Hereditary Orotic Aciduria and Megaloblastic Anaemia: A Second Case, with Response to Uridine


Although orotic acid is an important precursor in the synthesis of pyrimidines (Figs. 1 and 6), only minute amounts are found in normal blood and urine (Smith and Baker, 1959; Lotz et al., 1963). The urinary excretion of large amounts of orotic acid was first reported by Huguley et al. (1959), occurring in a male child with a refractory megaloblastic anaemia.

Their patient was chronically ill with anaemia, repeated respiratory infections, and diarrhoea from the age of 3 months. Severe megaloblastic changes were found in several bone-marrow specimens, but there was no response to treatment with vitamin B₁₂, folic acid, pyridoxine, ascorbic acid, and iron. Although adrenal steroids improved the anaemia, megaloblastosis was unaltered. Crystalluria had been noted and identification of the excreted material as orotic acid led to the suggestion that there was a congenital defect in the pathway of de novo synthesis of pyrimidine nucleotides. This conclusion was supported by the response obtained to the administration of the pyrimidine nucleotides, uridylic and cytidylic acids, contained in a yeast extract. The nucleotides, given at the age of 2 years 6 months, produced a striking clinical improvement accompanied by a haematological remission and marked reduction in orotic acid excretion. However, the yeast extract was poorly tolerated, relapse occurred, and the patient died from generalized varicella aged 2 years 9 months.

Huguley et al. could find no previous report of a similar case and we are not aware of any subsequent account. This report describes the clinical features of a child who is believed to have the same disease and his response to treatment with the pyrimidine nucleoside uridine.

Case Report

The patient was born on 26 October 1961, the delivery being normal. His birth weight was 9 lb. 2 oz. (4.150 g.). He was
bottle-fed and sucked well. Initial weight gain was satisfactory. From about 3 months of age he was noted by his mother to be pale and to move and cry less than had her two other sons. At 1 year he made no effort to lift his head and shoulders and still did not sit unsupported. During this time he had no specific illnesses.

In November 1962, when aged 13 months, he was admitted to Kawakawa Hospital, North Auckland, with bronchopneumonia, which responded to treatment with chloramphenicol. The haemoglobin was 4.6 g./100 ml.; W.B.C. 2,400/c.mm.; reticulocytes were less than 0.5% and platelets 220,000/c.mm. The red cells showed anisocytosis. The urine was said to be normal. He was transfused and given iron by mouth for one month, after which his haemoglobin was 6.4 g./100 ml.

When he was 14 months old he was transferred to Whangarei Hospital, North Auckland, for further investigation. At this time he was pale and nutrition was poor. He was lethargic, made minimal movements, but did reach for objects. He seemed withdrawn, had no speech, and was sitting. He had a squint. There was no enlargement of liver, spleen, or lymph nodes.

Investigations at Whangarei Hospital.—Peripheral blood: haemoglobin 9.1 g./100 ml.; W.B.C. 3,300/c.mm. Bone-marrow aspiration: an active marrow with megaloblastic changes. Serum bilirubin 0.3 mg./100 ml.; Coombs test negative; serum iron 11 ug./100 ml. Total non-protein nitrogen 40 mg./100 ml.; total plasma proteins 6.9 g./100 ml. (albumin 4.4 g., globulin 2.5 g.); serum ceruloplasmin 15 mg./100 ml. Serum cholesterol 172 mg./100 ml.; Kahn and Laughead tests negative; toxoplasmosis dye and complement-fixation tests negative. Urine: a trace of protein; no reducing substances detected; ferric-chloride test negative; no abnormality detected in urate; no abnormal amino-acids. X-ray pictures of chest and skull and a barium meal were normal. Radiological bone age 12 months (chronological age 15 months).

Treatment at Whangarei Hospital.—In December 1962 he was given intramuscular iron (Imferon) 2 ml. daily for four consecutive days. There was no reticulocyte response although the serum iron increased to 85 ug./100 ml. One week after iron was begun he was given folic acid, 20 mg. by intramuscular injection, followed by 15 mg. daily by mouth for the next eight weeks. Eight days after folic acid was started vitamin B12 was given intramuscularly, 300 µg. as an initial dose followed by 11 injections of 100 µg. over the next two weeks. A gluten-free diet was begun in February 1963 and in the same month he was given pyridoxine 50 mg. daily for two weeks. A second bone-marrow examination still showed marked megaloblastic changes. Serum protein-bound iodine was low at 3 µg./100 ml., and in March 1963 L-thyroxine 100 µg. daily was given for one week. There was no reticulocyte response. He was then transferred to the Princess Mary Hospital for Children.

