pressure when given orally. One death probably attributable to the drug is reported, and also three probable cases of bromide intoxication.

Reasons are given for believing that the sedative effect of the bromide ion, aided by ancillary factors, was one of the main agents in the subjective improvement in these patients.

We are grateful to our ward sisters, without whose co-operation this work could not have been done; to Dr. J. Lister and Dr. J. Angus for their unfailing help in the treatment of these cases; and to Mr. D. G. Nutt for his skilled biochemical assistance. We also wish to thank Messrs. May and Baker Ltd. for the adequate supply of the drugs necessary to conduct this trial, and Mrs. E. D. Price for her skilled secretarial help in writing this paper.

ADDENDUM.—Since the above was written we have used the drug in a further 12 cases, with results exactly as before. Only one patient showed any response to oral therapy as an out-patient. On 4 g. of hexamethonium bromide daily her blood pressure fell from 260/140 to 120–140/70–95, and she complained of persistent dizziness and vertigo. Her serum-bromide level was 35 mg. per 100 ml. Intramuscular ephedrine— $\frac{1}{2}$ gr. (32 mg.) given on four occasions—did not result in an elevation of blood pressure. Without the hexamethonium bromide her blood pressure kept at this level for 48 hours, and then slowly climbed to its previous height with relief of all her symptoms. She had no desire to continue taking the drug.

We note that two cases of bromide poisoning (Rosenheim, 1951; Holt, 1951) have now been reported. We are also investigating the value of the drug when given subcutaneously as recommended by Smirk (1950).

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Because bats are nocturnal creatures and sleep by day in caves, their habits remain something of a mystery. Members of the Devon Speleological Society are now studying individual bats which have received a numbered aluminium ring on the forearm to permit subsequent recognition, and find (*Nature*, April 7, p. 555) that the greater horseshoe bats of South Devon change their sleeping quarters at least weekly, even in midwinter, flying fifteen or more miles in the process. Sometimes the bats sleep alone, sometimes in clusters of anything from six to three hundred individuals, aggregated without distinction of sex. They do not move around with fellow-members of any given cluster but retain their single independence.

ACUTE LEUKAEMIA TREATED WITH A-METHOPTERIN

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The use of folic acid antagonists in acute leukaemia arises from the observation that the administration of pteroylglutamic acid or its conjugates apparently intensifies the leukaemic process (Farber *et al.*, 1947; Heinle and Welch, 1948). The use of synthetic anti-folic-acid compounds was therefore applied in the treatment of acute leukaemia. Several of these compounds are available, all of which, though structurally related to folic acid, are biologically antagonistic (Smith *et al.*, 1948). Meyer (1948) treated five cases of acute leukaemia with the folic acid antagonists pteroylaspartic acid and methylptericoic acid, and obtained temporary clinical and haematological remissions in four; and Farber and his colleagues (1948) reported significant remissions in 10 out of 16 children treated with 4-aminopteroylglutamic acid ("aminopterin").

In a later report, Farber (1949) summarized data on 60 children with acute leukaemia treated with aminopterin, 4-amino-N10-methylpteroylglutamic acid ("a-methopterin"), and 4-aminopteroylaspartic acid ("amino-an-fol"). Clinical and haematological remissions were obtained in 50% of these patients, and in two cases were maintained for 16 and 23 months. The reported incidence of remissions in cases treated by other authors varies from 9% (Meyer *et al.*, 1949) to 45% (Pierce and Alt, 1948). Dacie *et al.* (1950), in a study of 13 cases treated with aminopterin, found that remissions were induced in nine. Seven of these patients were children, and all showed a significant response of varying duration, the maximum period of survival being nine months. Only two of the six adults had partial remissions lasting four to six weeks. The lymphoblastic type of leukaemia appeared to be most responsive.

In this paper we report the results of treatment with a-methopterin in seven cases of acute leukaemia. It was hoped that this antagonist might prove less toxic than aminopterin yet as efficacious in inducing remissions, but the results obtained have been largely disappointing in this respect.

Case 1. Acute Myeloblastic Leukaemia

A housewife aged 35 was transferred from another hospital on October 17, 1949, for treatment with folic acid antagonists. She had been admitted there on October 8 with a two months' history of increasingly severe palpitations, shortness of breath, menorrhagia, and loss of weight. Examination disclosed severe anaemia, enlargement of the spleen and liver, and a leucocytosis of 28,000 per c.mm., some 93% of the cells being leukaemic blast cells. She was transfused with a litre of blood before being sent to Hammersmith Hospital.

On admission the patient was well nourished but pale. Her temperature was 100.2° F. (37.9° C.). Her skin and throat appeared healthy. Only one small lymph node was

palpable, in the right sub-mandibular group. Her spleen was felt 4 cm. and her liver 10 cm. below the costal margin, and her left kidney was palpable. No other abnormalities were found on clinical examination, and examination of the urine was negative. A chest radiograph was normal.

A blood count showed: red cells, 2,600,000 per c.mm.; Hb, 8.9 g. per 100 ml.; reticulocytes, 2.1%; platelets, 130,000 per c.mm.; white cells, 69,000 per c.mm. (myeloblasts 96%, polymorphs 1.5%, lymphocytes 2.5%). There were 10 normoblasts per 100 leucocytes.

On sternal puncture the bone marrow was very cellular and characteristic of myeloblastic leukaemia, the cells being predominantly myeloblasts. Mature granulocytes were few. Erythropoiesis was reduced but normoblastic in type.

Progress and Treatment

Procaine penicillin, 600,000 units daily, was given throughout the illness. Treatment with folic acid antagonists was begun on October 22, 1 mg. of aminopterin being given by mouth for three days. On October 25, when the white cells had risen to 95,000, a-methopterin was substituted, and was given on most days in doses of 5 mg. intramuscularly until November 18; the total amount given was 160 mg. A transfusion of packed red cells from 2 litres of blood was found necessary on the seventh day of treatment because

count fell gradually, and on November 18 treatment was discontinued. The leucocyte count was 15,000 per c.mm., but 99% of the cells were still myeloblasts. The sternal marrow at this stage showed reduced cellularity but no increase in maturity of the granulocytes. Clinically, the patient remained unchanged; dysphagia had almost disappeared and there was no significant alteration in the size of the spleen or liver. She remained febrile, and her haemoglobin had fallen to 7.2 g. since the previous transfusion.

