Neurological complications of childhood leukaemia

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SUMMARY We have reviewed the neurological complications not directly attributable to leukaemic infiltration in a group of 438 children with leukaemia or lymphoma. 61 children had one or more complications due chiefly to bleeding, infection, or drug toxicity. Early death from intracranial haemorrhage occurred in 1% of children with lymphoblastic leukaemia and 7% of children with myeloblastic leukaemia. Measles and chicken pox were the most serious infective complications; one child remains severely retarded after presumed measles encephalitis, one child with chicken pox died, and a second remains disabled. 2 additional cases of measles encephalitis and one of progressive multifocal leucoencephalopathy are described.

Drugs which caused neurotoxicity included vincristine, cytosine arabinoside, L-asparaginase, and phenothiazines, but most problems were caused by methotrexate. Methotrexate toxicity was more prevalent and more serious in children who had had previous central nervous system leukaemia. We conclude that viral infections and methotrexate pose the greatest neurological hazards to children with leukaemia.

As the prognosis of children with acute lymphoblastic leukaemia (ALL) improves the complications of management assume greater importance. Among the most serious problems are neurological complications, which may cause permanent disability in children with prolonged leukaemia-free survival. As treatment of the acute myeloid leukaemias (AML) improves, a similar range of problems may be encountered. We have reviewed the neurological complications *not* directly attributable to leukaemic infiltration of the central nervous system (CNS) seen in children who attended the leukaemia clinic at The Hospital for Sick Children during a 10-year period.

Patients

438 children with leukaemia or lymphosarcoma diagnosed between January 1967 and December 1976 attended the leukaemia clinic for regular follow-up. The nonleukaemic neurological complications which have so far occurred in this group of children are listed in Table 1, and are divided into three main groups: haemorrhagic, infective, and drug-related. We have not included the post-irradiation somnolence syndrome previously described from this hospital (Freeman *et al.*, 1973). There were 68 complications occurring in 61 children: 5 children had two complications and one child had three.

Received 12 April 1977

Table 1 *Prevalence of neurological complications 1967-1976*

Diagnosis	Total no. patients	No. of complications					
		Haemorrhage	Infection		Drug related		Miscellaneous
			Viral	Other	Methotrexate	Other	
Lymphoblastic leukaemia	333	3	11	8	17	11	4
Myeloblastic leukaemia	73	5	1	—	—	2	—
Chronic granulocytic leukaemia	12	—	—	—	—	3	—
Lymphoma	20	—	—	1	—	2	—
Total	438	8	12	9	17	18	4

During the same period serious nonleukaemic neurological complications were seen in 3 other children with leukaemia; 2 were referred to the neurology unit from other hospitals, and a third child, treated at this hospital since 1964, developed neurological complications in 1971. These 3 additional cases are described in detail but have been omitted from Table 1.

The patients were treated with a variety of therapeutic regimens. Since 1969 most children with ALL have been treated on protocols designed by the Medical Research Council Working Party on Leukaemia in Childhood (Medical Research Council, 1971, 1973, 1976). Since 1972, children with ALL have received CNS 'prophylaxis' soon after remission induction with cranial irradiation 2400 rad, and either high-dose (2400 rad) spinal irradiation alone or intrathecal methotrexate with or without low-dose (1000 rad) spinal radiotherapy. The treatment of established CNS leukaemia is discussed elsewhere (Gribbin *et al.*, 1977).

Children with AML were treated with a variety of drugs but from 1969 onwards received combination chemotherapy with daunorubicin, cytosine arabinoside, and other drugs. From 1973 onwards children with AML who achieved remission received intrathecal cytosine arabinoside or methotrexate as CNS 'prophylaxis'.

Complications

Intracranial haemorrhage. 8 children developed signs of intracranial haemorrhage during the first days or weeks after diagnosis of acute leukaemia; 5 had AML and 3 ALL (Table 2). 2 of the 3 children with ALL had very high blast counts and became unconscious within 24 hours of admission; the third developed bleeding in association with infection and disseminated intravascular coagulation. 3 of the 5 children with AML also had evidence of DIC.

Infections. Infections of the CNS occurred in 21 of the 438 children and were viral or of presumed viral aetiology in 12 and bacterial in 9.

Virus infections. Details of 9 of the 12 children with infections are given in Table 3 together with 2 additional cases (9, 10) which had been referred to the neurology unit. All these, with the exception of Case 15, were in remission at the time of the infection and all except 1 (Case 19 who had AML) had ALL. Blood counts in 10 of these 11 children at or just before the onset of their illness showed moderate neutropenia in 2 cases, but 7 children had lymphopenia ($<1 \times 10^9/l$).

