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AMINOPTERIN IN THE TREATMENT OF ACUTE LEUKAEMIA

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[WITH PHOTOGRAPHURE PLATE]

Since the synthesis of pteroylglutamic acid (folic acid) by Angier *et al.* (1945), several analogues having either a similar or a biologically antagonistic activity have been prepared (Smith *et al.*, 1948). Of the antagonists, the most potent is 4-aminopteroylglutamic acid ("aminopterin"), produced by the substitution of an NH_2 group for the OH group in the 4 position of the pteridine ring of the folic acid molecule (Seeger *et al.*, 1947).

The first report of the use of folic acid antagonists in acute leukaemia was that of Meyer (1948), who obtained temporary clinical and haematological improvement in four of five cases treated with pteroylaspartic acid and methylpterotic acid. Subsequently, Farber *et al.* (1948) reported important remissions in 10 out of 16 children with acute leukaemia treated with aminopterin. The drug seemed to have a pronounced effect on leukaemic bone marrow, causing a decrease or disappearance of leukaemic cells and a reversion to normal of the peripheral white cell count, whether initially high or leucopenic. Immature cells in the blood decreased in numbers or disappeared, and in favourable cases there was an increase in the proportion of mature leucocytes and a rise in red cells, platelets, and haemoglobin. Visceral deposits were affected as well, and when present, enlargement of the spleen, liver, and lymph nodes diminished.

The remission rate in the above series was far beyond the rate of spontaneous remissions to be expected in acute leukaemia. Similar but less striking results have been reported after the use of aminopterin and other antagonists by Pierce and Alt (1948), Stickney *et al.* (1948), Dameshek (1948), Meyer *et al.* (1949), and Wolman *et al.* (1949). In a more recent report, Farber (1949), using aminopterin, "amethopterin" (4-amino-N10-methylpteroylglutamic acid), and "amino-an-fol" (4-aminopteroylaspartic acid), has reported a 50% remission rate in 60 children with acute leukaemia treated for three months or more, including remissions of 16 and 23 months. All authors stress the temporary nature of the remissions induced and the unpredictability of action and the narrow therapeutic margin of the drugs used.

This study is based on 14 cases of acute and subacute leukaemia in adults and children treated with aminopterin. One patient died within 36 hours of admission and has been excluded from the series. The results of treatment in 13 cases are presented.

Case 1. Acute Monocytic Leukaemia

A male school-teacher aged 45 first noticed undue dyspnoea on exertion and sore throat whilst mountaineering on August 18, 1948. These symptoms became worse, and a week later he developed a purple rash on the abdomen, night sweats, and increasing general weakness. By September 15 the rash had become generalized and splinter haemorrhages had appeared beneath the nails. He was admitted to another hospital, where his condition rapidly deteriorated, and on September 20 he was transferred to Hammersmith Hospital as a case of acute leukaemia.

On examination he was seen to be a well-built man, but wasted and weak, with a temperature of 103°F . (39.4°C). A purplish maculo-papular rash involved the face, trunk, and extremities, with some oedema of the underlying tissues. In addition there were purpuric spots on the legs, which were confluent in places. The gums were spongy but not bleeding, and he had stomatitis and a purulent tonsillitis. All superficial lymph nodes were enlarged. No abnormalities were found in the lungs or in the cardiovascular or central nervous systems. The liver was enlarged $2\frac{1}{2}$ in. (6.3 cm.), and the spleen $\frac{1}{2}$ in. (1.25 cm.) below the costal margins. The urine contained albumin and excess urobilinogen. A radiograph of the chest was normal. A blood count showed: red cells, 2,600,000 per c.mm.; haemoglobin, 8.6 g. per 100 ml.; platelets, 230,000 per c.mm.; white cells, 6,000 per c.mm. (polymorphs 10%, lymphocytes 15%, monocytes 75%).

Marrow Biopsy.—Sternal puncture. About 60% of the marrow cells were large atypical mononuclears of varying maturity, the most primitive resembling reticulum cells. Slightly less primitive cells had large nuclei with several nucleoli and a moderate amount of basophilic cytoplasm. The most mature cells resembled monocytes. Less than 1% of the total nucleated cells were erythroblasts (Plate, Fig. 1).

Skin biopsy of a cutaneous papule showed the dermis to be infiltrated with mononuclear cells, the appearance being that of leukaemic infiltration.

Treatment and Progress

Parenteral penicillin was given throughout the illness. A total of 20 mg. of aminopterin in daily doses of 1 mg. was given intramuscularly from September 24 to October 16, and several blood transfusions were found necessary. The result of treatment was that the throat condition rapidly resolved, the temperature fell, and the patient's general condition improved remarkably. He regained his appetite, and his weight rose. The cutaneous infiltrations began to disappear soon after treatment started and had faded before it was completed. The lymph nodes, liver, and spleen were still enlarged, but had diminished considerably in size. Purpura had vanished.

Treatment was complicated by the development of a large haematoma in the right thigh at the site of a penicillin injection; this broke down and formed an indolent ulcer, but by the end of October it had healed and he was able to get up feeling reasonably well. Puncture of a vertebral spine on October 16 showed that the marrow was much less leukaemic. Only 5% of the cells were reticulum cells or monocytes and 20% were erythroblasts. Erythropoiesis was predominantly normoblastic, but a few intermediate megaloblasts were present (Plate, Fig. 2). This improvement in the marrow was reflected in the peripheral blood. The proportion of mature polymorphs rose to 50-60% and only 2-5% of the cells were abnormal monocytes. The total white cells rose to normal levels and platelets increased to 350,000 per c.mm. (Fig. A).

A second course of aminopterin was started on November 5 because of a rising total white cell count with a diminution in the proportion of mature polymorphs and the appearance in the blood of primitive granulocytes. Vertebral puncture then showed that the marrow had become overtly leukaemic again; some 75% of the cells were monocytes of varying degrees of differentiation, with a few developing granulocytes and erythrocyte precursors. By November 27 a further 13 mg. of aminopterin had been given, and two more transfusions. The total white count was then within normal limits, but the proportion of abnormal mononuclears was still high and 5-6% of blast cells and myelocytes were present. The patient's general condition, however, was well enough to allow him to be discharged home on November 28, at which time there was some improvement in the marrow picture.

On December 13 he was readmitted because of haematemesis, generalized purpura, faucial angina, and ulcero-necrotic gingivitis. All superficial lymph nodes, liver, and spleen were

greatly enlarged. He died that day from an intracerebral haemorrhage. The white cell count was 320,000 per c.mm., the majority of cells being abnormal monocytes and blast cells.

