cases CNS involvement was diagnosed in the terminal stages on clinical evidence alone—headaches, vomiting, and papilloedema in one case, blindness in another; in 2 further cases undiagnosed involvement of the CNS was found at necropsy (at weeks 38 and 74).

Throughout this period the form of treatment was varied, the commonest regimens being combinations such as those described by Gee, Yu, and Clarkson (1969), Crowther, *et al.* (1970), the Medical Research Council (1974) and others. As far as can be determined no particular regimen was associated with a particularly high or low incidence of CNS disease. However, among the 12 children who received some sort of CNS prophylaxis there have so far been no cases of meningeal leukaemia. Prophylaxis has included cranial (and spinal) irradiation and intrathecal methotrexate and/or cytosine arabinoside. Taking the period starting 6 weeks after diagnosis, which was the usual point at which CNS prophylaxis began, a comparison can be made of the relative incidence of CNS leukaemia in the time at risk between those who did and those who did not have CNS prophylaxis. Among 82 cases without prophylaxis, totalling 2707 weeks at risk, there were 15 cases of CNS disease, an incidence of 1 case per 180 weeks: this can be compared with 12 cases who received some sort of prophylactic treatment to the CNS, none of whom developed CNS leukaemia during a total of 544 weeks at risk.

Summary

In 130 cases of acute myeloid leukaemia in children below the age of 14 years in Great Britain, there were 21 cases in which the central nervous system was involved. The incidence and timing is similar to that of acute lymphoblastic leukaemia; in a small number of patients who received prophylactic treatment, involvement of the central nervous system was prevented.

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Multiple major cerebral artery thromboses with profound thrombocytopenia in acute leukaemia

Cytotoxic, corticosteroid, and antibiotic therapy in leukaemia are associated with an increase in fungal infections (Bodey, 1966). Having to deal with the clinical problems of thrombocytopenia and bleeding in leukaemia is not uncommon. In this situation it is very unusual to find at necropsy extensive antemortem thrombosis in the cerebral arterial circulation.

Case report

A 5½-year-old girl was found to have acute lymphatic leukaemia (ALL), with a haemoglobin of 7.4 g/dl, a platelet count of 30 000/mm³, and leucocytes at 4900/mm³ with 2% neutrophils, 68% lymphocytes, and 30% blast cells. Bone marrow biopsy showed that 96% of the nucleated cells were blasts.

She was treated over a 9-week period, according to the protocol of the MRC UKALL III Ordinary Schedule with intravenous vincristine and oral prednisone to induce remission, followed by oral 6-mercaptopurine, intravenous asparaginase, intrathecal methotrexate, and cerebral irradiation. After 4 weeks her peripheral blood and bone marrow had returned to normal. During the 10th week she had one dose of oral methotrexate after which her leucocyte and platelet counts began to fall abruptly.

She was readmitted during the 12th week with fever, respiratory distress, widespread purpura, and rectal bleeding. She was anaemic (Hb 5 g/dl), leucopenic (total white blood count 2000/mm³) and thrombocytopenic (platelets 20 000/mm³). A blood culture grew meningococci. The bone marrow was hypoplastic. All cytotoxic therapy was stopped and she was given penicillin, sulphadimidine, and prednisone. While in this thrombocytopenic state she fell out of bed and developed a large frontal haematoma, the blood later gravitating down to surround both eyes. The skin overlying the

haematoma and at the inner canthus of each eye sloughed, leaving deep ulcers. Swabs from the sloughed areas grew *Esch. coli* and *Klebsiella aerogenes*, but fungi were not specifically sought.

For repeated rectal haemorrhages she was transfused with 16 units fresh blood and 40 units of platelets, without effect upon the thrombocytopenia or the bleeding. *Pseudomonas aeruginosa* was cultured from an infusion wound in her leg and she developed a few haemorrhagic vesicular skin lesions suggestive of pseudomonas septicaemia; she was treated with gentamicin and carbenicillin. During the 18th week of her illness she deteriorated rapidly, with fever, pain above the left eye, drowsiness deepening to coma, and signs of infection in the left lung. At the time of death she was thought to have had a large intracerebral haemorrhage.

