis fungoides obtained some improvement.

6-MP is of low toxicity and no serious complications have followed its use.

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ERYTHRAEMIC MYELOSIS TERMINATING IN ERYTHROLEUKAEMIA

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Malignant hyperplasia of the erythron, analogous to leucoblastic proliferation in leukaemia, was first described by Copelli (1912) and later defined as a pathological entity by Di Guglielmo (1923, 1926, 1937) when he recorded three cases as examples of true "erythraemic myelosis." These cases, with others published on the Continent, have been exhaustively reviewed by Di Guglielmo (1945, 1946) and Leitner (1949).

As with leukaemias, acute and chronic forms are recognized. Acute erythraemic myelosis (Di Guglielmo, 1945), pursuing a fatal course of one or two months, presents with severe anaemia, irregular fever, splenomegaly, slight hepatomegaly, and erythroid hyperplasia, with atypical erythroblasts in the blood, many of which

fail to mature. The chronic form (Duesberg, 1940; Heilmeyer and Schöner, 1941; Di Guglielmo and Quattrin, 1942) runs a longer course, up to two years, and the circulating erythroblasts are orthochromatic and less atypical.

In this country four examples of the chronic form appear to have been recognized, three of which have been published in Britain (Israëls, 1939; Neumark, 1948; Emery, 1951; Mackenzie and Stephenson, in *Blood*, 1952). A subacute form, terminating in acute granulocytic leukaemia, has also been recorded (Discombe and Nickol, 1954).

If in the case described below the patient had died within the first two months a diagnosis of acute erythraemic myelosis would have been accepted, but repeated blood transfusions sustained life for a further four months, during which the erythroleukaemic nature of the disease became manifest. In this respect our case closely resembles those of Verloop, Deenstra, and van der Hoeven (1952) and Discombe and Nickol (1954), lending support to the theory that erythraemic myelosis and erythroleukaemia are probably unusual variants in the onset of acute leukaemia.

Case Report

A single woman aged 30 gave up work in a soda-water factory early in August, 1953, because she felt very tired and breathless on the slightest exertion. Two weeks later she developed lumbar pain, headache, and nausea with vomiting.

On admission on August 25 she was very pale, had a temperature of 102° F. (38.9° C.) and fetid breath but no ulceration of the gums or fauces. The liver was palpable and the spleen descended five fingerbreadths in inspiration. There was no relevant personal or family history. Clinically she was considered to be a case of leukaemia, but subsequent blood and marrow pictures (see below) indicated erythraemic myelosis.

Owing to the severe anaemia she was given repeated blood transfusions, 26 pints (14.8 litres) in all, over a period of six months, the highest haemoglobin achieved being 78% (12.4 g.). Transient improvement followed each transfusion; vomiting ceased, the appetite returned, and the temperature subsided.

As her condition could not be maintained despite transfusions, liver, cyanocobalamin ("cytamen"), iron, vitamins, folic antagonists, and corticotrophin, it was decided to remove her spleen. This was done without incident on December 18. Improvement followed splenectomy, the haemoglobin remaining at 66% (10.5 g.), and in January, 1954, she was sent home on corticotrophin. She was now apyrexial, eating well, and gaining weight.

She was readmitted on February 19, 1954, with recurrent vomiting and pyrexia and the haemoglobin had now fallen to 42% (5.7 g.). Further transfusions had little effect and she continued to go downhill. Early in March a large gluteal abscess, following an injection of corticotrophin, was evacuated and 11 oz. (320 ml.) of pus obtained. The wound continued to discharge, and shortly before death on March 23 the haemoglobin had fallen to 16% (2.5 g.). Transfusions were now withheld, as she was obviously in the terminal stages of her illness.

Investigations

General.—Histamine-fast achlorhydria. Urobilinogen excess in urine but no haemosiderin in centrifuged deposit. Bile pigments scanty. Serum bilirubin, 1.2 mg. per 100 ml.

Blood.—Three representative blood counts are set out in the Table. Red cells showed marked anisocytosis, poikilocytosis, and moderate polychromasia. Platelets were scanty