At necropsy the body was covered with a petechial rash. There was generalized moderate enlargement of lymph nodes and of the lymphoid tissue in the large intestine. The spleen (1,440 g.), liver (5,000 g.), and kidneys were all greatly enlarged, and the appendix was infiltrated with whitish tissue. Histologically, these changes were due to infiltration of the organs with leukaemic cells having the character of monocytes. The

bone marrow was generally red and the femur was filled with reddish marrow from end to end. There were a number of thromboses in the vessels of the white matter of the brain and small haemorrhages in both occipital lobes and in the right temporal and frontal lobes. Many small vessels in all the organs were plugged with leukaemic cells, and scattered haemorrhages were fairly numerous. The liver showed extensive leukaemic infiltration of the sinusoids and portal tracts. A similar perivascular infiltration was found in other organs, notably the lungs.

Comment. — The initial response to treatment was a clinical and haematological remission lasting five weeks. During this period a considerable reduction in the proportion of leukaemic cells in the bone marrow was reflected in the peripheral blood, in which abnormal monocytes decreased in number while platelets and mature granulocytes rose to normal levels. When he subsequently relapsed aminopterin proved of no value.

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

Case 2. Acute Myeloblastic Leukaemia

This patient* was a girl aged 3 years 9 months. Early in September, 1948, her mother observed the gradual onset of swelling and discoloration around both eyes, together with drowsiness, loss of energy, and anorexia. These symptoms became more pronounced and she began to vomit. On September 30 she was admitted to another hospital, where she was found to be febrile and to have generalized enlargement of lymph nodes. During the next three weeks her condition deteriorated, the eyes and face swelling beyond recognition. She was transferred to Hammersmith Hospital on October 20 as a case of acute leukaemia.

*This patient and Case 3 were transferred to our care through the courtesy of Dr. R. E. Bonham-Carter.

J. V. DACIE, E. DRESNER, D. L. MOLLIN, AND J. C. WHITE: AMINOPTERIN IN ACUTE LEUKAEMIA

FIG. 1.—Case 1. Bone-marrow smear on admission. ($\times 400$.)

FIG. 2.—Case 1. Bone-marrow after first course of aminopterin. ($\times 400$.)

FIG. 3.—Case 4. Bone-marrow before aminopterin treatment. ($\times 470$.)

FIG. 4.—Case 4. Bone-marrow after first course of treatment. ($\times 470$.)

FIG. 5.—Case 5. Bone-marrow before treatment. ($\times 470$.)

FIG. 6.—Case 5. Bone-marrow after treatment. ($\times 470$.)

PETER STORY: HISTOLOGICAL REACTIONS TO INJECTIONS OF PROCAINE PENICILLIN IN OIL

FIG. 1.—Deltoid muscle (haematoxylin-eosin): oil cysts, muscle degeneration, and oedema. ($\times 65$.)

FIG. 2.—Degenerate muscle fibres and cellular reaction round oil droplet in deltoid muscle; H.-E. ($\times 125$.)

FIG. 3.—Oil globule surrounded by foam cells and a multinucleate giant cell; H.-E. ($\times 300$.)

On admission the child was pallid, wasted, and febrile. Weight 34 lb. (15.4 kg.). There was marked enlargement of both parotid and submandibular salivary glands, but the most striking features were tense swellings of both upper and lower lids, which were discoloured and purple (Fig. B). The

conjunctivae were injected and chemotic, but there was no proptosis and ocular movements were full. The skin, mouth, and throat were healthy. All the superficial lymph nodes were moderately enlarged. The liver and spleen were not palpable. Other systems were normal, as were the urine and radiograph of the chest. A blood count showed: red cells, 2,800,000 per c.mm.; haemoglobin, 8.3 g. per 100 ml.; platelets, 200,000 per c.mm.; white cells, 17,000 per c.mm. (polymorphs 10%,

FIG. B.—Case 2. Periorbital leukaemic infiltrations. Before treatment. October 20, 1948.

eosinophils 1%, lymphocytes 38%, monocytes 10%, blast cells 8%, neutrophil myelocytes 3%, "smudge" forms 30%).

Marrow Biopsy.—Marrow was aspirated from the head of the tibia. The majority of the cells were primitive, with deeply basophilic agranular cytoplasm, and were considered to be myeloblasts. There was little, if any, differentiation from normal erythropoiesis or leucopoiesis.

Treatment and Progress

Five intramuscular injections of 1 mg. of aminopterin were given between October 22 and 30, and two blood transfusions, each of 560 ml. Oral penicillin was also given. The result was a rapid fall in the total white cell count to 650 per c.mm. on November 1, and thereafter a steady rise to normal levels. During the leucopenic phase all types of white cells were depressed, but with the rising count mature polymorphs increased to 72% of the total, and immature granulocytes disappeared from the blood.

Marrow biopsy two weeks after discontinuation of aminopterin showed that leucopoiesis and erythropoiesis were taking place normally and that reticulum and stem cells were substantially reduced in the marrow. The haemoglobin rose spontaneously to 15.5 g. by November 22 and platelets rose concurrently to 380,000 per c.mm. There was subjective and objective clinical

FIG. C.—Case 2. Resolution of periorbital leukaemic infiltrations following treatment. November 5, 1948.

improvement; the temperature subsided, lymph-node enlargement resolved, and the weight rose, but the most striking improvement was in the condition of the eyes.

By November 5 the periorbital leukaemic infiltration had disappeared and the eyes appeared normal (Fig. C) except for a residual keratitis with an hypopion ulcer on the right side. A further 3 mg. of aminopterin was given during November

25-27 because of a rise in total leucocytes to 23,000 per c.mm. and a slight relapse in the condition of the eyes. After this she improved enough to be discharged on December 6 (Fig. D). The patient was seen again on December 13, when she appeared fairly well; but a week later she died at home suddenly following a convulsion. Death was thought to be due to acute uraemia.

At necropsy (Dr. A. G. Sheara) the significant findings were enlargement of the kidneys (224 g.), which were infiltrated with

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

white nodules, and there were similar infiltrations in the pancreas and gastric mucosa. The liver and spleen were not enlarged and appeared normal to the naked eye, and there was moderate enlargement of the mesenteric glands.

Histologically, the kidneys, stomach, pancreas, and mesenteric nodes were infiltrated with large round mononuclear cells, showing numerous mitoses. Surprisingly, sections of the vertebral marrow showed well-differentiated actively erythropoietic and leucopoietic tissue, with only a slight excess of primitive cells, in marked contrast to the visceral lesions and to the pre-treatment aspiration biopsy.

Comment.—The remission induced in this case was dramatic, though short-lived, and necropsy revealed that, though the leukaemic process seemed to have been largely eradicated from the bone marrow, visceral infiltration was nevertheless pronounced.

