chlorothiazide and relief of these symptoms. The symptoms of swelling were decreased, but this decrease was of little value, as the patients were not troubled by these symptoms and did not consider themselves improved until the irritability, depression, and headache had been relieved.

From a practitioner's point of view the only object is the relief of symptoms whatever their precise aetiology, and once this has been achieved the patient is cured. Organic disease must therefore be excluded and then an attempt made to provide symptomatic relief. Other workers have obtained high rates of cure with drugs of the progesterone type and with diuretics. In this present series of unselected patients the majority were much improved by meprobamate and a third by chlorothiazide.

The division of patients into those responding to one drug and those responding to another suggests various types of the premenstrual syndrome differing in aetiology and optimum treatment. The results of this study suggest that psychological factors are responsible for the symptoms in a large number of cases. Hormonal imbalance and water retention are probably of major importance in others. It is, however, impossible to differentiate one group from another on present evidence, and it therefore seems reasonable to start treatment with meprobamate, and if that is not effective to give chlorothiazide, progesterone, or a combination of drugs.

Summary

Earlier studies on the aetiology and treatment of premenstrual tension are reviewed, and a study of 30 consecutive patients in general practice is reported. All of these patients received treatment with chlorothiazide, meprobamate, ethisterone, dimethisterone, and a placebo. Over half of the patients obtained complete relief or marked improvement with meprobamate, one-third with chlorothiazide, and one-fifth with progesterone derivatives.

Possible conclusions to be drawn from the results of this series are discussed.

I thank Merck Sharpe and Dohme Limited for supplying chlorothiazide ("saluric") and identical placebo tablets, British Drug Houses Ltd. for supplying ethisterone and dimethisterone ("secrosteron") tablets, and John Wyeth & Brother Limited for supplying meprobamate ("equanil") tablets. I also thank Dr. B. W. Cromie for his help with the bibliography involved in this study.

REFERENCES

Argonz, J., and Abinzano, C. (1950). *J. clin. Endocr.*, **10**, 1579.
Bickers, W. (1958). *Virginia med. Monthly*, **85**, 613.
—— and Woods, M. (1951). *Tex. Rep. Biol. Med.*, **9**, 406.
Davis, M. E. (1958). *Med. clin. N. Amer.*, **42**, 257.
Fortin, J. N., Wittkower, E. D., and Kalz, F. (1958). *Canad. med. Ass. J.*, **79**, 978.
Greene, R., and Dalton, K. (1953). *Brit. med. J.*, **1**, 1007.
Greenhill, J. P., and Freed, S. C. (1941). *Amer. J. med. Ass.*, **117**, 504.
Hauser, G. A., Marti, M., and Wenner, R. (1959). *Geburtsh. u. Frauenheilk.*, **19**, 299.
Morton, J. H. (1950). *Amer. J. Obstet. Gynec.*, **60**, 343.
Nixon, W. C. W. (1956). *Practitioner*, **177**, 589.
Pennington, V. M. (1957). *Amer. J. med. Ass.*, **164**, 638.
Phillips, R. E. (1956). *Amer. Practit.*, **7**, 1573.
Rees, L. (1953). *Brit. med. J.*, **1**, 1014.
Stieglitz, E. J., and Kimble, S. T. (1949). *Amer. J. med. Sci.*, **218**, 616.
Sweeny, J. S. (1934). *Amer. J. med. Ass.*, **103**, 234.
Swyer, G. I. M. (1955). *Brit. med. J.*, **1**, 1410.

TOXIC COMPLICATIONS OF TREATMENT WITH 6-MERCAPTOPURINE

TWO CASES WITH HEPATIC NECROSIS AND INTESTINAL ULCERATION

BY

P. A. CLARK, M.R.C.S., L.R.C.P.
Senior House Officer

Y. E. HSIA, M.A., B.M., M.R.C.P.
Senior House Officer

AND

R. G. HUNTSMAN, M.A., M.B., M.R.C.P.
Senior Registrar

The Group Laboratory, Lewisham Hospital, London

6-Mercaptopurine (6-M.P.) in a dose of 2.5 mg./kg. body weight is an established treatment for acute leukaemia which, if successful, produces a remission in four to eight weeks. It is generally agreed to be innocuous though slow-acting (Bernard and Seligmann, 1954), toxic effects other than marrow aplasia being rare (Bodley Scott, 1958).