Mumps was the most common infection and was seen in 5 children. One of these children died: a

Table 2 Intracranial haemorrhage

Case no.	Year of diagnosis	Age (yrs)	Sex	Type of leukaemia	WBC at presentation ($\times 10^9/l$)	Platelets at presentation ($\times 10^9/l$)	Clinical features	Post-mortem findings
1	1969	4	M	Monocytic	274	70	Unconscious day 5; fixed dilated pupils; areflexia	—
2	1969	10	M	Promyelocytic	6.4	15	Continuing disseminated intravascular coagulation; heparinized; comatose day 9	Large L-sided subarachnoid haemorrhage
3	1972	3	F	Promyelocytic	145	44	No response to treatment; rising blast count week 5	R-sided intracranial haemorrhage
4	1974	11	F	Myelomonocytic	29	19	Vomited and became unconscious day 4; signs of left-sided haemorrhage; disseminated intravascular coagulation	—
5	1976	13	F	Myelomonocytic	490	250	Collapsed and unconscious on day 2; pupils non-reactive; disseminated intravascular coagulation	—
6	1969	2	F	Lymphoblastic	4.5	2	Klebsiella septicaemia; comatose and convulsion day 11; disseminated intravascular coagulation	—
7	1972	4	M	Lymphoblastic	216	25	Unconscious day 1	Intracranial haemorrhage
8	1972	4 m	F	Lymphoblastic	660	75	Unconscious on admission	Multiple small intracranial haemorrhages; large bleed in both orbital and temporal regions

Table 3 Virus infections associated with central nervous system involvement

Case no.	Sex	Age (yrs)	Diagnosis	WBC at time of infection ($\times 10^9/l$)		Infection	Clinical features and laboratory data
				Neutrophils	Lymphocytes		
9	M	9	ALL	0.65	0.8	Measles	No history of contact or rash; severe neurological disorder progressing to death within 3 m; measles virus in brain; high CF antibodies in serum & CSF*
10	M	4	ALL	—	—	„	Rash 3 m before severe neurological disorder; alive 15 m later; high CF antibody in serum & CSF*
11	F	13	ALL	2.9	0.6	„	No history measles or rash; severe acute encephalitis; remains retarded; serum CF antibodies 256 and HI antibodies 64
12	M	12	ALL	3.69	0.31	Varicella	Typical rash followed by coma; residual dysarthria
13	M	8	ALL	1.9	0.17	„	Typical rash followed by coma and complete recovery; varicella CF antibody titre rose from <4 to 4096
14	M	8	ALL	2.51	0.8	„	Typical rash; sudden coma during recovery; disseminated varicella at post mortem; varicella CF antibody titre rose from <4 to 256
15	M	4 m	ALL	5.38	11.46	Mumps	Virus isolated from CSF; died in relapse
16	M	5	ALL	1.3	1.2	„	Headache & fever; CSF WBC $0.3 \times 10^9/l$; CF antibody 64
17	F	6	ALL	0.8	0.2	„	Convulsions followed after 2 w by clinical mumps; CSF <1 WBC; virus isolated from throat
18	M	4	ALL	3.3	0.7	„	Headache & vomiting; CSF WBC $0.167 \times 10^9/l$; virus isolated from CSF
19	M	6	AML	1.3	1.29	„	Headache & vomiting; CSF WBC $0.29 \times 10^9/l$; virus isolated from CSF

*Smyth *et al.* (1976).

ALL = acute lymphoblastic leukaemia; AML = acute myeloid leukaemia; CF = complement fixing; HI = haemagglutination inhibition.

4-month-old infant (Case 15) who was in relapse and in whom mumps virus was isolated from the cerebrospinal fluid (CSF); the remaining 4 patients made a rapid and complete recovery after a clinically mild meningitic illness.

Encephalitis caused by measles virus affected 3 children: 2 of these (Cases 9, 10) have been previously reported as cases of the recently described syndrome of 'atypical measles encephalitis' (Smyth *et al.*, 1976). The encephalitis followed 3 months after clinical measles in Case 10 but in Case 9 seroconversion to measles occurred without clinical measles, and measles antigen and measles virus were shown in the brain by immunofluorescence and by electron microscopy.