Case 3. Subacute Lymphoblastic Leukaemia

A boy aged 3 years first complained of stiffness of the back on November 23, 1948. A week later he also complained of pain in both legs, and by December 20 was unable to walk owing to pain and stiffness of the spine and legs and was anorexic and very pale. He was admitted to another hospital, where he was found to be anaemic, with generalized enlargement of lymph nodes; and radiological bone changes were found in the lumbar spine and right femur. The white cell count was 3,000 per c.mm., with 86% lymphocytes, and sternal puncture showed that the cells in the marrow were almost all lymphoblasts. He was transferred to Hammer-smith Hospital on January 1, 1949, as a case of aleukaemic leukaemia.

On admission he was seen to be an intelligent child, but pale and anorexic. Weight 29 lb. (13.2 g.). The skin, throat, and mouth were clear, and the liver and spleen were not felt. No abnormalities were found in the other systems. Some small lymph nodes were palpable in the neck, but none elsewhere, and the salivary glands were not enlarged. There was no bone tenderness, but the dorsolumbar spine was rigid and movement was resisted. He could stand only with support. The urine and radiographs of the chest were normal.

Radiographs of the long bones and spine revealed a pseudo-fracture with adjacent periosteal elevation at the upper end of the right humerus and a similar condition in the metaphysis at the lower end of the right femur. There was collapse of the second lumbar vertebra with anterior wedging. Other vertebrae and long bones were normal. A blood count showed: red cells, 4,600,000 per c.mm.; haemoglobin, 11.1 g. per 100 ml.; platelets, 340,000 per cmm.; white cells, 5,800 per c.mm. (polymorphs 32%, lymphocytes 63%, monocytes 2%, plasma cells 3%).

Marrow Biopsy.—The upper end of the tibia was punctured. About 90% of the total cells were of the lymphocyte series, mostly lymphoblasts, but with some differentiation to adult forms. The picture was that of lymphoblastic leukaemia.

Progress and Treatment

Two short courses of aminopterin, each of 1 mg. intramuscularly for four days, were given between January 10 and 21. This was followed by a moderately severe ulcerative stomatitis which lasted eight days. He then developed a respiratory infection and consolidation of the left lower lobe, which was treated with sulphadimidine. By the middle of February his chest was clear, he was afebrile, and there was great symptomatic improvement. His appetite returned and he gained weight. The glandular enlargement in the neck had resolved and the stiffness and pain in the spine had disappeared and he was able to walk unaided.

Radiographs showed healing of the fracture of the right humerus, resolution of the osteitis at the lower end of the right femur, and a return to normal architecture in the structure of the second lumbar vertebra. The haemoglobin level was maintained, and the white count was 7,000 per c.mm. with 50% polymorphs, and no immature cells were present. The platelet count rose to 400,000 per c.mm. Tibial puncture on March 2 showed active leucopoiesis, but without evidence of leukaemia, blast cells forming less than 1% of the total, and erythroblasts, granulocyte-precursors, and megakaryocytes were present in normal numbers. He was discharged home active, and with no abnormal signs, on February 23.

He was seen again on April 14, when he appeared clinically well, with a haemoglobin of 15.5 g. per 100 ml. and a normal blood count, but sternal puncture revealed a resurgence of the leukaemic process in the marrow, some 35% of the cells being lymphocytes of varying maturity, of which half were

nucleolated blast cells. He was readmitted, and 9 mg. of aminopterin was given orally from May 7 to 16. His general condition remained good during treatment. The white cell count, 13,000 per c.mm. on admission, fell to 3,000 per c.mm., with 30–40% polymorphs and 50–60% lymphocytes. He was discharged on May 30, clinically well, weighing 33 lb. (15 kg.). The bone pattern was still radiologically normal at all the sites of previous infiltration. He remained well throughout the summer, but his condition began to deteriorate towards the end of August.

When admitted for the third time on August 29 he was found to have lost weight, and his liver, spleen, and lymph nodes were found to be enlarged. Anaemia, thrombocytopenia, and granulocytopenia were present; of 5,000 white cells per c.mm., only 3–4% were polymorphs. Moderate numbers of lymphoblasts were present. The bone marrow was leukaemic. A third course of aminopterin totalling 12 mg. was given, during which time his condition continued to deteriorate. He died on September 19, three days after treatment was discontinued, following a short bout of diarrhoea and vomiting.

At necropsy there was generalized lymph-node enlargement, histologically marked by sheet-like growth of leukaemic lymphocytes in the medullary stroma, congestion of capillaries, and some areas of cellular degeneration and depletion; the reticulum cells of the follicles were hyperplastic and degenerate, the splenic Malpighian bodies being affected similarly. The bone marrow was red and gelatinous, crowded with leukaemic cells and primitive stem cells, and showed areas of haemorrhage, cellular degeneration and depletion, and oedema of sinusoids. A 20-cm. segment of the jejunum was the site of haemorrhagic necrosis, with adjacent oedema and prominence of lymphoid tissue.

Comment.—The initial response to aminopterin was most satisfactory from both clinical and haematological aspects. Primitive stem cells were reduced from about 90% to less than 1% in the marrow, radiological changes in the spine and long bones disappeared, and clinically he became indistinguishable from normal. On the second occasion the response to aminopterin was less satisfactory from the haematological point of view, but he remained well until his final relapse some nine months from the onset of symptoms.

Case 4. Myeloblastic Leukaemia

A boy aged 2 years began to lose weight and appetite in October, 1948, and became unsteady on his legs and increasingly pale. On November 4 he was admitted to another hospital for investigation of anaemia and was transfused, but was discharged on November 25 because he developed mumps. On December 28 he was admitted to a second hospital with general weakness, inability to walk, and marked pallor. He was there found to be febrile and anaemic, with generalized enlargement of the lymph nodes. On the evidence of blood examination and marrow biopsy a diagnosis of aleukaemic leukaemia was made and he was transferred for treatment on January 1, 1949.

On admission he was found to be febrile and pale, with no purpura or icterus. Weight 25½ lb. (11.5 kg.). No abnormality was found in the throat or in the respiratory, cardiovascular, and central nervous systems. Firm enlarged glands were felt in the neck, but none elsewhere. The edge of the liver was just palpable, but the spleen could not be felt. A radiograph of the chest was normal and there was no abnormality in the urine. A blood count showed: red cells, 1,900,000 per c.mm.; haemoglobin, 3.7 g. per 100 ml.; platelets, 131,000 per c.mm.; white cells, 4,600 per c.mm. (polymorphs 9%, lymphocytes 91%).

Marrow Biopsy.—The head of the tibia was punctured; 90% of the cells were blast cells with scanty basophilic cytoplasm, stippled nuclear chromatin, and one or more nucleoli. Only a few lymphocytes and erythroblasts were seen. The appearance was that of myeloblastic leukaemia (Plate, Fig. 3).

First Admission

A transfusion was given on January 2. The haemoglobin rose to 11.5 g., and thereafter this level was maintained. During the first two weeks seven 1-mg. injections of aminopterin were given. Throughout January his condition was poor; he vomited persistently, became very dehydrated, and developed a left basal pneumonia. However, by February 1 he was much improved; his chest was normal and pyrexia had subsided. His appetite increased, his weight rose, and he was allowed up. The cervical glands and spleen were no longer palpable. The white cell count at this time was

FIG. E.—Case 4. First admission. Treatment and progress.