6-M.P. causes hepatic necrosis and intestinal ulceration in experimental animals (Clarke *et al.*, 1953; Philips *et al.*, 1954). In leukaemic patients the complication of liver damage ascribed to treatment with 6-M.P. rather than to the disease process itself has been reported (Burchenal *et al.*, 1953; Gaffney and Cooper, 1954; Frei *et al.*, 1958; McIlvanie and MacCarthy, 1959), but intestinal ulceration has not been specifically described as a complication of this treatment.

From a series of 34 cases of acute leukaemia treated at Lewisham Hospital with 6-M.P. since 1955, we now report two consecutive cases in which the patients died with hepatic necrosis and intestinal ulceration prior to any remission.

Case 1

A boy aged 5 years, weight 36½ lb. (16.6 kg.), was admitted to hospital on April 30, 1959, with a history of spontaneous bruising for one month, and bleeding from the gums for one week. His mother stated that she was twice *x*-rayed during pregnancy.

On examination he was found to have a palpable spleen but no enlarged lymph nodes. His haemoglobin was 48% (7.1 g./100 ml.), white-cell count 4,400/c.mm. (polymorphonuclear leucocytes 308, lymphocytes 2,068, myelocytes 44, promyelocytes 1,056, myeloblasts 704, Türck cells 176, unclassified cells 44/c.mm.). The platelet count was less than 10,000/c.mm. A diagnosis of acute myeloid leukaemia was confirmed by sternal marrow biopsy.

Treatment was started on April 30, but in view of his poor clinical condition it was thought unlikely that he would survive long enough to obtain a remission on 6-M.P. alone, and so he was given methotrexate (amethopterin) 1.25 mg. daily in addition to 50 mg. daily of 6-M.P. Methotrexate was withheld between May 20 and 27 because of gastro-intestinal bleeding, and was finally discontinued on June 3; 6-M.P. was continued at the same dose throughout until June 16. Fresh blood transfusions and antibiotics were given as indicated.

Minimal jaundice was first noticed on June 15, towards the end of his seventh week on 6-M.P., becoming obvious by the next day. The liver-function tests on June 16 showed: alkaline phosphatase 6 K.-A. units, direct bilirubin ++, indirect bilirubin 6.6 mg./100 ml., thymol turbidity

and flocculation were negative; electrophoresis of serum proteins was normal. The same day he developed blood-stained diarrhoea, lapsed into coma, and died.

Necropsy (Dr. L. Bitensky) was performed seven hours after death. The body weight was 30 lb. (13.6 kg.); he was emaciated, jaundiced, and had many skin haemorrhages. Subpleural, subepicardial, and bilateral renal haemorrhages were present; the lower lobe of the left lung was consolidated and contained multiple haemorrhages. The liver weighed 768 g., with subcapsular haemorrhages, but otherwise appeared macroscopically normal. No obstruction was demonstrated in the extrahepatic biliary system. The spleen weighed 97 g. The mesenteric and paratracheal lymph nodes were slightly enlarged. The stomach had petechial haemorrhages; the small intestine showed ulceration with haemorrhages, maximal in the terminal ileum.

Microscopically the liver tissue was severely damaged, there being large areas of early necrosis involving the central portions of the lobules; in some places this was very extensive, and only a few surviving liver cells remained near the portal tracts. Within the necrotic areas most of the liver cells were swollen and granular, and had lost their nuclei. The sinusoids in these areas were dilated, and in places the necrotic areas were haemorrhagic. There was no leucocytic response to the tissue necrosis; myeloid cells were not present; and the portal areas contained only occasional leucocytes (see Fig. 1).

The bone-marrow was hypoplastic, and consisted mainly of lymphocytes, fibroblasts, and histiocytes; very few normal haemopoietic cells were present. Areas of mucosal ulceration were confirmed in the ileum.