Admission to Princess Mary Hospital

On admission to our care at 1 year 5 months he weighed 21 lb. (9.5 kg.) (below the third percentile). He was slightly pale and had an expressionless facies (Fig. 2a). There was an alternating strabismus. His hair was pale and fine. He showed little interest in his surroundings, but did pick up and play with toys. He did not say words. He could not sit up, but was able to maintain a sitting position. There was no attempt to bear weight. Psychometric assessment indicated abilities within the 7- to 11-months range. Head circumference was 18½ in. (47 cm.). Blood-pressure was 110/80 mm. Hg. The spleen was just palpable. There were no other abnormalities on physical examination, in particular no glositis and no specific neurological findings.

Investigations

Peripheral Blood.—Haemoglobin 8 g./100 ml.; haematocrit 25%; mean cell haemoglobin concentration 32%; reticulocytes 2%; E.S.R. 13 mm. in one hour (Westergren); W.B.C. 5,000/c.mm. (neutrophils 42%, lymphocytes 52%, monocytes 6%). Film (Fig. 3a): The red cells showed a marked degree of anisocytosis and poikilocytosis. There were numerous macrocytes present, many strikingly large and oval in shape with long diameters up to 15 µ. Many macrocytes were hypochromic. Other cells were microcytic and irregular in shape. There were occasional polychromatohyal cells, stippled cells, Howell-Jolly bodies, Cabot’s rings, and nucleated red cells, the latter showing megaloblastic features. Multisegmented neutrophils and giant platelets were present.

Bone-marrow.—The marrow obtained in February 1963 was reviewed. The marrow was cellular and there was a reversed myeloid-erythrocyte ratio of 1:2. Two-thirds of the nucleated red cells showed severe megaloblastic changes and there were numerous giant myelocytes and metamyelocytes.

Other Investigations.—There was a histamine-fast gastric achlorhydria. Serum vitamin B12 580 µg./ml. (normal 140 to 900 µg./ml.). Serum folic acid 28 mg./ml. (normal 5.9 to 21 mg./ml.). Direct Coombs test negative. Gregerson’s test for faecal occult blood negative on two specimens. Serum levels of total proteins, albumin, globulin, calcium, phosphorus, and alkaline phosphatase were within the normal range. Urinary protein nil. Urinary deposit: W.B.C. 0-2/H.P.F.; R.B.C. nil/H.P.F.

Urinary Orotic Acid.—The similarity of the case to that described by Huguley et al. (1959) led one of us (D. M. O. B.) to examine the urine for the presence of orotic acid. Urine specimens were clear when fresh, but on standing for several hours a large amount of

<table>
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<th>Therapy</th>
<th>No. of Specimens</th>
<th>24-hour Orotic Acid Excretion</th>
<th>Range (g.)</th>
<th>Mean (g.)</th>
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<td>6</td>
<td>0:69–1:34</td>
<td>1-15</td>
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<td>0:56–0:79</td>
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<tr>
<td>3,000 mg./day</td>
<td></td>
<td></td>
<td>0:20–0:41</td>
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Fig. 1.—Chemical formula of orotic acid and terminology used for pyrimidine derivatives.

Fig. 2.—Hereditary orotic aciduria. (A) Patient aged 1 year 5 months, before uridine started. (B) Aged 2 years 9 months, after 14 months’ treatment with uridine, showing hair growth.
white flocculent precipitate developed. A feature of the deposit was the firm adherence of particles to the sides of glass containers. Microscopically the deposit consisted of colourless fine needle-shaped crystals (Fig. 4). Identification of the deposit as orotic acid was confirmed by Dr. James A. Bain, Emory University School of Medicine, Atlanta, Ga., according to criteria previously published (Huguley et al., 1959). Quantitative estimations also were based on the method described by Huguley et al. The 24-hour excretion before treatment varied from 0.69 to 1.34 g., with a mean of 1.15 g. (see Table), and a concentration of 0.22 to 0.3 g./100 ml. No attempt was made to estimate orotic acid in blood.