10,000 per c.mm., of which 42% were mature polymorphs, and no abnormal cells were present. The platelets had risen to 417,000 per c.mm. Tibial puncture at the end of January revealed a marrow that was almost indistinguishable from normal. There was active leucopoiesis and erythropoiesis, with blast cells forming only 3% of the total and a normal proportion of segmented neutrophils and normoblasts (Plate, Fig. 4, and see Fig. E, above).

During March he remained well in spite of an upper respiratory infection and parotitis, and when discharged on March 9 he was active, had no abnormal signs, and weighed 27 lb. (12.2 kg.). The white cell and platelet counts were normal, and aspiration of the marrow revealed no positive evidence of leukaemia.

Second Admission

The patient remained well until readmitted on April 24 with a four-days history of anorexia, vomiting, and the passage of blood in the stools. He appeared well nourished and was not anaemic, but small glands were felt in the neck, axillae, and groins, and the liver and spleen were palpable 1 in. (2.5 cm.) below the rib margins. The white cell count was 28,000 per c.mm., with 72% myeloblasts and only 3% mature granulocytes, and the platelets had fallen to 21,000 per c.mm. Aspiration of the marrow showed once more an almost complete replacement by myeloblasts and micromyeloblasts.

FIG. F.—Case 4. Second admission. Treatment and progress.

Aminopterin, 10 mg., was given by mouth in the course of ten days and at the end he was miserable, slightly febrile, and completely anorexic. The liver, however, was no longer palpable and only the tip of the spleen could be felt. Enlargement of lymph nodes had diminished. The white cell count fell to 3,000 per c.mm. on May 5; only 2% of the cells were blasts, but no polymorphs could be found and the platelets remained very low. His general condition improved, but by May 20 the white cell count had risen to 122,000 per c.mm. and the liver and spleen were re-enlarging rapidly (Fig. F, above).

A third course of oral aminopterin and a small transfusion were given, with the result that the white cell count was again markedly depressed, but blast cells persisted in the blood and

polymorphs remained absent. As before, there was a temporary diminution in the size of the liver and spleen, but two weeks later a complete relapse occurred and he died on June 24. Both courses of treatment during this admission were complicated by buccal stomatitis.

At necropsy the hyperplastic bone marrow was red in colour and crowded with small primitive cells and cells evidently

was the site of mucosal necrosis and oedema without significant leukaemic infiltration; neighbouring Peyer's patches were ulcerated, and were infiltrated by leukaemic cells.

Comment.—When first admitted, a relatively small amount of aminopterin caused a reversion almost to normal in the state of the bone marrow and peripheral blood and a clinical remission of about three months. When he relapsed two larger courses of the drug each induced a pronounced though transient depression of the leucocyte count with some diminution in the size of the spleen, but without a corresponding improvement in the marrow and without any sustained clinical benefit.

Case 5. Acute Myeloblastic Leukaemia

A schoolboy aged 13 was referred to his doctor early in March, 1949, because of increasing pallor. There was no bleeding or bruising, and he was attending school. He was admitted to a hospital for investigation and was found to be severely anaemic, with an enlarged spleen and liver. The leucocyte count varied from 10,000 to 18,000 per c.mm., most of the cells being immature, and a diagnosis of acute leukaemia was confirmed by marrow biopsy. He was transfused, and on March 25 was transferred to Hammersmith Hospital for further treatment.

On admission he was found to be an intelligent active boy, but very anaemic. There was no purpura and the mouth and throat were normal. The tonsillar glands were palpable, but no other glands were felt. The liver and spleen were palpable 1 in. (2.5 cm.) below the costal margins. Other systems were normal. Weight 88 lb. (39.9 kg.). Temperature 99.6° F. (37.55° C.). A radiograph of the chest was negative. A blood count showed: red cells, 2,000,000 per c.mm.; haemoglobin, 6.1 g. per 100 ml.; platelets, 55,000 per c.mm.; white cells, 10,000 per c.mm. (blast cells 79%, polymorphs 5%, lymphocytes 15%, monocytes 1%) (see Fig. G).

Marrow Biopsy.—Sternal puncture showed the marrow to be replaced by primitive cells having the characteristics of micromyeloblasts (Plate, Fig. 5).

Progress and Treatment

During the first week after admission he had frequent small epistaxes, and was given a blood transfusion on April 1, which raised his haemoglobin to 8.9 g. A total of 13 mg. of aminopterin was given by mouth from April 4 to 12. Towards the end of treatment he had severe and repeated epistaxes, and was transfused three times; the total volume of blood given was 4.7 litres. He also developed a moderately severe vesicular stomatitis lasting one week, for which he was given parenteral penicillin. By April 23 epistaxes had ceased and, his condition being much improved, he was allowed up.

He was discharged home on May 10, free of symptoms. The liver and spleen were no longer palpable, and no glands could be felt. He was normally active and had gained 5 lb. (2.3 kg.) in weight since admission. Aminopterin had caused a fall in the total white cell count to 930 per c.mm. on April 22. The leucopenic phase lasted about one week, and then the white cell count rose to normal levels. Blast cells and immature granulocytes disappeared from the blood, and at the time of discharge he had 8,000 leucocytes per c.mm., of which 67% were polymorphs, and his platelets were 200,000 per c.mm. The bone marrow had been transformed. On April 23 there were few recognizable blast cells present, and granulopoiesis and erythropoiesis were active. On May 6, although a few myeloblasts were present, developing granulocytes and erythroblasts were well represented, and megakaryocytes were abundant (Plate, Fig. 6).

The patient was readmitted on May 31 because marrow biopsy showed an increased proportion of primitive cells and about 20% of the leucocytes in the peripheral blood were blast cells. Between June 1 and 16, 17 mg. of aminopterin was given by mouth. The drug was then discontinued because of severe and intractable epistaxis. His haemoglobin fell to

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

belonging to the granulocyte series. Several groups of lymph nodes were enlarged, their medullary stroma having a cellular composition similar to that of the bone marrow and spleen. The liver showed periportal, and the kidneys perivascular, leukaemic infiltration. The pharynx was affected by acute necrotizing inflammation. A 17-cm. length of terminal ileum

6.1 g. and another transfusion was required. The changes in the blood and bone marrow were not so dramatic as on the first occasion. The total white cells fell to 3,700 per c.mm. on June 22, and thereafter remained steady at about 8,000 per c.mm. There was some reduction in the number of circulating primitive cells and a rise in the proportion of polymorphs, but blast cells were not entirely removed, either from the blood or from the bone marrow. In view of the severe bleeding, further treatment at that time was considered inadvisable, and he was discharged home on July 2, free of symptoms and with no glandular or splenic enlargement but with a slight fall in weight. A month later he was readmitted, severely anaemic and with a very large spleen. Again treatment with aminopterin had to be abandoned owing to almost continuous epistaxis after only 6 mg. had been given. He died on August 11. Necropsy was not performed.