Both children had high titres of measles complement-fixing (CF) antibody in the serum and CSF. Case 9 died 2 months after the onset of his neurological disorder; Case 10 is unusual in that he remains alive 18 months after the onset of brain disease but is severely brain damaged. The third patient (Case 11) developed a severe neurological disorder with coma and convulsions lasting 2 months and remains severely retarded. Although she did not suffer from clinical measles before the onset of neurological symptoms, the titre of both CF and

haemagglutination-inhibiting measles antibody in her serum early in the neurological illness was sufficiently raised to be highly suggestive of recent measles infection. However, CF antibody was not detected in the CSF of this child.

Three children developed an acute CNS disorder during or soon after typical chicken pox. Case 12, after a prolonged period of coma during which there was severe inappropriate antidiuretic hormone activity, was markedly ataxic and dysarthric during recovery. His speech disorder appears now to be permanent. The second boy (Case 13), who became semiconscious during the attack of chicken pox, recovered completely. The third (Case 14), while apparently recovering from a severe attack of chicken pox treated with adenine arabinoside, suddenly developed convulsions 6 days after fresh lesions, became comatose, and died within 21 hours. At necropsy there was visceral dissemination of varicella. Microscopical examination of the brain showed infiltration with mononuclear cells and polymorphs; no virus was cultured from the brain.

Four children with presumed viral infections are not listed in Table 3. One girl, in whom ALL was diagnosed in 1964 and who never had CNS leukaemia, developed focal fits, ataxia, and nystagmus

7 years after diagnosis. The disorder progressed to diminishing consciousness and bulbar palsies and she died 1 month after the onset of neurological symptoms. The brain showed typical changes of progressive multifocal leucoencephalopathy. No viruses were cultured from the brain using conventional tissue culture techniques.

A transient mild encephalopathic disorder with complete recovery occurred in 3 children after febrile illnesses which were of presumed viral origin. Unfortunately a specific diagnosis could not be established by the virological and serological tests which were carried out.

Bacterial infections. Bacterial infections were less frequent. 4 children developed meningitis in association with intraventricular reservoirs; 3 of these were due to *Staphylococcus epidermidis* and one to *Acinetobacter lwoffii* (*Mima polymorpha*). All the infections responded to antibiotics which were given systematically in all 4 and intrathecally in 3 children.

There were 5 other children with bacterial infections. Meningococcal meningitis occurred in one child in remission who recovered without sequelae after conventional antibiotic treatment. A dual infection with *Proteus vulgaris* and *E. coli* occurred in one boy with ALL who was in relapse. An old cerebral abscess was found at necropsy in another child who had previously had septicaemia and osteomyelitis of the humerus. During the infection she had developed status epilepticus and a right hemiplegia but had made a complete clinical recovery. A fourth child is thought to have had bacterial meningitis at the time of presentation of ALL but fully recovered after intensive antibiotic treatment and granulocyte transfusions. She was febrile and the initial CSF contained only 32 WBC (14% neutrophils, 86% lymphocytes), but after granulocyte transfusions the neutrophils in the CSF rose to over 500/mm³. No organisms were cultured from the CSF.

The value of the recently introduced computerized axial tomography was shown in the fifth patient, a boy with lymphosarcoma who presented with a pulmonary abscess in his right upper lobe from which *Nocardia asteroides* was cultured. After surgical drainage of the abscess he developed generalized convulsions and a transient hemiplegia. Abscesses in the right frontal and left occipital regions in the brain were visualized on scanning. He made complete recovery after treatment with co-trimoxazole.

Drug toxicity.

Methotrexate. 17 of the 333 children with ALL developed neurological disorders related to treatment with methotrexate. The type of disorder and

incidence in relation to previous CNS leukaemia are given in Table 4. Clinical details of the children with these complications are given in Table 5. 4 of the 5 children with no previous overt CNS leukaemia (Cases 20–23) had convulsions and/or signs of meningeal irritation but no residual neurological abnormality; in one child (Case 22) a fit followed the first prophylactic injection of intrathecal methotrexate. No other cause for the fit was found and further methotrexate was given without mishap.