**Initial Treatment (Fig. 5)**

During a preliminary five-week period of observation the haemoglobin remained between 7.6 and 8.8 g./100 ml. and the reticulocyte count between 2 and 3%. Red-cell morphology remained markedly abnormal and a third bone-marrow aspiration on the day prior to beginning treatment confirmed that megaloblastosis persisted.

**Cytidylic Acid.**—The nucleoside uridine was selected as the agent for initial trial, but before this could be obtained 10 g. of the nucleotide cytidyl acid became available. Cytidyl acid was given by mouth for 12 days, 900 mg. (2.6 mMol)/day divided into six 150-mg. doses. The treatment was complicated by an Escherichia coli enteritis on the sixth day, which resulted in dehydration and loss of weight. Otherwise his condition was unchanged and haematological response was slight. The maximum reticulocyte count was 3.2% on the fifth day and haemoglobin reached 10 g./100 ml. on the twelfth day. There was no change in abnormal red-cell morphology. There was, however, an appreciable reduction in orotic acid excretion. Four 24-hour specimens collected during the 12-day period had a mean orotic acid content of 0.67 g. (58% of the pretreatment level). Ten days after discontinuing cytidyl acid orotic acid excretion had increased to 1.1 g./day.

**Uridine.**—Treatment with the nucleoside uridine was begun in May 1963, at an initial dose of 150 mg. five times daily—that is, 750 mg. (3.1 mMol)/day. This dose of uridine was maintained for 11 days, again without marked haematological response. After 11 days the haemoglobin had increased from 8 to 9.4 g./100 ml., but there had been no reticulocyte response and red-cell morphology was unchanged. Orotic acid excretion again decreased, three 24-hour urine specimens having a mean content of 0.74 g. (63% of the pretreatment level). On the eleventh day the dose of uridine was doubled to 300 mg. five times daily, a total of 1,500 mg./day. There was a definite haematological response. The reticulocyte count increased to a maximum of 5.4% on the fifth day, then decreased to remain below 1% subsequently. By the twelfth day haemoglobin had increased to 11.3 g./100 ml and remained above 11 g./100 ml. during succeeding weeks. The bone-marrow was examined on the seventeenth day of treatment at the higher-dose level and was now normal. Over several weeks the peripheral-blood film became near normal in appearance (Fig. 3b). The unusual hypochromic macrocytes disappeared but a small number of irregular microcytes persisted.

Accompanying the haematological remission there was an impressive clinical response. His colour, activity, and interest in his surroundings improved. Appetite increased markedly and there was a weight gain of 3 lb. (1,360 g.) in three weeks. Notably, there was a sudden spurt in the growth of his hair and nails, the latter requiring to be trimmed for the first time in six months.

![Fig. 3.—Peripheral blood. (A) Before treatment with uridine. (B) After six months' treatment with uridine. (Leishman. ×1,140.)](image)

![Fig. 4.—Orotic acid crystals in urine (×515). The crystals in this stored specimen are slightly larger than in the fresh state.](image)

![Fig. 5.—Changes in weight, haemoglobin, reticulocytes, and orotic acid excretion during the periods of observation and initial treatment.](image)
The higher dose of uridine further reduced orotic acid excretion. Nine 24-hour urine specimens were collected during the first month, in which 1,500 mg. of uridine was being given daily. Orotic acid excretion ranged from 0.19 to 0.41 g./day, with a mean of 0.3 g./day (26% of the pretreatment level). The dose of uridine was then doubled to 600 mg., five times daily to determine if excretion could be further depressed. There was no significant change by the eighth day, the urine still containing 0.2 g. of orotic acid. After 10 days the dose of uridine was returned to 1,500 mg. daily, and this was continued for the next eight months.

Subsequent Course

He made steady progress in his development. After two months of effective treatment he began creeping on his abdomen and was able to stand holding his cot. Just before 2 years he began to feed himself by spoon. At 2 years 2 months he began to say single words. He walked unaided at 2 years 5 months.

Weight increased rapidly to 32 lb. (14.7 kg.) after eight months' treatment—that is, from below the 3rd percentile to near the 90th percentile. His gain in height was less remarkable, reaching the 10th percentile at 2 years 4 months. Growth of hair and nails continued, although the hair remained short, sparse, and fine. Dental assessment at 2 years showed his teeth to be normal, apart from slight hypoplastic discoloration of the enamel.