Comment.—Aminopterin in this case produced a marked remission on the first occasion it was used, but when the patient relapsed a few weeks later treatment had to be abandoned because of severe epistaxis, and the improvement in the blood and bone marrow was much less striking. On the third occasion continuous epistaxis virtually precluded further attempts at treatment.

Case 6. Subacute Myeloblastic Leukaemia

A 47-year-old housewife first consulted her doctor in August, 1948, because of pallor, dyspnoea on exertion, and weakness, symptoms which became progressively more severe during the next five months, and to which were later added palpitations, swelling of the ankles, and loss of weight. There was no external bleeding and the menses were regular. On February 3, 1949, she was admitted to another hospital, where she was found to be very anaemic and to have a white cell count of 39,000 per c.mm., of which the majority were immature granulocytes. She was transfused, and on February 7 was transferred to Hammersmith Hospital as a case of myeloblastic leukaemia.

On admission she was febrile and very pale, but apart from a recent haemorrhage in the left fundus there were no external signs of bleeding and no icterus. The throat, mouth, and gums appeared normal and there were no palpable glands. The tip of the spleen was just palpable; the liver was not felt. No abnormalities were apparent in the lungs or in the cardiovascular and central nervous systems. The urine and radiographs of the chest were normal. A blood count showed: red cells, 1,600,000 per c.mm.; haemoglobin, 5.3 g. per 100 ml.; packed cell volume, 16%; platelets, 100,000 per c.mm.; white cells, 40,000 per c.mm. (blast cells 28%, promyelocytes 2%, neutrophil myelocytes 4%, metamyelocytes 8%, polymorphs 35%, lymphocytes 16%, monocytes 1%, "smudge" forms 6%).

Marrow Biopsy.—Marrow was aspirated from the spinous process of a lumbar vertebra. The picture was of subacute myeloid leukaemia; 25% of the cells were myeloblasts and most of the remainder developing granulocytes. A few lymphocytes were present, but erythroblasts were very scanty and no megakaryocytes were seen.

Treatment and Progress

Soon after admission penicillin therapy was started, and she was transfused on February 21 and 28, with the result that the haemoglobin was raised to 14.7 g. During her first ten days under observation she developed a further haemorrhage into the left fundus, septic lesions at the transfusion sites on the left arm and ankle, and ulcerative lesions of the lips with a marked tendency to bleed.

Aminopterin, 34 mg., was given intramuscularly in 2-mg. daily doses between March 1 and 9. A generalized purpuric rash developed and she bled from ulcers on the lips, nose, transfusion sites and vertebral puncture site, and haematomata formed at the sites of penicillin injections. Spreading superficial ulceration developed on both forearms and legs and over the sternum. The throat, tonsils, and tongue became ulcerated and there was severe menorrhagia, which was partially controlled by large doses of stilboestrol. The spleen enlarged

and the liver became palpable. She continued febrile and anorexic and her weight fell. A third transfusion was given on March 16 as the haemoglobin had fallen to 4.6 g.

The effect of aminopterin on the peripheral blood was a steady fall in the white cell count to 3,800 per c.mm. on March 21 and thereafter a rise to 17,000 per c.mm. a week later, following which the total white count remained at normal levels till death. There was at first no change in the differential count, but about April 1 the proportions of blast cells and immature granulocytes fell, and that of the polymorphs rose. On April 16, a week before death, 54% of 5,000 total white cells were polymorphs and only

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

11% were immature cells. As will be seen (Fig. H), platelets remained very low or absent during the whole illness.

After discontinuation of aminopterin, cutaneous ulceration healed, sloughs in the mouth separated, and the fundal haemorrhages were absorbed, but the patient remained anorexic and became increasingly cachectic. She was transfused again on April 7, but on April 10 there was a severe rectal haemorrhage lasting several days which almost exsanguinated her. Further transfusions were refused. The haemoglobin fell to 3 g. and she died on April 22. Necropsy was not performed.

Comment.—The history in this case was fairly long-standing and the course was downhill from the start of

treatment. The effect of aminopterin on the blood was to reduce the total white cell count to normal levels with an increase in the maturity of the granulocytes, but the thrombocytopenia was uninfluenced, and the haemorrhagic manifestations ultimately proved fatal.

Case 7. Subacute Lymphoblastic Leukaemia

A schoolboy aged 7 developed painful red swellings of both elbows, with malaise and low fever, early in November, 1948, and during the next four weeks had migratory painful swellings of the elbows, wrists, knees, and ankles, and occasionally of the face, and was pale and sweating. A diagnosis of acute rheumatism was made. On March 11, 1949, he was admitted to a hospital for incision of an abscess of the buttock, but fever persisted and he complained of pain in the limbs, although there were no further joint swellings. He was anorexic and pallor increased. Investigation of the blood and bone marrow led to the diagnosis of an acute stem-cell leukaemia, and radiographs showed bone changes in the left humerus. He was transfused and transferred for treatment on April 14, 1949.

On admission he was thin, with a good colour but in obvious pain. Temperature 99.4° F. (37.4° C.). Weight 42 lb. (19 kg.). There was no purpura or bleeding, and his mouth and throat were healthy. Small mobile lymph nodes were palpable in the neck, axillae, groins, and epitrochlear regions. Salivary glands were not enlarged, and the liver and spleen were not palpable. The heart and lungs were normal. The upper third of the shaft of the left humerus was tender and movements of the left shoulder and elbow were restricted. The left knee was held semiflexed and all movements were extremely painful. There was marked tenderness over the lower end of the femur and gross wasting of the quadriceps, but no effusion into the joint.

X-ray Examination.—Radiologically the chest was normal. There was periostitis throughout the length of the left humerus and considerable cortical destruction of the upper third resulting in a pathological fracture. The femora and left knee showed no change, but there was a wedge deformity of the ninth dorsal vertebral body. The x-ray appearances were consistent with leukaemic infiltration of bone.

A blood count showed: red cells, 4,200,000 per c.mm.; haemoglobin, 13.5 g. per 100 ml.; platelets, 70,000 per c.mm.; white cells, 2,500 per c.mm. (polymorphs 5%, lymphocytes 86%, blast forms 8%, monocytes 1%).

Marrow Biopsy.—On sternal puncture the marrow was very cellular. The great majority of the cells were blast forms, considered to be lymphoblasts.