Table 4 *Methotrexate complications in lymphoblastic leukaemia*

	No previous CNS leukaemia (n = 239)	Overt CNS leukaemia (n = 94)
Arachnoiditis only	1	0
Convulsions: no persisting abnormality	3	4
Permanent CNS impairment	1	8
Total no. complications	5 (2%)	12 (13%)

Case 24 was the only child with no previous CNS leukaemia who developed persistent neurological abnormalities. He was treated initially on the MRC Concord protocol (Medical Research Council, 1971) which includes high-dose methotrexate and folinic acid and intrathecal methotrexate. After a relapse one year after stopping treatment he received further oral methotrexate (10–15 mg/m² per day for 5 days every 4 weeks) in combination with 6-mercaptopurine for 10 months, and then methotrexate alone for 5 days every 2 weeks for 18 months. At the time of development of symptoms he was taking oral methotrexate 30 mg/m² per week with oral thioguanine. Symptoms responded to withdrawal of methotrexate and administration of folinic acid.

The other children (Cases 25–36) had all had one or more episodes of overt CNS leukaemia. In 5 (Cases 25–29) convulsions followed intrathecal methotrexate injections (given in Cases 28 and 29 via an Ommaya reservoir). In 3 others (Cases 30, 33, 34) the main features were depression and progressive intellectual impairment. Case 30 improved with substitution of cytosine arabinoside (Ara-c) for methotrexate. Case 33 developed left facial weakness, hemiparesis, depression, and dementia after 4½ years on treatment. She had had one previous marrow relapse and three CNS relapses but there was no evidence of CNS leukaemia at the time. After withdrawal of oral and intrathecal methotrexate the hemiplegia improved. Case 34 developed progressive right-sided weakness, tremor, rigidity, and mask-like facies with no overt evidence of CNS leukaemia at the time. She was thought clinically to have lesions of the

Table 5 Complications related to methotrexate (MTX)—17 patients

Case no.	Age (yrs)	Sex	No. previous episodes CNS leukaemia	Previous radiotherapy*	No. previous intrathecal MTX injections	Total duration of treatment (w)	Clinical features	Follow-up
20	6	M	None	No	1	6	Arachnoiditis	Full recovery
21	12	M	None	No	3	14	Arachnoiditis; fit	" "
22	3	M	None	No	0	8	Fits	" "
23	3	F	None	P	5	14	Fits	" "
24	15	M	None	No	6	208	Fits; depression; dementia	Some improvement
25	10	F	3	T	25	210	Fits	Full recovery
26	5	M	2	T	16	104	"	" "
27	1	M	1	No	3	18	"	" "
28	5	M	1	P	17	164	"	" "
29	3	M	1	P	23	104	"	Recurrent fits; ataxia
30	7	F	2	T	16	208	Depression; dementia	Improvement on withdrawal of intrathecal MTX
31	14	M	3	T	18	52	Mental slowing	Some improvement
32	3	M	1	No	4	65	Ataxia	Residual signs
33	11	F	3	T	22	234	Depression; dementia; left hemiparesis	Slow improvement
34	6	F	6	T	27	203	Depression; dementia; cogwheel tremor; failure upward gaze; right hemiparesis	Some improvement, subsequent CNS relapse
35	7	M	2	T	29	209	Dementia; fits; unconscious 2 d	Recovery of consciousness; no further fits
36	8	F	3	T	22	195	Fits; coma	No recovery; died in haematological relapse

*T = therapeutic; P = prophylactic.

mid-brain and basal ganglia. Withdrawal of all methotrexate was followed by improvement but she had a marrow relapse 6 months later and a further CNS relapse after 9 months. She died one year after the onset of the symptoms and necropsy showed heavy leukaemic infiltration of the meninges with perivascular extension into the parenchyma.

Case 35 had a CNS relapse 2 years after diagnosis. After a second relapse an Ommaya reservoir was inserted into the right lateral ventricle and he was given monthly intrathecal methotrexate. He developed progressive intellectual deterioration, ataxia, right-sided convulsions, and became comatose for 2 days. He regained consciousness and withdrawal of intrathecal methotrexate was followed by intellectual improvement. After marrow relapse he was given high-dose intravenous methotrexate with folinic acid rescue but died without achieving remission. Necropsy showed disseminated necrotizing leucoencephalopathy. Case 36 had three meningeal relapses in the 2 years after diagnosis. After successful treatment of her third meningeal relapse she developed headaches, convulsions, status epilepticus, and became comatose. She died from CNS and marrow relapse 5½ months after chemotherapy was stopped. Necropsy showed widespread cerebral necrotizing leucoencephalopathy.