Necropsy examination. Relevant findings included two areas of total skin loss without granulation tissue on either side of the nose, medial to each inner canthus, measuring 1.5 cm in diameter. Underlying bone was visible. The skull and dura were normal.

Brain. The left frontal lobe was swollen and congested with a little yellowish exudate on the inferior surface. The intracranial portion of the left internal carotid, the left middle cerebral, both anterior cerebral arteries, and the first part of the right middle cerebral artery were totally occluded by thrombus. The vertebral, basilar, and posterior cerebral arteries appeared normal.

After fixation in formol-saline multiple coronal sections showed extensive infarction of the cortex and adjacent white matter of the left inferior frontal lobe. In the parietal lobes there was extensive symmetrical haemorrhagic necrosis of both internal capsules, the caudate and lentiform nuclei and the thalamus (Fig. 1). The necrotic areas broke away easily from the surrounding cerebral tissue.

There was partial collapse of the lower lobe of the left lung and a white mucoid exudate in the trachea. The liver (830 g), spleen (50 g), and lymph nodes were normal macroscopically. The upper gastrointestinal tract contained fresh blood with numerous petechial haemorrhages in the gastric mucosa.

FIG. 1.—Showing the extensive symmetrical haemorrhagic necrosis of both internal capsules and basal ganglia.

FIG. 2.—Showing numerous fungal hyphae in the lumen and wall of a cerebral artery. Gomori's methenamine silver. $\times 275$.

Microscopical examination. An inflammatory exudate in the leptomeninges of the inferior surface of the frontal lobe contained numerous pyknotic neutrophils prominent around thrombosed blood vessels. The underlying cerebral cortex and adjacent white matter was necrotic. Sections from the internal capsules and basal ganglia confirmed extensive infarction. Many branching, nonseptate hyphae were present in the meningeal exudate and necrotic cerebral tissue mainly in relation to blood vessels. Cultures were not obtained but morphological appearances were compatible with mucormycosis. The hyphae were also found within the thrombosed cerebral arteries, and in some sections within the vessel walls (Fig. 2). The hyphae stained faintly with haematoxylin but were shown well by the P.A.S. staining method and by silver methenamine stain.

Sections from the lower lobe of the left lung showed an area of necrosis containing numerous fungal hyphae, similar in appearance to those in the brain and cerebral arteries. The bone marrow was hypoplastic. In no system was there evidence of leukaemic infiltration.

Discussion

Mucormycosis accounted for 2 of 16 cases of childhood cerebral arterial occlusion in a series reported in 1961 from the U.S.A. from where most descriptions of this disease have originated (Banker, 1961). The fungus infiltrates blood vessels and causes thrombotic occlusion, even in the presence of severe thrombocytopenia. This has rarely been reported in a child before (Hutter, 1959). In our patient, who had suffered severe bleeding in life,

the finding of extensive arterial thrombosis came as a surprise.

Mucor occurs commonly in soil and decaying vegetable material. It can infect diabetics (Sandler *et al.*, 1971), those with malignant disease, and occasionally otherwise healthy children (Blodi, Hannah, and Wadsworth, 1969). Its usual route of entry is via the paranasal sinuses and any suspect black sloughing lesion near the orbit or nose should be promptly biopsied as culture is difficult and unreliable (Hart, Russell, and Remington, 1969). The branching nonseptate hyphae are readily distinguishable from *Penicillium* and *Aspergillus* (Fetter, Klintworth, and Hendry, 1967).