Progress and Treatment

During the first week he was febrile and ill, with constant severe pain in the left knee and arm. Aminopterin, 13 mg. in daily doses of 1 mg. by mouth, was given from April 22 to May 5. The bone pains ceased after five doses of aminopterin, but treatment was complicated by a haemorrhagic stomatitis, and a fall in haemoglobin to 4.5 g. necessitated a transfusion. After this episode he became afebrile, and a general improvement began which was maintained until his discharge. Tenderness of the left knee and arm disappeared within three weeks and he was able to move his shoulders, elbows, and knees freely, and he began to walk. His appetite returned and his weight increased. The immediate effect of treatment on the blood was a reduction in the total leucocyte count to 800 per c.mm. on May 12 and thereafter a rise to normal levels. Sternal puncture on June 9 showed that while 60% of the cells were lymphocytes, most were mature, and only 6% were blast cells. Developing granulocytes and erythroblasts were well represented.

A second course of aminopterin totalling 8 mg. was given from June 14 to 21 without untoward effect, and when he was discharged home on June 28 he was walking fairly well, had no palpable glandular or splenic enlargement, and was apparently normal. Radiographs of the left humerus on May 26 showed consolidation of the periosteal new bone with

sclerosis of the cortex and union of the fracture previously demonstrated.

On August 9 he was readmitted because of pain in the back. This was found to be due to collapse of most of the dorsal and the second to fifth lumbar vertebral bodies. The bone marrow was again leukaemic. The white blood cell count was 5,000 per c.mm. with only 13% of polymorphs. A third course of aminopterin, totalling 13 mg., produced no improvement in the peripheral blood or in the appearance of the bone marrow, but the bone pain was relieved. After a transfusion of 1,100 ml. of blood a fourth course of 8 mg. of aminopterin by mouth was given. His condition rapidly deteriorated and the total leucocyte count rose to 63,000 per c.mm., of which 80% were lymphoblasts. He died on November 10, with generalized purpura and bleeding from the stomach and rectum.

At necropsy there was generalized enlargement of lymphoid tissue and leukaemic infiltration of the heart, pericardium, pleurae, lungs, spleen, liver, and kidneys. The marrow of the long bones was red and gelatinous. The vertebrae were collapsed and filled with greyish-red marrow and the periosteum over the upper end of the left humerus was greatly thickened by leukaemic infiltration. Microscopically, the bone marrow was found to be very cellular, the normal tissue being replaced by primitive leukaemic cells.

Comment.—Leukaemic bone infiltration was a striking feature in this case. The initial response to treatment was symptomatically and haematologically satisfactory, but increased amounts of aminopterin were without effect when given for his subsequent relapse. At necropsy there were no changes which could be attributed to the treatment.

Case 8. Subacute Lymphoblastic Leukaemia

A girl aged 5½ years first had slight pallor in December, 1948, but it did not become pronounced until after an attack of bronchitis early in January, 1949, when she complained of increasing tiredness, loss of weight, and night sweats. She was admitted to another hospital on February 1 and was found to be severely anaemic with splenomegaly and generalized enlargement of the lymph nodes. The white cell count was 4,200 per c.mm., with a preponderance of lymphocytes; marrow biopsy confirmed the diagnosis of lymphatic leukaemia. During April her condition deteriorated; anaemia and lymph-node enlargement increased and the parotids became swollen. She was transferred on April 29 with the diagnosis of aleukaemic leukaemia.

On admission she was thin and pale, with petechial haemorrhages in the buccal mucosa and ecchymoses of both arms. Temperature 102° F. (38.9° C.). Weight 41 lb. (18.6 kg.). Small hard glands were felt in the neck, axillae, and groins. The parotids and the left submandibular salivary gland were swollen and tender. The spleen was palpable one fingerbreadth and the liver three fingerbreadths below the costal margins. The throat and gums were healthy and no abnormalities were detected in the lungs, heart, or central nervous system.

Radiographs revealed an area of cortical bone destruction, with periosteal elevation at the distal end of the left tibia, and periostitis of the shaft of the first left metatarsal—changes compatible with leukaemic infiltration. A blood count showed: red cells, 2,000,000 per c.mm.; haemoglobin, 7.4 g. per 100 ml.; platelets, 46,000; white cells, 2,700 per c.mm. (polymorphs 32%, lymphocytes 58%, monocytes 4%, plasma cells 6%).

Marrow Biopsy.—The iliac crest was punctured. About 75% of the cells were of the lymphocyte series, the majority being blast cells with one or two nucleoli and uniform cytoplasmic basophilia; a few were mature lymphocytes. The appearance was that of lymphoblastic leukaemia.

Progress and Treatment

A transfusion of 570 ml. of blood on May 5 raised the haemoglobin to 9.7 g. A total of 15 mg. of aminopterin in 1-mg. oral doses was given from May 10 to June 1. Clinical

improvement was noticed after 6 mg. had been taken. She became afebrile, her appetite improved, and she began to walk, but limped slightly on the left foot. At the end of treatment a few small glands were felt in the neck only, and the salivary glands, liver, and spleen were no longer palpable. Her weight had increased and her colour had improved. Radiographs showed no further progress in the bone lesions. The aminopterin had no apparent effect on the peripheral blood; the white cell count remained at 4,000–8,000 per c.mm., with 20–30% polymorphs and 50–60% of mature lymphocytes. Iliac-crest puncture on June 9, however, showed a great reduction in the leukaemic process in the marrow. About half the cells were lymphocytes, but only 1% were as primitive as before treatment, and normally developing granulocytes and erythroblasts were numerous. The patient was discharged home on June 16, and when seen again two months later she weighed 48 lb., was clinically normal in every way, and there were no abnormal cells in the peripheral blood.

However, by the beginning of September there were clinical and haematological signs of relapse. She was admitted and given 7 mg. of aminopterin from September 12 to 18. At the end of treatment there was great improvement, both in her clinical well-being and in the appearance of the bone marrow. She was discharged on September 27 to continue aminopterin as an out-patient, in a dosage of 0.25 mg. by mouth on alternate days.

A month later her haemoglobin had risen spontaneously to 17.2 g. and the platelets to 400,000 per c.mm. There were 15,000 white cells per c.mm., the differential count being normal. She was clinically well and had gained 4½ lb. (2 kg.) in weight. However, at the beginning of December her haemoglobin started to fall, she became anorexic and listless, and a marrow biopsy confirmed that she had relapsed. The dose of aminopterin was increased to 0.25 mg. daily, but without avail. Her peripheral blood became flooded with lymphoblasts, and she died on December 26.

Necropsy revealed a moderate generalized lymph-node enlargement as well as infiltration of the solid viscera with leukaemic cells.

Comment.—This case was aleukaemic from the outset, and aminopterin had little apparent effect on the peripheral blood. Nevertheless, the bone marrow showed a very satisfactory improvement and the clinical effect was good. In its subacute course, clinical picture, with bone involvement, and in its marrow cytology the disease in this child closely resembles that of Case 5, and the initial response to treatment was similar in both cases.