Vincristine. Vincristine has been presumed to be the cause of convulsions which occurred in 6 children (4 with ALL, 1 with chronic granulocytic leukaemia in blast crisis, and 1 with lymphosarcoma which had converted to leukaemia) between 18 hours and 6 days after administration (Table 6). In Cases 38, 39, and 40 the effects were short-lived, but Case 37 remained unconscious for 3 days. Case 41 had received a second course of COAP (vincristine, cyclophosphamide, Ara-c, and prednisolone) and intrathecal Ara-c as induction therapy for 'poor-risk' ALL. 4 days later he complained of abdominal pain and 6 days later had repeated generalized convulsions; he remained unconscious for 3 weeks. No other cause was found for the convulsions; the blood platelet count, glucose, and electrolytes were normal and CSF was sterile. No evidence of viral infection was found. Computerized axial tomography showed some scattered low density areas but no real focal lesion. His vision remained poor for several weeks and his electroencephalogram (EEG) showed reduced occipital discharge after visual stimulation. Case 42 remained unconscious for 2 days and also had transient disturbance of vision; he was also hypocalcaemic and recovering from uric acid nephropathy. Further vincristine has been given to 3 of the children with no further ill effects.

Table 6 Vincristine neurotoxicity

Case no.	Age (yrs)	Sex	Diagnosis	Symptoms	Time since VCR given (d)	No. previous VCR injections	Follow-up
37	4	M	ALL	Status epilepticus fits for 3 d	6	1	6 further injections
38	3	F	ALL	Generalized convulsion	1	3	2 further injections; no ill effects
39	13	M	ALL	BP 116/110 mm Hg	20 h	14	VCR not repeated
40	13	F	CGL, blast crisis	Generalized convulsion	6	1	13 more injections; no ill effects
41	5	M	ALL	Right-sided convulsions; comatose; blind; unconscious 3 w	6	1	No further VCR; good neurological recovery over 2 m
42	8	M	ALL (LSA)	Recovery from urate nephropathy; hypocalcaemic (1.15 mmol/l) BP 160/110 mm Hg; convulsions; comatose; blind for 2 d	2	5	No further VCR; recovery over 2 w

CGL = adult chronic granulocytic leukaemia; LSA = lymphosarcoma; VCR = vincristine.

Cytosine arabinoside. Intrathecal Ara-c has caused arachnoiditis in 4 patients, 3 with ALL and 1 with adult chronic granulocytic leukaemia in blast crisis; the symptoms were headache and neck stiffness and one child had minimal cerebellar signs. All children improved within 2 days and had no residual neurological deficit.

L-asparaginase. A boy of 3 with ALL diagnosed in 1971 was receiving a 3-week consolidation course of daily asparaginase at the end of which he had a grand mal convulsion. CSF, brain scan, and EEG were nondiagnostic and he made a full recovery but has received no L-asparaginase since then.

Phenothiazines. Phenothiazine derivatives, used either as antiemetics or as sedatives before bone-marrow aspiration, have precipitated hospital admission in 7 children. The main symptoms have been rigidity and oculogyric crises.

Other complications. 2 children developed transient hemiplegia after insertion of an intraventricular reservoir; these and other complications have been described (Gribbin *et al.*, 1977). One child with ALL aged 15 months with a presenting white cell count of $410 \times 10^9/l$ and platelet count of $29 \times 10^9/l$ developed generalized convulsions and became unconscious within 24 hours of starting treatment. She was hypocalcaemic (serum Ca 1.18 mmol/l; 4.7 mg/100 ml) and uraemic (blood urea 31.4 mmol/l; 189 mg/100 ml) at the time but CSF was normal. She recovered gradually but was left with a slowly improving hemiparesis and failure of upward gaze. It was not clear whether these complications resulted from intracranial haemorrhage, metabolic disturbance, or a combination of both.

One child with ALL in remission but with recurrent CNS leukaemia was admitted at 118 weeks from diagnosis with fever and hypotension. She rapidly became opisthotonic and comatose. Viral and bacterial cultures proved negative and CSF contained no cells but a low glucose (25 mg/100 ml; 1.4 mmol/l). There was evidence of liver failure with a prothrombin time of 54 seconds (control 18) and raised aspartate transaminase 744 IU/l (normal up to 17) and alanine transaminase 558 IU/l (normal up to 12). She died within 24 hours of admission and necropsy showed mild fatty change and chronic venous congestion of the liver. There was marked cortical brain cell death but no oedema or inflammatory or leukaemic cell infiltration. This case has been published in detail with a suggested diagnosis of Reye's syndrome (Johnston, 1973).