Three days after the discontinuation of treatment her temperature rose abruptly to 104° F. (40° C.), and she suddenly developed deafness in the left ear. Her leucocyte count fell to 1,800 per c.mm. Physical examination revealed a left middle-ear type of deafness and signs of bronchopneumonia at both lung bases. Her throat appeared normal. On the following day, November 22, she developed hyperpyrexia and hyperpnoea and died.

Necropsy Findings

Necropsy (Dr. A. J. M. Reese) revealed a few petechial haemorrhages on both arms. Both lungs were oedematous, with exudation of protein-rich fluid into the alveoli, but without leucocytic infiltration. The mouth, pharynx, and upper oesophagus were normal, but the lower two-thirds of the oesophagus was oedematous and the hyperaemic mucosa was covered with ulcers, confluent in places, which formed longitudinal areas of ulceration with black, sloughing bases and raised red margins. Three similar ulcers were present in the stomach and six were scattered throughout the ileum. The remainder of the intestinal tract was normal. Histologically, these ulcerated areas showed an absence of cellular infiltrations, although there was oedema of the submucosa and slight perivascular infiltration of leukaemic cells in the adjacent mucosa. The liver and spleen revealed nothing remarkable to the naked eye, but on section both organs showed a moderate degree of myeloblastic infiltration.

The kidneys were not enlarged and appeared normal macroscopically, but section demonstrated a little sub-capsular leukaemic infiltration. The lymph nodes generally were uniformly infiltrated with primitive cells. The bone marrow of the sternum, vertebral bodies, and femur was red and rather pale, and in the centre of the femur it was gelatinous. Microscopically, it was uniformly cellular, and that from the femoral diaphysis was oedematous. Most of the cells were primitive. Giant cells with two to five nuclei were frequent, as were mitotic figures. Normoblastic erythropoiesis was present, though diminished.

The remainder of the organs were macroscopically and microscopically normal, apart from the demonstration of haemorrhage into the left middle-ear cavity.

Comment.—A course of 3 mg. of aminopterin and 160 mg. of a-methopterin produced a gradual reduction in the leucocyte counts in a case of myeloblastic leukaemia. Treatment was discontinued when the leucocyte count had fallen from 69,000 to 15,000 per c.mm., but the count fell to leucopenic levels after the drug was stopped, and bleeding occurred into the left middle ear. Death occurred four days afterwards. At necropsy there was leukaemic infiltration of viscera, lymph nodes, and bone marrow. Ulceration of the oesophagus, stomach, and ileum was present and was associated with leukaemic infiltration.

Case 2. Acute Lymphoblastic Leukaemia

A girl aged 2 was well until five weeks before admission, when she was noted to be pale and fretful and to have lost her appetite. Two weeks later she became feverish and developed petechial haemorrhages on the limbs and trunk. The child was admitted to another hospital on October 11, 1949, for investigation. She was found to have lymphoblastic leukaemia, and after a transfusion of 560 ml.

FIG. 1.—Case 1. Treatment and progress.

of a fall in the haemoglobin to 6.2 g. (Fig. 1). On November 9, after 70 mg. of a-methopterin had been given, there was no great clinical change in the patient's condition, although the spleen and liver appeared to be slightly reduced in size. Her white cell count was 77,000 per c.mm., of which 99% were myeloblasts. Reticulocytes were low (1%) and the platelets had fallen to 68,000 per c.mm. Sternal puncture showed no change in the bone marrow.

After 120 mg. of the drug had been given, the patient complained of a little dysphagia, but there were no abnormal physical signs and the leucocyte count was still 56,000 per c.mm. Her mouth and throat remained clear and there was no overt bleeding. From then onwards the white cell

of blood was sent to Hammersmith Hospital on October 21 for further treatment.

On admission the child was very ill and looked pale and sallow. Her temperature was 104° F. (40° C.). Petechial haemorrhages were present in the skin over the trunk and limbs and in the mucosa of the palate, and there was a recent bruise above the right eye. Her gums were swollen and friable, and her pharynx was injected. All superficial lymph nodes were greatly enlarged. The liver was palpable at the level of the umbilicus, and the spleen, which was firm and tender, extended down into the left iliac fossa. The heart, lungs, and nervous system were clinically normal, and no abnormality was noted in radiographs of the chest and long bones.

A blood count showed: red cells, 2,200,000 per c.mm.; Hb, 6.4 g. per 100 ml.; reticulocytes, 0.4%; platelets, 36,000 per c.mm.; white cells, 13,000 per c.mm. (blast cells 4%, segmented polymorphs 12%, large and small lymphocytes 83%, monocytes 1%).

Bone marrow was obtained by tibial puncture. Most of the cells present were of the lymphocyte series, about half being lymphoblasts. Erythropoiesis and granulopoiesis were minimal. Megakaryocytes were very scanty. The appearance was of an acute lymphoblastic leukaemia.

Progress and Treatment

The cells of 1 litre of blood were given by transfusion on the day after admission, and a-methopterin, in doses of 2.5 mg. by mouth daily, was begun on October 24; five doses, totalling 12.5 mg., were given. In spite of the transfusion there was no improvement in the patient's condition. Purpura became widespread, and an incision over the right ankle, made for the purpose of transfusion, bled freely and remained unhealed. Her temperature was still high. She died on October 29, eight days after admission. On the day of death her leucocyte count was 1,000 per c.mm., 64% of the cells being lymphocytes and the remainder polymorphs.

Smears of the tibial bone marrow made immediately after death showed 60% of the cells to be of the lymphocyte series, about a third of them lymphoblasts. Compared with the pretreatment biopsy, developing granulocytes were quite numerous, and there were some erythroblasts; haemopoiesis appeared to be more normal.