Other Cases

Details of the following patients are presented in summary form through lack of space.

Case 9 was an adult suffering from an advanced stage of acute myeloblastic leukaemia, severely anaemic, and with widespread purpura. His total white cell count fell precipitously after three doses of 3 mg. of aminopterin. He died four days after admission. At necropsy relative hypoplasia of the bone marrow suggested that widespread destruction of marrow tissue had taken place.

Cases 10–12 were adults suffering from subacute paramyeloblastic leukaemia. In one case there was an appreciable improvement lasting approximately four weeks after the first course of therapy; the other two cases failed to respond.

Case 13 was a boy aged 4½ years suffering from lymphoblastic leukaemia. A dramatic remission was observed and he remained well for eight weeks. Subsequent attempts at therapy were, however, of no benefit.

Results

The results of treatment in the 13 cases, tabulated according to age and type of leukaemia, are as follows:

Adults:

Myeloblastic and paramyeloblastic	5 cases	No improvement in 4; temporary remission in 1
Monocytic	1 case	Temporary remission

Children:

Myeloblastic	3 cases	} Temporary remissions in all
Lymphoblastic	4 cases	

Remissions have been observed following treatment in each of the seven children, but in only two of the six adults. In the children the remissions have taken the form of an almost complete clinical restoration to normality and in most the peripheral blood has also become normal, or almost so, for a time. Changes in the bone marrow have been striking, but in no case has there been a complete disappearance of the primitive leukaemic cells, and this has no doubt meant that relapse has been inevitable. When relapse has occurred the evidence of this in the blood, and more particularly in the bone marrow, has antedated the clinical symptoms.

The duration of the remissions has varied from a few weeks to several months. The remissions in the two adult cases were partial and very short-lived. In the adults who failed to respond the effect of aminopterin may have been actually harmful, causing an increased tendency to bleed and perhaps increasing the incidence of septic complications.

Dosage and Toxicity

The dosage of aminopterin was largely empirical, but, in general, children were given 1 mg. daily and adults 1–3 mg. daily until there was a pronounced haematological effect or toxic symptoms compelled its withdrawal. The drug was at first given by intramuscular injection, but later it became evident that the therapeutic and/or toxic effects were the same, dose for dose, when given by mouth, and the drug has since been given only by this route. It is readily soluble in water and is almost tasteless.

In the treatment of these cases we have given a course of aminopterin initially, and have repeated it when it became obvious that the patient was relapsing. American workers have continued treatment with smaller maintenance doses when the patient is in remission (Farber, 1949; Dameshek, 1949).

There appears to be no certain guide to the amount of aminopterin required to induce a remission; each case has to be regarded as a therapeutic experiment. With children, a total dose of 5–10 mg. seems to be the maximum tolerated. Acting upon the belief that it is therapeutically important to give the maximum possible dose in a relatively short time, we have persisted with treatment until signs of toxicity have developed. The most important of these have been stomatitis with buccal ulceration, purpura, an increased tendency to bleed, diarrhoea, and leucopenia. Vomiting and alopecia have also been noted. In only two of the children did there seem reason for serious anxiety on this score, but both recovered and experienced remissions thereafter (Cases 5 and 12). Our experience with adults is very limited, but the two cases which remitted received 15 and 20 mg. of aminopterin in daily doses of 1–2 mg. Whether larger doses are advisable is uncertain.

We have attempted to counter the toxic effects of aminopterin by the administration of antibiotics, blood transfusions when indicated, and by withdrawal of the drug. Crude liver extract, folic acid, and vitamin B₁₂ have been used, and seem to be ineffective (Farber, 1949; Dameshek, 1949).

Discussion

The principle of biological antagonism is now well established, and it has been shown that substances with the same basic structure as normal essential cellular metabolites may enter into combination with specific enzymes or other cellular proteins and cause a block in the normal metabolic pathways (Woolley, 1947). For instance, in the case of a metabolite essential for bacterial growth, Fildes and Rydon (1947) have shown that the substitution of groups distinct from the combining groups may be enough to convert a growth factor into an inhibitor.

Pteroylglutamic acid is a growth factor of wide biological importance, and in particular it seems to be essential for normal haemopoiesis (see Thiersch and Philips (1949) for literature). The 4-amino compound (aminopterin) acts, however, as an antagonist to pteroylglutamic acid, but the exact way in which this is brought about is obscure. In the case of *Lactobacillus casei* it may be the synthesis of purines and thymine which is interfered with by aminopterin (Rogers and Shive, 1948); and Stokstad *et al.* (1948), working with *Streptococcus faecalis* R, have obtained evidence of interference by methyl-folic acid of purine and pyrimidine synthesis. However, these effects may not be wholly due to simple antagonism; for instance, aminopterin inhibits the growth of chick embryos, but large doses of pteroylglutamic acid do not overcome this (Karnofsky, Patterson, and Ridgway, 1949), and pteroylglutamic acid similarly fails to neutralize the inhibitory effect of aminopterin on the growth of *Lactobacillus leishmannii* (Stokstad *et al.*, 1949).

As quoted in the introduction to this paper, there is evidence that aminopterin is capable of causing remissions in human acute or subacute leukaemia, particularly in childhood, and our own small series has yielded similar results.

Role of Blood Transfusions

The possible effect of blood transfusions in relation to remissions must be considered. In this series, with the possible exception of Case 1, it seems unlikely that the transfusions that have been given have done more than replace red cells and haemoglobin. The volumes of blood transfused were relatively small, and one patient who had a comparatively prolonged remission (Case 4) was not transfused at all. Similarly, the likelihood that all the remissions were spontaneous cannot be seriously entertained: their incidence in this, and other reported series, is too high and their relation to therapy too close to be coincidental.

The exact incidence of spontaneous remission in acute leukaemia is unknown, but Farber (1949) quotes Diamond as having found a 10% rate of spontaneous remissions in a study of 300 cases in childhood, with an average duration of under 10 weeks. Second remissions were observed in only two of the 300 cases. A few authenticated instances of apparently spontaneous prolonged haematological and clinical remissions have been reported, the longest being 21 months. Most of these were in cases of monocytic leukaemia (Whitby and Christie, 1935; Birge, Jenks, and Davis, 1949). The latter authors collected records of 11 such cases reported between 1931 and 1949.

Effect on Leukaemic Cells

In the case of the acute leukaemias which respond to aminopterin it is evidently the primitive undifferentiated cell types which are affected. Such cells rapidly diminish in numbers in the bone marrow and peripheral blood during the administration of the drug. There is also, as the result of treatment, a profound fall in the numbers of mature granulocytes in the peripheral blood, presumably due to

the destruction of their more primitive precursors. Normal lymphopoiesis does not seem to be so easily affected (Berman *et al.*, 1949), but leukaemic lymphoblasts are undoubtedly susceptible (Dameshek, 1949). Thiersch (1949) has investigated the bone-marrow effects of aminopterin in man.