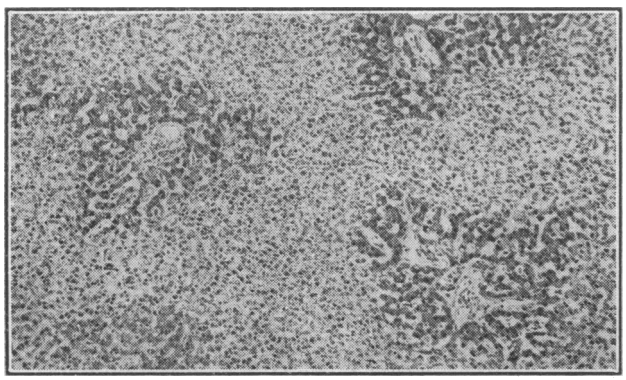

FIG. 1.—Case 1. Section of liver showing extensive centrilobular necrosis. (×60.)

Case 2

A haulage contractor aged 40, weight 164 lb. (74.4 kg.), was admitted to hospital on June 17, 1959, with a two-months' history of tiredness, dyspnoea, and loss of weight of 15 lb. (6.8 kg.). He had had a sore throat for three weeks, which responded temporarily to oral penicillin. There was no relevant past history.

On examination he was found to have a right-sided paratonsillar swelling, generalized enlargement of lymph nodes, and enlargement of the liver and spleen; purpura was present. His haemoglobin was 47% (7 g./100 ml.), total white-cell count 20,000/c.mm. (polymorphonuclear leucocytes 600, eosinophilic leucocytes 200, lymphocytes 4,000, monocytes 200, monocytoid leucocytes 2,000, myelocytes 800, premyelocytes 200, myeloblasts 7,600, unclassified cells 4,200, nucleated erythrocytes 200). The platelet count was less than 10,000/c.mm. A diagnosis of acute myeloid leukaemia was confirmed by sternal marrow biopsy.

Treatment was started on June 20 with 6-M.P. 150 mg. daily; this dose was readjusted to 200 mg. daily on June 24. Fresh blood transfusions and antibiotics were given as indicated.

On July 3 he began to complain of malaise, anorexia, and abdominal distension. By July 9 his symptoms had become worse, and he was tender in the right hypochondrium. Liver-function tests on July 16 showed: alkaline phosphatase 17 K.-A. units, direct bilirubin negative, indirect bilirubin less than 0.5 mg./100 ml., thymol turbidity and flocculation tests negative; serum albumin 3.3 g./100 ml., serum globulin 1.4 g./100 ml., electrophoresis of proteins was normal; serum glutamic-oxalacetic transaminase (G.O.T.) 92 units, serum glutamic-pyruvic transaminase (G.P.T.) 365 units. (The normal range for both is 20–100 units in this laboratory.)

Minimal jaundice was evident on July 17, in the fourth week of treatment. In view of the hepatic necrosis in the

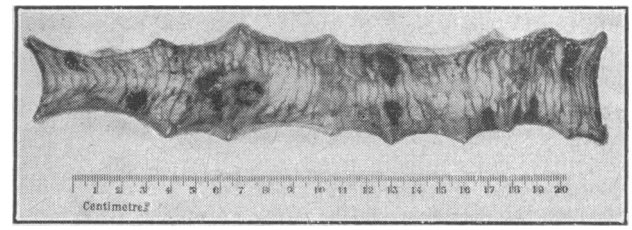

FIG. 2.—Case 2. Ileum at necropsy, showing multiple ulceration.

previous case, the dose of 6-M.P. was halved to 100 mg. daily on that day, and discontinued on July 22 because he had become obviously jaundiced. Liver-function tests on July 22 gave: alkaline phosphatase 15 K.-A. units, direct bilirubin ++, indirect bilirubin 4.2 mg./100 ml.; G.O.T. 60 units, G.P.T. 240 units. On July 24 the liver-function test results were: alkaline phosphatase 10 K.-A. units, direct bilirubin ++, indirect bilirubin 9.5 mg./100 ml., thymol turbidity and flocculation remaining negative; G.O.T. 40 units, G.P.T. 140 units. During that night he developed blood-stained diarrhoea for the first time, and died the following morning.