Necropsy Findings

The post-mortem examination was carried out by Dr. B. Lennox. The trunk, limbs, and buccal mucosa were covered with petechial haemorrhages, and there was an unhealed cut-down wound over the right ankle. Internally, petechiae were widespread on the serous surfaces of the heart, lungs, and abdominal viscera, and in the mucosa of the stomach and small intestine. Scattered small haemorrhages were present beneath the meninges and in the cortical grey matter of the brain. All the lymph nodes were moderately enlarged, and their architecture was replaced by a uniform infiltration with lymphocytes. The thymus also was densely infiltrated with leukaemic cells. The liver was moderately enlarged and its cut surface presented scattered white nodules. Microscopically, these consisted of areas of lymphocytic infiltration. The spleen was greatly enlarged and its pulp replaced by leukaemic tissue. The kidneys showed subcapsular haemorrhages and patchy interstitial leukaemic infiltrations. The bone marrow of the sternum, long bones, and vertebrae was deep red and gelatinous. Microscopically its structure was as seen in the post-mortem aspiration.

Comment.—In this case of lymphoblastic leukaemia in a child of 2 years with a very short history death occurred from haemorrhagic complications after 12.5 mg. of a-methopterin had been given. The marrow appeared to be responding by increased granulopoiesis and erythropoiesis, as judged by the final blood count and by the appearance of the bone marrow after death as compared

with that before treatment. The course of the illness after admission was too short to assess the effects of treatment on liver, spleen, and lymph-node enlargement.

Case 3. Subacute Myeloblastic Leukaemia

A boy aged 15 was admitted on November 1, 1949, with a history of increasing fatigue, joint stiffness, and breathlessness on exertion of four weeks' duration. On admission he was found to be gravely anaemic with signs of right-heart failure. His superficial lymph nodes, liver, and spleen were all palpable and moderately enlarged. There were no other abnormalities on physical examination, and a radiograph of the chest was normal.

His blood count was as follows: red cells, 630,000 per c.mm.; Hb, 3.4 g. per 100 ml.; platelets, 45,000 per c.mm.; white cells, 178,000 per c.mm. (blast cells 17%, promyelocytes 5%, myelocytes 13%, metamyelocytes 19%, polymorphs 39%, lymphocytes 7%).

Sternal puncture revealed a highly cellular marrow with numerous peroxidase-negative myeloblasts and promyelocytes, but there was also a good deal of differentiation to adult granulopoiesis, indicating a subacute type of myeloblastic leukaemia. Erythropoiesis was scanty but of normoblastic type. Few megakaryocytes were present.

Progress and Treatment

The patient was transfused during his first week in hospital. In view of the subacute nature of the leukaemia and the high initial leucocyte count, it was felt that deep x-ray therapy offered the best chance of successful treatment. Accordingly, he was treated by generalized body irradiation for one month. During the early stages of treatment he developed arthralgia and painful effusions in his finger-joints and left knee and ankle. There were no radiographic changes and the symptoms subsided completely in 10 days. After the course of irradiation was completed his liver and spleen were no longer palpable and his peripheral leucocyte count was reduced to 63,000 per c.mm. There was, however, no change in the distribution of leucocytes, and the appearance of the sternal bone marrow was unaltered. The haemoglobin and red cell counts fell consistently during treatment, and further blood transfusions were required.

Three weeks after irradiation the leucocyte count had risen to 200,000 per c.mm., most of the cells being immature granulocytes. His liver, spleen, and lymph nodes were once more palpable, and he had developed a purpuric rash. He complained of pains in both hands, feet, and elbows, and had effusions in his metacarpo-phalangeal joints. Radiographs showed periostitis of the right fibula and the third right metacarpal. Treatment with a-methopterin was begun on December 30, 2.5 mg. being given daily by mouth. The drug was discontinued on the eleventh day, after 27.5 mg. had been given, because of the sudden development of bilateral middle-ear deafness. The total and differential white cell counts in the blood were unchanged, but the liver and spleen were smaller and the joint effusions had absorbed rapidly after treatment had begun. Next day the patient became comatose and died of an intracerebral haemorrhage.

Necropsy Findings

Post-mortem examination (Dr. I. Doniach) revealed scattered petechial haemorrhages on the limbs and trunk. The cause of death was a massive intracerebral haemorrhage, and bleeding had occurred into both middle-ear clefts. The pericardial surface of the heart and the gastric mucosa were covered with petechial haemorrhages. The liver, spleen, and lymph nodes generally were all greatly enlarged and firm. The sternum and long bones were filled with bright red marrow. The rest of the viscera, endocrine glands, and alimentary tract appeared normal. Histologically, the small vessels throughout the body contained many white cells, and there was widespread infiltration of the tissues by leukaemic cells. The pericardium, heart, lungs, stomach,

liver, kidneys, spleen, lymph nodes, and testes all showed varying degrees of infiltration, which involved also the synovial membrane and periosteum of the right knee, right third metacarpo-phalangeal joint, and right ankle. Bone marrow from the sternum and long bones showed intensive and uniform proliferation of primitive leukaemic cells.

Comment.—This case of subacute myeloblastic leukaemia showed only a very transient and partial response to deep x-ray therapy. A course of a-methopterin was discontinued after 27.5 mg. had been given, because of haemorrhage into both middle ears, and this was immediately followed by a fatal cerebral haemorrhage. At necropsy all organs were heavily infiltrated with leukaemic cells and the bone marrow was hyperplastic and leukaemic.

Case 4. Myeloblastic Leukaemia

A schoolboy aged 14 had acute appendicitis in January, 1949. At operation it was noted that there were many calcified lymph nodes in the mesentery and one that was acutely inflamed and suppurating. The boy recovered from the operation and appeared to be well until October, 1949, when he was abnormally pale and tired easily. These symptoms increased, and by the end of November he was confined to bed with general weakness, anorexia, dyspnoea on exertion, and fever. He was admitted to hospital on December 6 for investigation.