In those cases which respond favourably to aminopterin there is, in addition to a spontaneous rise in red cell and platelet counts, a rise in the total white cell count to approximately normal levels, the majority or all of the cells being normal adult forms. At this stage the marrow may seem to be almost normal, with active erythropoiesis and leucopoiesis. In our series, however, blast cells resembling the leukaemic cells previously present never completely disappeared.

It is impossible to say by looking at marrow smears whether aminopterin destroys the primitive cells by causing an absolute deficiency of folic acid or by a more general cytotoxic action. Farber (1949) has noted hypersegmentation of neutrophils in the blood and megaloblasts in the marrow, and we have seen the development of megaloblast-like cells in two cases following treatment. In two others, however, "megaloblasts" were present in the marrow before aminopterin was given.

The regeneration of all normal marrow elements after successful therapy seems to indicate a return to normal haemopoiesis. It is uncertain whether the subsequent reaccumulation of leukaemic cells, which apparently seems to be inevitable, is due to proliferation of residual unaffected leukaemic cells or to previously normal precursors becoming leukaemic. In practice it seems impossible to destroy all the leukaemic tissue without destroying the whole marrow and causing the death of the patient (see Case 3).

Subsequent Relapses

It is most disappointing to observe in patients who have once responded favourably that subsequent attempts at treatment are less successful and may completely fail. The leukaemic tissue appears to become more and more resistant. This acquired resistance does not seem to be a general one, for the patient appears to develop signs and symptoms of general toxic effects quite as readily in subsequent courses as when the drug is given for the first time. It is possible that continuous therapy with small doses of aminopterin will prove to be more satisfactory than the intermittent dosages we have used (Dameshek, 1949), and it is conceivable also that the substitution of another anti-folic-acid compound for the preparation originally used might prove to be a worth-while procedure. The cause of this acquired resistance is obscure. Rather similar problems exist in connexion with the chemotherapy or radiotherapy of malignant disease in general. Possibly in the case of leukaemia and aminopterin the leukaemic cells develop alternative metabolic pathways to the ones blocked by aminopterin, or it may well be due simply to persistence and proliferation of a strain of cells originally resistant.

Toxic Effects

As is seen, the toxic effects of aminopterin (or similar compounds*) are serious, and it does not seem likely that remissions can be initiated unless doses big enough to cause some toxic effects are given. The therapeutic margin, in fact, appears to be extremely small. The effects on mucous membranes causing stomatitis and diarrhoea with intestinal

*Aminopterin seems to be the most potent of the folic-acid antagonists so far employed. The other compounds used, such as a-methopterin and amino-an-fol, seem to be equally toxic if employed in doses large enough to be effective (Farber, 1949). A-ninopterin may, however, prove to be relatively slightly less toxic than aminopterin (Dameshek, 1949).

ulceration are among the most obvious toxic signs, and their development, presumably due to interference with the growth of the lining epithelial cells, is an indication to withhold the drug. Haemorrhage is a special and serious problem and repeated blood transfusions may be necessary, but may prove ineffective. The cause of the bleeding is obscure; it has been claimed in thrombocytopenic purpura and in untreated leukaemia that the amount of heparin-like substances in the blood is increased (Allen, Bogardus, Jacobson, and Spurr, 1947). Whether additional changes occur as the result of giving aminopterin, other than the depression of platelet numbers, is uncertain.

Indications and Limitations

In view of the temporary nature of the remissions and the ultimately disappointing results of the use of folic-acid antagonists in human acute leukaemia, and of the very small therapeutic margin and extreme toxicity of the drugs, it may well be asked what, if any, should be the role of aminopterin or allied compounds in the treatment of acute leukaemia. Although our experience is small it has been large enough for initial enthusiasm to be tempered and for us to realize the serious limitations of our attempts at treatment. It is impossible to be enthusiastic; the hopes of patients, parents, and doctors are raised only to be dashed by later experience.

Nevertheless, that remission can be observed at all is remarkable, and it seems difficult to withhold the drugs, should they be available, just because relapse will inevitably follow remission, any more than transfusions can be withheld just because they also are temporary expedients. It is always possible, if improbable, that a particular patient may have a prolonged and really worth-while remission, and further experience and different schemes of dosages may produce better results.

Summary

The results of treatment of 13 cases of acute and subacute leukaemia in children and adults with the folic-acid antagonist aminopterin are reported.

Clinical and haematological remissions were obtained in all of seven children treated, and in two of six adults. In those cases which responded there was a clinical return to normality and the peripheral blood was rendered normal, or almost normal, for varying periods. Although striking improvements were obtained in the bone marrows, leukaemic cells were never completely eradicated from them.

All patients who originally benefited have relapsed, and have eventually died after becoming more or less refractory to treatment.

The action of aminopterin in any given case is unpredictable and the toxic effects of the drug are severe. Great caution is necessary in its use.

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EXTERNAL ILIAC ARTERY THROMBOSIS

BY

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[WITH PHOTOGRAPHURE PLATE]

On attendance at the neurovascular clinic at the Manchester Royal Infirmary, patients with the symptoms of intermittent claudication undergo a routine clinical examination which enables the underlying vascular disease to be assessed (Boyd *et al.*, 1949). In several cases the examination failed to reveal any underlying pathological condition. Subsequent investigation showed that in two cases the lesion was a unilateral thrombosis of the external iliac artery. As a search of the literature has not produced any description of such a lesion and its sequelae, a detailed account of these two cases is given. No discussion is made of other and now well-recognized causes of "proximal" arterial block such as the aortic bifurcation syndrome (Leriche and Morel, 1948).

Case 1

Whilst felling a tree on December 15, 1947, a man aged 28 was struck across the lower part of the abdomen and thigh by a large branch, causing extensive bruising. Subsequent x-ray examination did not show any bony injury. The accident occurred at 10 a.m., and at 1 p.m. his right foot felt numb and colder than the left. The sensation spread upwards to the knee within the next hour, but after about twelve hours it gradually receded. The patient noticed no weakness or colour change in the right leg. After ten days in hospital the contusions resolved and he was discharged.

When he resumed his ordinary activities he found that on walking about 100 yards (91 metres) a deep sickening ache was felt in the right calf and, to a less degree, in the right thigh: this disappeared after a short rest. He noticed nothing else abnormal apart from a vague sense of weakness in the leg; his general health was excellent and he continued to work as a market gardener. Because of the pain in the leg he attended the local hospital as an out-patient and was given an extensive course of short-wave diathermy and massage—without relief. He was referred to the neurovascular clinic on February 1, 1949.

The patient's general condition was that of a healthy young man; nothing abnormal was detected on systemic examination; the blood pressure was 150/90 mm. Hg. On inspection the legs