His haemoglobin remained between 10 and 12 g./100 ml. After eight months' treatment macrocytes reappeared in the peripheral blood. A minority of erythroid cells in the bone-marrow were megaloblastic, although the appearances were not those of florid relapse. Because of the patient's rapid growth the dose of uridine, originally 150 mg./kg. body weight, now represented only 100 mg./kg., this being near the level previously found to be ineffective. The dose of uridine was increased to the former level of 150 mg./kg.—that is, 750 mg. t.d.s.—and nine days later the bone-marrow had returned to normal. He remained well and was discharged from hospital in April 1964 aged 2 years 6 months. Fig. 2b shows hair growth at the age of 2 years 9 months, after 14 months' treatment.

At 3 years he was active and progressing well. There had been further growth of hair. His weight was at the 90th percentile and his height about the 50th percentile. He had abilities at the 2-year-old level. His peripheral blood was normal and orotic acid excretion was approximately 0.5 g./day.

Points of Difference Between the Two Cases

Gastro-intestinal symptoms were never prominent in our patient, whereas J.M.R. suffered persistent diarrhoea. Both children had gastric achlorhydria, but this was histamine-fast in our patient and not in J.M.R. The deficiency of hair and nail growth prominent in our patient was not noted in J.M.R., but the renewal of growth with remission indicates that this was a further manifestation of the disease.

Nature of the Biochemical Defect

Megaloblastic anaemia is uncommon in infancy, but in our patient most of the accepted causes (Smith, 1960) could be excluded on the basis of history, relevant investigations, and failure of response to conventional therapy. Excretion of orotic acid provides the key to elucidation of the nature of the disease. The position of orotic acid as an intermediary in the de novo synthesis of pyrimidines was first established in bacteria and in some animal tissues (Carter, 1956; Hepple and Rabinowitz, 1958). The pathway summarized in Fig. 6 was generally assumed to be that responsible for the net synthesis of pyrimidines.

Huguley et al. (1959), assuming that similar pathways operated in man, suggested that a defect in either of the two sequential enzymes orotidyl pyrophosphorylase or orotidyl decarboxylase could result in the accumulation and excretion of orotic acid. The reduction in pyrimidine nucleotide synthesis through effects on nucleoprotein and coenzyme metabolism could account for the megaloblastosis and other clinical features of their case. The effect of administration of pyrimidine nucleotides would be to bypass this metabolic block.

Confirmation that the synthesis of orotic acid in man occurred through similar pathways was obtained after the death of J.M.R. (Smith and Baker, 1959). The two suspect enzymes, orotidyl pyrophosphorylase and orotidyl decarboxylase, were then studied in his family and reduced activity of both enzymes...
was found in the erythrocytes of the parents and two of the three siblings (Smith et al., 1961; Fallon et al., 1962). The results for orotidyl decarboxylase were confirmed in leucocytes, but these cells were unsatisfactory for assay of pyrophosphorylase. The results strongly suggested that the parents and the two siblings were heterozygous for an autosomal recessive trait, which in the homozygous state would be characterized by further reduction or absence of these two enzymes.

Our patient has provided the first opportunity for study of the presumed homozygous state using these techniques. Additional information has been gained from his response to treatment.

Therapeutic Approach.—Reference to Fig. 6 indicates the relevance of determining the effect of administration of orotic acid or orotidine, as a response to either would imply significant activity of orotidyl decarboxylase. Unfortunately, the cost of giving the theoretically effective dose of each is prohibitive, and, furthermore, it is likely that parenteral administration would be required. Either of the nucleotides, uridylic acid or cytidylic acid, probably would have been effective, but the nucleoside uridine was preferred on the grounds of being substantially cheaper, and, by analogy with other mammalian systems, presumably convertible to uridylic acid in vivo. The response obtained with uridine confirms that this material can be utilized, but does not contribute further information on the basic enzyme defect. Suppression of orotic acid excretion during remission parallels the finding in the previous case and supports the suggestion of Huguley et al. that there might be a negative feedback control on pyrimidine biosynthesis (Fig. 6), similar to that which has been demonstrated in bacterial systems (Yates and Pardee, 1956).

Other Biochemical Investigations

These have been carried out at several centres in the United States and only preliminary results are reported here.