On admission the boy was well nourished but very anaemic. His temperature was 104° F. (40° C.). His skin, throat, and mouth appeared to be healthy. Lymph nodes in the cervical, axillary, and inguinal groups were moderately enlarged and firm. His liver was enlarged 4 cm. and his spleen to 1 cm. below the costal margins. No other abnormality was found on physical examination, and radiographs of the chest and long bones were normal.

A blood count showed: red cells, 1,900,000 per c.mm.; Hb, 7.3 g. per 100 ml.; reticulocytes, 1.3%; platelets, 50,000 per c.mm.; white cells, 67,000 per c.mm. (blast cells 90%, polymorphs 1%, lymphocytes 7.5%, monocytes 1.5%); nucleated erythrocytes, 2 per 100 white cells.

Sternal puncture revealed a highly cellular marrow, most of the cells being myeloblasts. Granulocyte and erythrocyte development was scanty.

Progress and Treatment

From the time of admission the patient had a remittent temperature rising to 104° F. (40° C.) and accompanied by rigors and sweating. On his third day in hospital he was transfused with packed red cells from 2 litres of blood, and on that day and the next he was given 5 mg. of a-methopterin by intramuscular injection. Shortly after the second injection he developed central abdominal pain and vomiting, and these symptoms increased during the succeeding days. Penicillin was administered parenterally, but his condition deteriorated progressively. He became drowsy and slightly icteric, and bled from the nose and gums. Petechial skin haemorrhages developed and fundal haemorrhages were noted. A further blood transfusion was given on December 14, but a few hours afterwards he became completely unconscious and died the same night, nine days after admission.

Although only 10 mg. of a-methopterin had been given there was a profound effect on the white cells, which fell from 65,000 per c.mm. on the day the first injection was given to 1,600 per c.mm. two days later and 200 per c.mm. on the day of death. Blast cells disappeared and were replaced by mature granulocytes and lymphocytes in equal proportions. The haemoglobin level fell rapidly after the first transfusion, and there were few platelets in the blood at any time.

Necropsy Findings

Post-mortem examination (Dr. C. V. Harrison) showed that the body was moderately jaundiced with a petechial cutaneous rash. Petechial haemorrhages were also present

under the pericardium and in the mucosa of the stomach and intestine. There was a haemorrhage into the lower lobe of the left lung. The lymph nodes generally were enlarged and fleshy except for those in the mesentery, which were calcified. Histologically they showed a sinus and medullary reaction and contained many foci of primitive cells. The mesenteric glands showed healed tuberculosis. The liver was enlarged, and on section contained many small ramifying abscesses with necrotic centres. They contained colonies of cocci with virtually no surrounding cellular reaction. There was no evidence of leukaemic infiltration.

The spleen was enlarged; in its pulp were clusters of marrow cells, many of them primitive myeloblasts. The long bones, sternum, and vertebrae were filled throughout with red marrow, with, microscopically, an almost complete absence of recognizable cells. Odd foci of leukaemic cells, mostly myeloblasts, were present, and large phagocytic macrophages were scattered throughout. The appearances suggested almost total destruction of the marrow, of recent origin. The kidneys were normal, and no abnormality was found in the remaining organs.

Cultures taken post mortem from the liver abscesses grew a penicillin-resistant *Staph. aureus*. Acid-fast bacilli were not found, and culture for *Myco. tuberculosis* was negative.

Comment.—Myeloblastic leukaemia in a boy, occurring eight or nine months after an attack of acute appendicitis, was complicated by jaundice and abdominal symptoms: 10 mg. of a-methopterin rendered the bone marrow aplastic. At necropsy a staphylococcal portal pyaemia was found, presumably related to the previous appendicitis.

Case 5. Paramyeloblastic Leukaemia

A housewife aged 32 had a three-months history of increasing fatigue, lassitude, palpitations, and headaches. For six weeks she had observed swelling of the hands and finger-joints, and for two weeks had breathlessness on exertion and a tendency to spontaneous bruising of the limbs and trunk. Increasing pallor had been noted for the same period. She was feverish, and had night sweats for a week before admission to hospital on January 4, 1950.

On admission the patient was in right-sided heart failure due to severe anaemia. She had a few old bruises on the legs and arms. Her superficial lymph nodes were all enlarged, and her liver and spleen were palpable 5 cm. below the costal margins. No abnormality was noted in the hands or other joints, and radiographs of the chest and hands were normal.

Her blood count was as follows: red cells, 900,000 per c.mm.; Hb, 3.8 g. per 100 ml.; reticulocytes, 1.5%; platelets, 11,000 per c.mm.; white cells, 42,000 per c.mm. (blast cells 54%, metamyelocytes 8%, polymorphs 18%, basophils 1%, lymphocytes 7%, abnormal monocytes 12%); nucleated erythrocytes 3 per 100 white cells.

On sternal puncture the bone marrow showed a predominance of primitive blast cells having the appearance of aberrant myeloblasts. They differentiated both to granulocytes and to abnormal monocyte-like cells. Mature granulocytes were few, and the scanty erythroblasts present were partially megaloblastiform in type. The appearance was of a paramyeloblastic leukaemia (Naegeli type "monocytic" leukaemia).

Progress and Treatment

The patient was given parenteral penicillin daily whilst in hospital, and during the first week small transfusions of packed red cells to bring her haemoglobin to 12.9 g.

Treatment with a-methopterin was begun on January 10, 5 mg. being given on most days by mouth. On January 29 the dose was increased to 10 mg., and treatment was discontinued on February 9 after 180 mg. had been given. For the first three weeks of treatment the patient's general

condition was fairly good, and she remained afebrile. She did, however, have an increased tendency to bleed, and for a few days had impaired vision due to bilateral fundal haemorrhages.