Necropsy was performed six hours after death. The body weight was 161 lb. (73 kg.); he was well nourished but jaundiced, with multiple skin haemorrhages. Bilateral multiple submucosal haemorrhages were present in the renal pelves. The liver weighed 3,230 g. and appeared somewhat darker than usual. No obstruction was demonstrated in the extrahepatic biliary system. The spleen weighed 870 g. The ileum (Fig. 2) contained multiple ulcers, maximal at the ileo-caecal junction; the remainder of the bowel was normal.

Microscopically the liver tissue had small centrilobular foci of necrosis scattered throughout its substance, but there was no generalized necrosis. The central cells of the lobules contained bile pigment. In the necrotic areas some of the hepatic cells had disappeared, and there were collections of red cells lying within the supporting framework of the lobule. Numerous immature cells of the

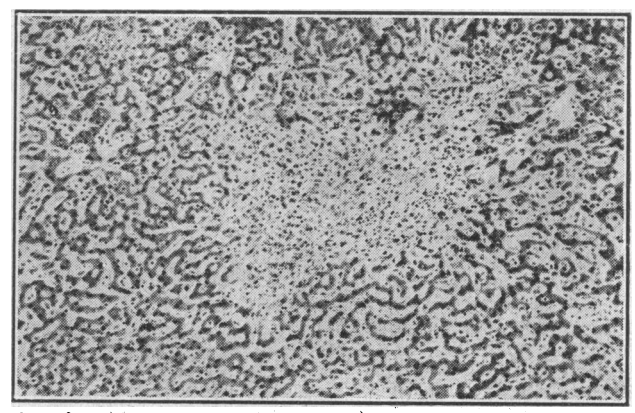

FIG. 3.—Case 2. Section of liver showing an area where necrosis is marked. (×60.)

myeloid series were present in the portal areas and scattered in the sinusoids. There was no leucocytic response to the tissue destruction in the necrotic areas (see Fig. 3).

The bone-marrow was hypoplastic, and consisted mainly of plasma cells, eosinophilic leucocytes, and degenerate cell forms. Areas of mucosal ulceration were confirmed in the ileum.

Discussion

It is clearly established from toxicity experiments on rats, mice, and dogs that 6-M.P. causes hepatic necrosis and intestinal ulceration as well as marrow depression; hepatic necrosis being unique to 6-M.P. among the purine analogues (Philips *et al.*, 1954), and it has been suggested that this hepatotoxic property may be intimately related to its mode of action on leukaemic tissue (Philips *et al.*, 1953).

In man, Burchenal *et al.* (1953) mentioned a case of carcinoma of the stomach given 6-M.P. which showed at necropsy widespread cancer, with focal atrophy and necrosis of the liver. Farber (1954) used 6-M.P. in 96 patients, and reported jaundice in 6, clearing after cessation of treatment. He stated that liver-function tests were inconclusive, but gave no further details. Gaffney and Cooper (1954) reported severe terminal jaundice in 2 of their 10 adult patients given 6-M.P., but said that at necropsy the liver sections did not explain the cause of jaundice. Frei *et al.* (1958), in a combined trial of 6-M.P. with methotrexate in 64 patients, reported jaundice in 10, 2 of whom had hepatic necrosis but also had septicaemia as a terminal complication. McIlvanie and MacCarthy (1959) reported "hepatitis" in 4 out of 29 cases treated with 6-M.P., methotrexate, and steroids. These four patients not only received the other drugs but also received at some time doses of 6-M.P. exceeding the accepted 2.5 mg./kg.—namely, 3.2, 3.75, 4, and 6.6 mg./kg. daily. Two of their cases had hepatic lesions similar to those in our cases; in another the jaundice had resolved before death; and necropsy was not made in the fourth.

In all their cases, in those of Frei *et al.*, and in our first case, methotrexate had also been given, which has itself been reported to produce jaundice and intestinal ulceration (Hertz *et al.*, 1958). Our second case is therefore noteworthy because he had been treated with no other cytotoxic drug or steroid.