A standard combination of antibiotics for leukaemia patients with leucopenia and fever has been suggested by Tattersall, Spiers, and Darrell (1972). They recommend adding amphotericin B if there has been no improvement in 48 hours. In the present case cerebral arterial occlusion had probably already started when the temperature rose a week before death. We can find no record of a leukaemic child with mucormycosis who survived.

This report shows yet again the need to be constantly on the lookout for unusual pathogenic organisms causing atypical lesions in debilitated children and emphasizes that quick diagnosis is essential if therapy is to succeed at all. Others have noted that severe infection becomes a problem during the period 3 to 6 months after starting the

UKALL III schedule and special vigilance is needed at that time.

Summary

A child with acute lymphoblastic leukaemia complicated by prolonged gastrointestinal and skin haemorrhages due to profound thrombocytopenia finally died of thrombotic occlusions of major cerebral arteries due to mucormycosis. Biopsy of any suspect lesion is needed urgently before prolonged therapy with amphotericin B is started. So far there have been no cures in childhood.

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Congenital rubella associated with hypsarrhythmia

Hypsarrhythmia, or infantile spasms, falls into two broad groups when considered on an aetiological basis. In one-third of cases there is no known predisposing factor, while in the other two-thirds a history of cerebral insult is a possible causative factor.

Some factors implicated in causing hypsarrhythmia have included cerebral birth injury, toxoplasmosis, postnatal head injury, meningitis, encephalitis, tuberous sclerosis, phenylketonuria, pyridoxine

deficiency (Millichap *et al.*, 1962), and infection with cytomegalovirus (Stern, Latham, and Tizard 1968). To our knowledge congenital rubella infection has never been implicated as a contributing factor.

Case report

In the 16th week of gestation the mother was infected with rubella. Diagnosis was confirmed by a rise in rubella antibody titre from 1:16 at the time of exposure to 1:2048 two weeks later. At 37 weeks' gestation a male infant was born after a 5½-hour labour. No resuscitation was required and physical examination showed no abnormality. Birthweight was 3.35 kg.

On the fifth day right-sided twitching, which later became generalized, was noted but was easily controlled with anticonvulsants. Examination of cerebrospinal fluid, blood culture, serum calcium, and blood glucose, was normal. Platelet count was not depressed and x-rays of the long bones were normal. Rubella virus was not grown from urine and nasopharyngeal secretions. Blood taken on the 6th day of life showed rubella HAI test titre of 1:2048 and a rubella specific IgM titre of 1:40.

The patient was hypotonic and lethargic for the next 3 days but by the 11th day of life physical examination was normal, and he was discharged with no medication. He was next seen at 6 weeks of age, was smiling and physical examination was again normal. At 5 months he began to have episodes of quickly raising both arms and shuddering for 2 or 3 seconds. Infantile spasms were suspected and confirmed by electroencephalogram (EEG), which showed the widespread slow activity with numerous high voltage spike waves typical of hypsarrhythmia (Fig.). Physical examination, serum chemistry, and cerebrospinal fluid were normal.

A course of ACTH (20 IU twice daily) was started 2 weeks after the spasms were first noticed by his mother. EEG 10 days after ACTH was started showed low voltage with irregular theta rhythm and some delta activity in all leads, no longer the pattern of hypsarrhythmia. After 6 weeks the ACTH dose was reduced in steps and was completely withdrawn 3 weeks later. At 9 months of age his EEG was normal.

Monthly assessments since birth showed that development was normal up to the onset of hypsarrhythmia. Development then began to lag. By 10 months he was functioning at a 5-month level using the Stycar tests (Sheridan, 1968). A review at 25 months showed normal hearing and no evidence of cataracts or retinopathy. A Griffiths assessment (Griffiths, 1954) showed delay in all areas. Delays were most marked in language development (9-month level) and hand-eye co-ordination (12-month level).

Discussion

There is no doubt that this child was exposed to rubella at 16 weeks' gestation as shown by his mother's antibody response. The rubella specific IgM titre of 1:40 on the 6th day of life is not particu-