During the last three days of treatment she developed slight pyrexia, sore throat, and superficial ulceration of the lips, throat, and fauces, symptoms which subsided three days after cessation of therapy. The results were disappointing. There was a slight diminution in the size of the enlarged liver, spleen, and lymph nodes, and the peripheral white cell count was reduced to 6,000 per c.mm. (Fig. 2), but there was no significant change in the distribution of leucocytes in either the blood or the bone marrow, and the platelet and reticulocyte counts remained low. A steady fall in the patient's haemoglobin level necessitated a further transfusion on February 11, and she was dis-

a transient lowering of the peripheral white cell count and slight objective clinical improvement, but had no effect on the differential white cell count in the blood or bone marrow. Haemorrhagic complications were severe. Further treatment with aminopterin, 1 mg. thrice weekly, the maximum dose tolerated, was ineffective in halting the course of the disease, and death ensued from cerebral haemorrhage.

Case 6. Lymphoblastic Leukaemia

A girl aged 8 was admitted from another hospital for treatment of lymphoblastic leukaemia. Her history dated from the middle of October, 1949, when she had a feverish illness, accompanied by headache, abdominal pain, and vomiting, which was diagnosed as influenza. The fever subsided in 14 days, but the child remained irritable, anorexic, and fretful, and enlarged glands were observed in her neck. Towards the end of November she developed, in addition, pains in the limbs. Investigation at another hospital during December revealed a moderate degree of anaemia, generalized lymphadenopathy, and enlargement of the liver and spleen. Examination of the blood showed an acute leukaemia, so she was transferred for treatment with folic acid antagonists on January 5, 1950.

On admission the child was well nourished and appeared only mildly anaemic. Her temperature was 101.4° F. (38.55° C.). Her skin, throat, and mouth appeared healthy. All superficial lymph nodes were considerably enlarged, and her left kidney was palpable. The spleen and liver were felt 2 cm. below the costal margins. No abnormality was found in the other systems, and radiographs of her chest, skull, spine, and long bones were negative.

Blood findings were as follows: red cells, 4,200,000 per c.mm.; Hb, 11.2 g. per 100 ml.; reticulocytes, 1.6%; platelets, 12,000 per c.mm.; white cells, 52,000 per c.mm. (blast cells 52%, polymorphs 2%, lymphocytes 46%).

On sternal puncture the normal bone marrow cells were seen to be almost entirely replaced by primitive cells with the characteristics of lymphoblasts. A small percentage of the cells present were adult lymphocytes, but there was little granulopoiesis or erythropoiesis.

Progress and Treatment

The child bled severely from a loose tooth during her first week in hospital, haemorrhage being arrested only after the tooth had been extracted and a litre of fresh blood had been transfused. On January 23 the white cell count had risen to 98,000 per c.mm. Treatment with a-methopterin was begun on that day, and 2.5 mg. of the drug was given by mouth daily for nine days, a total of 22.5 mg. During the first three days of treatment the child had migratory joint pains, but these ceased after four doses of a-methopterin had been given, and did not recur. The only radiographic change was the development of periostitis of the upper end of the left fibula; a radiograph taken three weeks later showed this to have resolved.

Severe toxic manifestations resulted from the administration of a-methopterin, and her general condition deteriorated considerably. She bled from the gums and developed widespread cutaneous and mucosal petechial haemorrhages and haematuria. She also vomited repeatedly. The enlarged lymph nodes, spleen, and liver, however, regressed considerably in size, and the left kidney became impalpable. A further blood transfusion was given on February 18, and

FIG. 2.—Case 5. Treatment and progress.

charged on February 13. Whilst at home she was instructed to take 1 mg. of aminopterin by mouth three times weekly.

Three weeks later the patient was readmitted, greatly exsanguinated, following a severe rectal haemorrhage. She had also developed generalized purpura and bleeding from the gums, and enlargement of the spleen, liver, and lymph nodes had increased. Her peripheral white cell count had risen to 30,000 per c.mm., of which 68% were myeloblasts or paramyeloblasts and 15% were abnormal monocytes. Two more transfusions of packed red cells were given, and treatment with aminopterin was continued in the same dosage—1 mg. thrice weekly. Although there was no recurrence of the rectal haemorrhages which had led to her admission, the patient had a constant tendency to bleed from the gums and into the skin, and this prevented any increase in the dose of the folic acid antagonist. The patient was discharged again on March 23, symptomatically improved, but with a still rising white cell count. She died at home a month later, after a short period of coma. The apparent cause of death was intracerebral haemorrhage. Permission for a necropsy was not obtained. The total amount of aminopterin given was 18 mg.

Comment.—The leukaemia in this case was of the paramyeloblastic type. A course of 180 mg. of a-methopterin, sufficient to produce symptoms of toxicity, caused

shortly afterwards the child began to recover. She ceased to bleed, her appetite returned, and she regained weight. By February 28 she was considerably improved and fit for discharge home. There was then no palpable enlargement of lymph nodes or viscera, and the child was walking and alert. Instructions were given for her to receive 2.5 mg. of a-methopterin by mouth thrice weekly whilst at home.

The effect of a-methopterin on the blood was to induce a leucopenia, the white cells falling for six days after the drug was withdrawn (Fig. 3). The lowest count, on February 7, was 650 per c.mm., 70% of the cells being lymphocytes and 30% polymorphs. At this stage the bone marrow was hypoplastic. Very few lymphoblasts, comprising only 1% of the marrow cells, were seen; 10% of the cells were lymphocytes, and the remainder were developing granulocytes and normoblasts in equal proportions. Three weeks later, at the time the child was discharged from hospital, the peripheral leucocyte count had risen to 7,000 per c.mm., with a normal distribution of leucocytes.

Two weeks after discharge she was seen again and had clearly relapsed. She was once more anaemic, and complained of pain in the abdomen and joints, vomiting, and epistaxis. Her lymph nodes, spleen, and liver were again greatly enlarged, and her left wrist and right knee were tender and their movements restricted. There were radiographic bone changes in the knees and left wrist. The white cell count had risen to 21,000 per c.mm.; 83% of the cells were blast cells and only 3% were polymorphs. Readmission was advised but was declined, and a-methopterin was continued at home in a dosage of 2.5 mg. on alternate days. The patient died at home 12 days later. Permission for a necropsy was not obtained.