1. Enzyme Studies (Smith et al., 1964).—No activity of orotidyl pyrophosphorylase and orotidyl decarboxylase was detected in red cells from our patient during relapse and in remission. There was no decarboxylase activity demonstrable in leucocytes, but pyrophosphorylase estimations were unsatisfactory in these cells. Conversely, increased activity of two enzymes earlier in the pathway, aspartate transcarbamylyase and dihydroorotase, was found in the red cells prior to treatment. These enzymes returned to normal during remission.

2. Urinary Metabolites (Bain and Huguley, to be published).—The presence of orotic acid was confirmed and increased excretion of two orotic acid precursors, carbamyl aspartic acid and dihydroorotic acid, was demonstrated. Orotidine was present at approximately 5 to 10 times the normal level.

3. Tissue Cultures (Howell, Klinenberg, and Krooth, to be published).—A satisfactory diploid-cell line has been established in tissue culture from a skin biopsy taken from our patient using methods previously described (Krooth and Weiberg, 1961; Krooth et al., 1962). Preliminary experiments have revealed grossly reduced levels of both orotidyl decarboxylase and orotidyl pyrophosphorylase in these cultured cells. The addition of either cytidine or uridine to the medium greatly stimulates cell growth.

Conclusions.—These preliminary results confirm the previous suggestion of a homozygous state characterized by defects in two enzymes in the pyrimidine pathway. There is, however, evidence for some activity of both enzymes, although at greatly reduced levels. Studies in tissue culture showed detectable levels of orotidyl decarboxylase. A small amount of pyrophosphorylase activity is suggested by the finding in the urine of orotidine, presumably derived from orotidyl acid.

Increased activity of enzymes earlier in the pathway of pyrimidine synthesis and return to normal during treatment gives direct evidence for the existence of a feedback controlling mechanism. This increased enzyme activity correlates with an increased excretion of precursors of orotic acid and with the fact that the daily excretion of orotic acid by the homozygotes exceeds estimates of the normal rate of pyrimidine synthesis (Weissman et al., 1962). In the presence of a near complete block in the major pathway of pyrimidine synthesis even marginal survival is surprising, and alternative metabolic pathways may be present.

An “Operon” Disease? —The results obtained in this case appear to confirm an apparent exception to the one gene/one enzyme hypothesis (Smith and Lotz, 1963). Recent hypotheses concerning the control of enzyme activity offer the theoretical possibility that the basis of the disease could be deletion of a single “operator” gene controlling the defective enzyme sequence (Jacob and Monod, 1961; Monod et al., 1963). However, it remains to be demonstrated that the enzyme sequence is a functional unit or “operon” under the control of such a gene.

Acquired Orotic Aciduria.—The antineoplastic agent 6-azauridine is a specific competitive inhibitor of orotidyl decarboxylase and produces an acquired and reversible orotic aciduria (Fallon et al., 1962; Lotz et al., 1963). Elves et al. (1963) examined the chromosomes of dividing leucocytes from patients treated with 6-azauridine and observed an abnormal ?.—globule chromosomes which, it was suggested, were due to faulty synthesis of nucleic acids. A similar phenomenon was looked for in our patient but could not be detected in the pretreatment bone-marrow following short-term incubation with colchicine.

Family Studies

Investigation of parents and siblings of J. M. R. had indicated a heterozygous state without clinical abnormality, but with diminished enzyme activities, a minimal increase in urinary orotic acid excretion, and probably a decreased ability to metabolize a load of orotic acid (Smith et al., 1961; Fallon et al., 1962; Lotz et al., 1963). Eighteen presumed heterozygotes were detected in a study of 63 members of the affected family (Fallon et al., 1964).

The parents of our patient are healthy. The father is Irish, the mother is a three-quarter caste Maori, and the possibility of consanguinity is remote. One older sibling is well. The other had arrested haemolytic anaemia and died from a subdural haemorrhage after a fall. Recently the mother has given birth to a healthy boy, a half-brother to our patient.

The activity of orotidyl decarboxylase and pyrophosphorylase in the father’s red cells was found to be decreased to levels similar to those previously found in heterozygotes. No orotic acid has been demonstrated in the urine of the mother, the eldest sibling, or the half-brother using methods sensitive to approximately 1 mg./100 ml.