The post-mortem histology in 25 of 34 cases treated with 6-M.P. in this hospital was reviewed. It showed four others in which similar histological features were present in the liver associated with terminal jaundice. One of these patients had been given busulphan, another corticotrophin, and a third cortisone. Five other patients died with terminal blood-stained diarrhoea, and at necropsy two of these had intestinal ulceration.

The frequency of these toxic effects therefore may be much greater than has been generally accepted. The early diagnosis of hepatic damage is a strong indication for withholding 6-M.P., since the extent of necrosis in our first case would seem to be incompatible with survival, whereas the lesser degree of necrosis in our second case might be attributed to earlier curtailment of 6-M.P. In Farber's experience, and that of McIlvanie and MacCarthy, timely withdrawal of the drug resulted in clearing of the jaundice.

The value of liver-function tests in early detection of hepatic damage seems to be limited. Detailed results published by McIlvanie and MacCarthy showed no consistent pattern, and in our cases the only significant abnormality was the raised G.P.T. in the second case.

Diagnosis of hepatic damage therefore must be made primarily on clinical grounds, nausea and tenderness in the right upper quadrant of the abdomen, as suggested by McIlvanie and MacCarthy, being an indication for stopping treatment before jaundice is manifest.

Summary

Hepatic necrosis and intestinal ulceration are unusual and grave complications of the treatment of acute leukaemia with 6-mercaptopurine.

Two fatal cases are reported in which both these complications occurred without a remission; in one of these, only 6-M.P. had been used.

A review of 34 cases of acute leukaemia treated with 6-M.P. at Lewisham Hospital showed four others with terminal jaundice and hepatic necrosis, and five patients who died with terminal blood-stained diarrhoea; two of these came to necropsy and were found to have intestinal ulceration. This suggests that the incidence of these complications may be higher than is generally accepted.

The serum glutamic-pyruvic transaminase was raised in the second case before the onset of jaundice. It is therefore possible that this test may be of value as an early sign of hepatic damage in such cases.

Jaundice or anorexia with tenderness in the right hypochondrium are suggested to be indications for withholding 6-M.P.

We are grateful to Dr. E. N. Allott, who suggested the publication of this report and for encouragement and advice; to Dr. C. A. Holman for his help and permission to publish his cases; to Dr. M. O. Skelton for his opinion and report on the histology; and to Mr. J. E. Andrews, who photographed the specimens.

REFERENCES

Bernard, J., and Seligmann, M. (1954). *Ann. N.Y. Acad. Sci.*, **60**, 385.

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.

Clarke, D. A., Philips, F. S., Sternberg, S. S., Stock, C. C., Elion, G. B., and Hitchings, G. H. (1953). *Cancer Res.*, **13**, 593.

Gaffney, P. C., and Cooper, W. M. (1954). *Ann. N.Y. Acad. Sci.*, **60**, 478.

Farber, S. (1954). Ibid., **60**, 412.

Frei, E., Holland, J. F., Schneiderman, M. A., Pinkel, D., Selkirk, G., Freireich, E. J., Silver, R. T., Gold, G. L., and Regelson W. (1958). *Blood*, **13**, 1126.

Hertz, R., Bergenstal, D. M., Lipsett, M. B., Price, E. B., and Hilbish, T. F. (1958). *J. Amer. med. Ass.*, **168**, 845.

McIlvanie, S. K., and MacCarthy, J. D. (1959). *Blood*, **14**, 80.

Philips, F. S., Sternberg, S. S., Clarke, D. A., and Hitchings, G. H. (1953). *Proc. Amer. Ass. Cancer Res.*, Abstracts **1**, 42.

—— —— Hamilton, L., and Clarke, D. A. (1954). *Ann. N.Y. Acad. Sci.*, **60**, 283.

Scott, R. Bodley (1958). *Brit. med. J.*, **1**, 1.

The mother and baby unit recently opened at West Middlesex Hospital provides accommodation for five mothers to stay in hospital with their children who are undergoing treatment. This fulfils a long-felt need for such accommodation in cases where, in the opinion of the paediatrician concerned, the separation of mother and child at a critical period in the child's illness would be harmful. In addition to cubicles for mothers and babies, a small day room or sitting-room and appropriate bathing and other facilities have been provided.