Comment.—A girl with acute lymphoblastic leukaemia and a high initial white cell count was given 22.5 mg. of a-methopterin in nine days. Toxic complications, which included bone marrow damage, were severe, but joint symptoms subsided and visceral enlargement regressed, and there was a coincident improvement in her general condition. The bone marrow and peripheral blood became much more normal in appearance. The clinical and haematological remission lasted less than four weeks. Relapse was not prevented by "maintenance" doses of a-methopterin, and death occurred within a month of discharge from hospital.

Case 7. Acute Lymphoblastic Leukaemia

A boy of 3½ years was admitted from another hospital as a case of lymphoblastic leukaemia for anti-folic-acid therapy. In February, 1950, the child had first been noted to be unduly pallid and was treated by his general practitioner for anaemia. There was no response to treatment, and during April he developed a haemorrhagic lesion in the pulp of the right index finger and a little bleeding from the mouth. He was admitted to another hospital, where a diagnosis of leukaemia was made, and on April 28 he was transferred to Hammersmith Hospital.

Although well nourished and not distressed, the child on admission was very anaemic. There were a few scattered bruises on his legs, and the terminal pulp space of the right index finger was swollen and discoloured by a haemorrhage into it. His throat appeared normal. One enlarged lymph node was palpable in the left axilla, but none else-

where. The liver and spleen were just palpable under the costal margins. There were no other abnormalities on physical examination, and radiographs of the chest and long bones were normal.

A blood count showed: red cells, 2,400,000 per c.mm.; Hb, 5.8 g. per 100 ml.; reticulocytes, 0.2%; platelets, 10,000 per c.mm.; white cells, 31,000 per c.mm. (blast cells 78%, polymorphs 1%, lymphocytes 21%).

Bone marrow obtained by sternal puncture was highly cellular, about 90% of the cells being nucleolated blast cells and the remainder more or less mature lymphocytes. There was little evidence of either granulopoiesis or erythropoiesis, and no megakaryocytes were seen. The appearance was of an acute lymphoblastic leukaemia.

FIG. 3.—Case 6. Treatment and progress.

Progress and Treatment

A blood transfusion given on the day after admission elevated the child's haemoglobin to 11.4 g. Seven daily doses of a-methopterin, each of 5 mg. by mouth, were given between May 2 and 10—a total of 35 mg. in nine days. On the day after treatment was begun he suddenly developed intense dyspnoea and inspiratory stridor and bled from the haematoma in the right index finger and from the rectum. The respiratory symptoms appeared to be associated with a haemorrhage into the left lung and did not completely disappear throughout the illness. During the next week the child developed a high remittent evening temperature, un-influenced by daily penicillin injection. He also developed petechial haemorrhages into the skin and buccal mucosa, and haematomata formed in the lower lip and in both right eyelids. Rutin given by mouth had no apparent effect on the bleeding. The haemoglobin level fell rapidly, and another blood transfusion was required on May 15. This appeared to have no effect on the course of the illness, and the child's condition deteriorated rapidly. On May 18 he became comatose and died. The immediate cause of death appeared to be a cerebral haemorrhage.

The effect of a-methopterin on the blood was to induce a leucopenia, maximal five days after discontinuing treatment.

The lowest white cell count was 1,400 per c.mm. on May 15; two days later it had risen to 2,500 per c.mm. Leukaemic blast cells disappeared from the peripheral blood; lymphocytes, mostly young forms with clear cytoplasm, constituted 85% of the leucocytes, the remainder being polymorphs and stab cells. Platelets were virtually absent from the blood during the illness. Owing to the child's critical state marrow biopsy was not repeated after admission.

Necropsy Findings

The post-mortem examination was carried out by Dr. I. Doniach. The body was covered with petechial cutaneous haemorrhages, and the right upper and lower eyelids were enlarged by haemorrhage. Internally, petechiae were widespread over the visceral peritoneum, the pleural, epicardial, and endocardial surfaces of the heart, and in the mucosa of almost the whole length of the alimentary tract. The stomach was filled with blood clot, and there was a massive haemorrhage into the left lung. The immediate cause of death was an extensive subarachnoid haemorrhage. The kidneys showed numerous parenchymal haemorrhages on section, and the mucosa of the renal pelvis and bladder was haemorrhagic. The liver and spleen were not enlarged and appeared normal macroscopically. The lymph nodes generally were slightly enlarged and congested. The bone marrow of the sternum, vertebrae, and long bones was plum-coloured and deeply haemorrhagic.

Histologically, there was a notable absence of leukaemic infiltration in any organ, the only abnormality being congestion and haemorrhages. The left lung showed haemorrhagic consolidation and an acute necrosing bronchiolitis. Details of the bone marrow were largely obscured by haemorrhage, but one relatively intact area in the sternum showed large numbers of lymphocytes and normoblasts and a few blast cells, but there was little evidence of active granulopoiesis.

Comment.—A short course of a-methopterin effectively reduced the peripheral white cell count in this case of acute lymphoblastic leukaemia and produced some improvement in the appearance of the blood. Haemorrhagic complications were exacerbated by the drug to an alarming degree and ultimately proved fatal. At necropsy there was a remarkable absence of visceral leukaemic infiltration, the only significant lesions being those due to haemorrhage.

Results

Five of the patients treated were children, of whom three had acute lymphoblastic leukaemia and two had myeloblastic leukaemia. Of the two adults, one had acute myeloblastic leukaemia and the other had paramyeloblastic leukaemia.

The results obtained were, to say the least, disappointing. In only one patient (Case 6) did there appear to be any beneficial response to treatment. This was a case of lymphoblastic leukaemia, clinically acute, and the administration of 22.5 mg. of a-methopterin caused regression of visceral enlargement and an improvement in the child's general condition. Concurrently there was a significant improvement in the state of the peripheral blood and bone marrow. Lymphoblasts in the marrow were reduced to about 1% and granulopoiesis and erythropoiesis became normal in amount. This state lasted, however, for only a very short time. Clinical and haematological relapse occurred within four weeks in spite of the continued administration of a-methopterin in "maintenance" doses, and the patient died shortly afterwards. In the initial stage of treatment a-methopterin had a pronounced ameliorative effect on leukaemic bone and joint lesions. This effect was also

noted in Case 3 and has been observed to occur in cases treated with aminopterin (Dresner, 1950).