Prognosis

Our patient has made substantial progress in the 18 months of uridine therapy. This progress is continuing, but it appears probable that there will be some permanent intellectual retardation. The prompt response suggests that had treatment been begun soon after birth normal intellectual development might have been achieved. Hereditary orotic aciduria can thus be grouped with those inborn errors of metabolism in which early diagnosis and a treatment are essential for normal development. Although extremely rare, the disease should be suspected in any child with megaloblastic anaemia, with unexplained crystalluria, or when mental retardation and anaemia coexist. Treatment of
heditary orotic aciduria is not difficult in principle, using small amounts of a palatable soluble chemical given by mouth and free acid excretion. Observation of the peripheral blood should be sufficient to control dosage, supplemented when necessary by bone-marrow examinations and estimations of orotic acid excretion. Through the generosity of Nutritional Biochemicals Corp., Cleveland, Ohio, uridine is at present supplied at a cost which is reasonable in comparison with that of treating many chronic diseases. The treatment of orotic aciduria detected in early infancy promises to be simple, economic, and rewarding.

Summary

A second case of hereditary orotic aciduria is described. This diagnosis was established in a 17-month-old boy with megaloblastic anaemia who failed to respond to treatment with vitamin B₁₂, folic acid, pyridoxine, and thyroxine. He was found to excrete more than 1 g. of orotic acid daily.

Preliminary results of biochemical studies support the previous hypothesis that this is an inborn error of pyrimidine metabolism in which there is marked reduction in activity of two sequential enzymes in the major pathway of pyrimidine synthesis. This is transmitted as an autosomal recessive trait.

Haematological remission was induced by the nucleoside uridine and has been maintained for 18 months. Previous physical and mental retardation has responded to treatment, although some degree of intellectual impairment is likely to persist. The likelihood of gratifying results from early diagnosis and treatment of this disease is emphasized.

We should like to thank Dr. G. T. Fox, senior paediatrician, for permission to publish this case. We are indebted to Dr. Charles M. Huguley, jun., and Dr. Lloyd H. Smith, jun., for advice on the management of the case; to Drs. Huguley, Smith, and Robert S. Krooth for permission to include preliminary results of their investigations; to Dr. F. H. Sims, Dr. R. K. Ralph, and Miss Anne Simmonds for chemical investigations; to Dr. J. M. Stawely, haematologist, Auckland Hospital, for opinions on bone-marrow specimens; to Dr. D. M. G. Beasley, paediatrician, Whangarei Hospital, for information on the early course of the patient; to Dr. J. M. Costello and Miss M. Blackwell for psychometric assessments; and to Sister H. J. Smyth for nursing care.

REFERENCES


Hypcholesterolaemia and Orotic Aciduria During Treatment with 6-Azauridine


The pyrimidine analogue 6-azauridine (6-AzUR) has been used in the experimental treatment of leukaemia (Wilkinson, 1963, 1964). It is a moderately potent antileukaemic drug, free from serious toxicity, which exhibits some unusual and interesting side-effects. The urinary excretion of large quantities of orotidine and orotic acid demonstrates the drug's interference with the normal synthesis of pyrimidine nucleotides (Handscharacher et al., 1960a), which is also reflected in the chromosomal changes seen in the leucocytes of leukaemic patients treated with 6-AzUR (Elves et al., 1963). Another effect, noted by Fallon et al. (1961), is an increased uric-acid clearance.

6-AzUR therapy may result in the appearance of megaloblastic changes in the marrow, presumably due to inhibition of orotic acid decarboxylase. An increased plasma clearance of intravenously injected folic acid and urinary excretion of formimino glutamic acid following a histidine load have also been noted (unpublished observation). We are reporting here a hitherto undescribed side-effect of 6-AzUR therapy—namely, the depression of serum-cholesterol levels.

This finding was noticed during the performance of liver-function tests to exclude hepatotoxicity of 6-AzUR. The importance of this finding lies in the fact that 6-AzUR is perhaps the only substance available at the present moment that appears capable of affecting both the nucleic acid and the lipid metabolisms. Besides affording exciting possibilities for future investigations, this property of 6-AzUR has a potential value in the lowering of the plasma-cholesterol level in clinical medicine. Apart from hypcholesterolaemia, 6-AzUR did not induce any other abnormality in the liver-function tests.

Methods

Clinical Studies.—Five patients with various types of acute leukaemia, one patient with lymphosarcoma, and another with multiple myeloma were each given 10 g. daily of 6-AzUR by a