Manifestations of a-methopterin toxicity occurred in all cases, and rendered treatment hazardous. The most prominent toxic effects were the development of leucopenia and a greatly increased tendency to bleeding. The onset of leucopenia usually came without warning, and in one case at least was irreversible and proceeded to complete marrow aplasia. In three of the patients the leucocyte counts continued to fall for three to five days after the drug was withdrawn. The amount of a-methopterin needed to influence the marrow in this way varied enormously. The bone marrow in Case 4 became aplastic after only 10 mg. of a-methopterin, whereas 120 mg. was given to Case 1 before there was any significant alteration in the white cell count.

Severe bleeding complicated treatment in every case, and, when present before the administration of a-methopterin, was greatly exacerbated by it. In addition to haemorrhages into the skin and mucosae and bleeding from mucosal surfaces, haemorrhages occurred into the lungs in two cases and into the middle ears in two cases. Haemorrhagic complications were probably responsible for the deaths of six of the patients.

In order to see whether there was any difference in the susceptibility of the leukaemic cells to different antagonists, aminopterin was substituted for a-methopterin in Case 5 after a course of 180 mg. of the latter drug had proved ineffective in controlling the disease. However, in the dosage given, the maximum tolerated, it also proved ineffective in retarding the progress of the illness.

Discussion

From the reports of other workers with a-methopterin it is evident that life may be prolonged in a certain proportion of cases of acute leukaemia in children and that adults are either completely refractory to treatment or, at best, have only short and incomplete remissions. The best results seem to be obtained in children with a subacute type of lymphoblastic leukaemia. Sacks *et al.* (1950) reported three complete temporary remissions lasting 11 to 16 weeks in a series of 20 cases treated—all children. Weber *et al.* (1950) were able to produce haematological or symptomatic improvement in 20 out of 24 children treated with a-methopterin and aminopterin, but remissions were never permanent, and death eventually occurred. Stickney *et al.* (1949) obtained similar remissions lasting up to four months in 5 out of 21 children and in 3 out of 33 adults. In a report by Meyer *et al.* (1950) on the treatment of 11 cases of acute leukaemia with a-methopterin, no particular relation was noted between the effect of the drug and the dosage given, or the age or sex of the patients, and, although the incidence of toxic effects was high, clinical improvement was brought about in only three patients. Although the white blood cells were affected in eight patients, in no instance did the differential count become normal, nor was there a spontaneous rise in haemoglobin or platelets in any case. All authors have noted the failure of further courses of treatment during relapse, and also the rapid development of resistance to increasing amounts of the drugs in patients under treatment.

The increased tendency to haemorrhage in patients treated with folic acid antagonists is perhaps the most serious complication in many of the cases, and was a prominent feature in this series. The haemorrhagic diathesis is not controllable by intravenous protamine

sulphate or toluidine blue (Sacks *et al.*, 1950; Weber *et al.*, 1950), and it therefore seems unlikely that an increased level of heparin-like substances in the blood is responsible, as suggested by Allen *et al.* (1947). Plasma prothrombin levels were estimated in one of our cases and were found to be normal. The increased tendency to bleeding induced by a-methopterin seems to be more severe than that caused by aminopterin. On the other hand, oropharyngeal ulceration, which is almost the rule when effective doses of aminopterin are given (Dacie *et al.*, 1950), was noted in only one of the cases treated with a-methopterin. The extensive gastro-intestinal ulceration found at necropsy in Case 1 appears to be a toxic effect of folic acid antagonists and not a primary leukaemic manifestation. It has been noted in four other cases we treated with aminopterin and in one case treated with a-methopterin by Sacks *et al.* (1950).

Experimentally, a-methopterin has been found effective in significantly prolonging the survival time of mice with the Ak4 strain of transplanted leukaemia, although no direct cytotoxic effect, such as characterizes the use of the nitrogen mustards, has been demonstrated (Burchenal, Burchenal, *et al.*, 1949; Burchenal, Johnston, *et al.*, 1949). Weir and his colleagues showed that a crude antagonist of pteroylglutamic acid (folic acid) caused a delay in the appearance of immature cells in the peripheral blood in normal mice, and in Ak4 leukaemic mice it prevented any notable increase in either total white cell count or proportion of blast cells. In mice rendered folic-acid-deficient in this way, the marrow is damaged and the erythroblasts disappear (Weir, Heinle, and Welch, 1948; Weir, Welch, and Heinle, 1949; Thiersch and Stock, 1949). Using a-methopterin, Burchenal, Biedler, *et al.* (1950) confirmed these findings and showed that in the usual therapeutic dosage it caused a slight leucopenia but no change in the differential count of normal mice. In mice with the Ak4 strain of leukaemia its use resulted in a prolongation of survival time, the leucocyte count remaining at approximately normal levels, with reduction in the numbers of abnormal cells and delay in the appearance of leukaemic infiltrations in the viscera and bone marrow.

New light is emerging on the relationship of folic acid and structurally similar antagonists. Sauberlich and Baumann (1948) described a factor necessary for growth of the organism *Leuconostoc citrovorum* 8081, and Sauberlich (1949) indicated a relationship of this factor to folic acid. Recent work indicates that in rat-liver slices the citrovorum factor is formed from folic acid, and that aminopterin both inhibits the conversion and competes with the product (Nichol and Welch, 1950). These workers also found that, although folic acid would not prevent the lethal action of aminopterin on rats, the citrovorum factor completely counteracted the toxic effects of the antagonist.

Burchenal, Babcock, *et al.* (1950) have also shown that, although the prolongation of survival time of leukaemic mice by the administration of a-methopterin can be partially prevented by simultaneous administration of folic acid, the effect of the a-methopterin is completely abolished by small amounts of the citrovorum factor. The citrovorum factor might therefore prove to be effective in countering toxic effects of folic acid antagonists in human leukaemia, although it would also reverse their destructive effect on the leukaemic cells.

The exact mode of action of a-methopterin in leukaemia is not yet fully determined, but the principle

involved is presumably the biological competition of structurally related compounds (Woolley, 1947). The possibilities have been fully discussed by Sacks (1949), Weber *et al.* (1950), and Sacks *et al.* (1950). In those cases in which a-methopterin or aminopterin is successful in inducing an initial remission in human acute leukaemia, resistance to further therapy rapidly develops during subsequent relapses. This acquired resistance appears to be similar to the development of "drug resistance" by bacterial cells. That resistance to folic acid antagonists develops in experimental leukaemias in mice has been demonstrated by Burchenal, Robinson, *et al.* (1950) by serial inoculation of leukaemic spleen emulsions in untreated mice and in mice treated with a-methopterin. Although there was no loss of transmissibility in the leukaemic cells as a result of treatment, there was progressive loss of susceptibility to the drug, and by the fifth serial inoculation this was complete, treated animals surviving no longer than the controls. This demonstration of the ability of initially sensitive populations of leukaemic cells to become resistant to a-methopterin may help to explain the eventual failure of treatment in patients with leukaemia. Although resistance may be acquired by the emergence of mutants or through altered metabolism during exposure to the antagonists (see Hinshelwood, 1946), it is also possible that a strain of resistant cells may be present from the beginning in small numbers, and eventually become predominant. Small numbers of leukaemic blast cells persist in the marrow of even the most satisfactorily responding cases.

Summary

The effect of the folic acid antagonist a-methopterin was studied in seven cases of acute leukaemia.

Significant remission was obtained in only one patient, a child with acute lymphoblastic leukaemia, and was of short duration.

Toxic effects were frequent and severe. In addition to effects previously noted with aminopterin, two patients suffered haemorrhage into the middle ear.

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TUBERCULOUS MENINGITIS

RESULTS OF TREATMENT WITH STREPTOMYCIN AND INTRATHECAL SULPHETRONE

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At a special unit for the treatment of tuberculous meningitis at Highgate Hospital 48 patients were treated between May, 1948, and November, 1949. These patients were included in a controlled trial of "sulphetrone" given intrathecally. All except three were under 15 years of age. The results of the trial form the subject of this report. Forty-seven cases were proved bacteriologically.

A sulphone derivative (tetrasodium 4:4'-bis-(γ -phenylpropylamino)-diphenylsulphone- α ; γ ; α' - γ' -tetrasulphonate), which has been given the registered name "sulphetrone,"* has been shown to possess high antibacterial activity against the tubercle bacillus with comparatively low toxicity (Brownlee, 1948). Smith, McClosky, and Emmart (1946) have shown that the effect of streptomycin is enhanced by the addition of a sulphone, and a synergistic action of the two compounds has been demonstrated in guinea-pigs (Brownlee and Kennedy, 1948).

Treatment

The intrathecal route of administration was considered advisable because of: (1) the small amounts of the drug found in the brain and cisternal fluid after intravenous or oral administration in animals (Brownlee, 1948); (2) the difficulty of daily intravenous administration in infants and young children; (3) the irregular absorption from the intestinal tract in children, particularly when

constipated; (4) the pain caused by intramuscular injection and the relatively large volume required.

Dosage.—The dosage was 200 mg., given with the daily dose of streptomycin intrathecally in the same syringe. Higher doses than this were tried, but were abandoned owing to the greatly increased incidence of convulsions.

C.S.F. and Serum Levels.—With this dosage, cerebrospinal fluid (C.S.F.) and serum concentrations of sulphetrone were very low—0.3 mg. per 100 ml. of serum, and 0.4 mg. per 100 ml. of C.S.F. at 24 hours after injection. Higher levels occurred in a few patients and were accompanied by convulsions.

Toxic Effects.—Toxic effects encountered were convulsions (5 cases), excessive head retraction and opisthotonos (7 cases), mental symptoms (3 cases), and cyanosis (1 case). In five patients the reactions were severe enough to necessitate interruption of treatment. Abnormal blood pigments were not identified and anaemia was not found, although the plasma showed a deep maroon discoloration.

Streptomycin.—The periods during which streptomycin was given to all patients are shown in the Chart. The daily dose was 0.02 g. per lb. (0.45 kg.) body weight in 24 hours intramuscularly and 0.1 g. in 10 ml. of normal saline intrathecally.

Miliary Disease of Lung.—Nine cases showed miliary disease of the lungs—four were in the streptomycin plus sulphetrone series (all survived) and five in the streptomycin only series (two survived).

Results

The 48 patients were all consecutive admissions who had not received any previous treatment. At first, alternate patients (irrespective of age and stage of disease) were given sulphetrone, and the remainder were used as controls. Later, when it was decided to subdivide the cases into groups so as to avoid either series being unduly "weighted" with infants or advanced cases, in whom an unfavourable outcome might be expected, the patients were first classified on admission according to age and stage of disease. Each patient was then allocated to the appropriate division of the six shown in Table I. Within each of these six divisions,

TABLE I.—Showing Age and Stage of Disease in Sulphetrone and Control Groups

Stage of Disease:	Early		Middle		Advanced		Total
	Under 3 yr.	Over 3 yr.	Under 3 yr.	Over 3 yr.	Under 3 yr.	Over 3 yr.	
Streptomycin (control group)	5	3	3	8	2	2	24
Streptomycin and sulphetrone (sulphetrone group)	4	2	2	10	2	4	24

alternate cases received streptomycin and sulphetrone, and the remainder received streptomycin alone. By this method an approximately equal number of patients were treated with and without sulphetrone in the two age groups and at each stage of disease on admission. Current admissions were used as control cases, so that any minor advantages in treatment recently developed would apply equally to both series.

The results of treatment are shown in Table II. All patients have been observed for a minimum period of

*We wish to thank Messrs. Burroughs Wellcome and Co. for supplies of sulphetrone in a form suitable for intrathecal injection.