Deaths. There were 13 deaths directly due to the neurological complications: 11 of these occurred in the main group of 438 children. 8 of the 11 deaths were due to intracranial haemorrhage, 1 to bacterial meningitis in relapse, 1 to varicella encephalitis, and 1 to coma of uncertain cause. 2 of the 3 extra cases also died, 1 from measles encephalitis and 1 from progressive multifocal leucoencephalopathy.

Long-term sequelae. 12 children, including the third extra case, sustained permanent neurological impairment. 2 children are severely handicapped after measles encephalitis and 1 boy remains dysarthric after varicella encephalitis. 9 children, of whom only 2 now survive, had intellectual impairment ascribed to methotrexate toxicity, with or without focal neurological signs; one remained unconscious for 23 weeks until death from haematological relapse after all therapy was stopped.

Discussion

As a result of the introduction of routine CNS prophylaxis overt CNS leukaemia is becoming far less common. There are, however, many other neurological problems which the leukaemic child may develop, usually as a result of haemorrhage, infection, or drug neurotoxicity.

We have not attempted to assess the incidence of haemorrhage in children in relapse. In our series fatal intracranial haemorrhage has precluded successful remission induction in 1% of children with ALL and 7% of children with AML. Children at risk were those presenting with a high white cell count and/or evidence of disseminated intravascular coagulation (DIC). In the former group, who may succumb before antileukaemic therapy can be effective, consideration should be given to leucopheresis. Recognition of the risks of DIC, particularly in the promyelocytic (Goldman, 1974) and myelomonocytic (Gralnick *et al.*, 1972) leukaemias, should engender liberal use of platelet concentrates and possibly heparin therapy.

Infections. Apart from the cases of meningitis in children with intraventricular reservoirs, the infective problems have been chiefly viral and emphasize the risks of measles and varicella. There have been several recent reports of an atypical form of measles encephalitis in children with ALL in remission (Murphy and Yunis, 1976; Drysdale *et al.*, 1976; Pullan *et al.*, 1976; Smyth *et al.*, 1976). The diagnosis is particularly difficult to make in view of the latent period preceding the onset of neurological symptoms and the absence of a clinical history of measles in some cases. Clinically the neurological illness somewhat resembles subacute sclerosing panencephalitis (SSPE) but without the typical EEG changes associated with that illness. However, this syndrome, like SSPE, may be associated with high CF measles antibody in serum and CSF. Measles virus has been difficult to culture by conventional methods but in some of these cases has been shown by electron microscopy and immunofluorescent studies of the brain. In a recent review (*British Medical Journal*, 1976) 7 of 10 children with this form of encephalitis had died and the risk to children without previous immunity was estimated at 3–5%. In our own clinic population, however, only one of 333 children with ALL has had evidence of measles encephalitis. Administration of conventional doses of pooled immunoglobulin may not protect contacts (Pullan *et al.*, 1976) and larger doses or a high titre preparation may be indicated. There is no treatment for established encephalitis, so prophylaxis is of importance.

The diagnosis of varicella-zoster virus infection presents little problem but prevention of infection is a continuing challenge. In one unprotected population of children on treatment for malignant disease, 60 children developed varicella, 32% had visceral dissemination, and 7% died (Feldman *et al.*, 1975). An even higher mortality of 32% in varicella-infected leukaemic children has been reported from Japan (Hattori *et al.*, 1976). Our own experience has not been so devastating but even so one child has died and one remains disabled following encephalitis. Administration of zoster immune globulin (ZIG) within 72 hours of exposure is effective in preventing or mitigating the severity of infection (Brunell *et al.*, 1972; Judelsohn *et al.*, 1974) but care in avoiding contact and ensuring adequate supplies of ZIG pose continuing problems. Treatment of severe established infection with cytosine arabinoside is unsatisfactory in our experience; we are currently evaluating adenine arabinoside in such cases.

Mumps meningoencephalitis has not been exceptionally severe in these children. Progressive multifocal leucoencephalopathy (PML) is now considered due to the JC strain of papovavirus (Narayan *et al.*, 1973). There have been few reports to date of PML in children with leukaemia (e.g. Simone *et al.*, 1972). Buckman and Wiltshaw have recently reported (1976) successful treatment of a patient with Hodgkin's disease and presumed PML with cytosine arabinoside.

Exotic infections have been rare; the only unusual infection being nocardiosis in a child with lymphosarcoma in remission who presented with a lung abscess, and this organism has been infrequently encountered by others (Cox and Hughes, 1975).

Drug toxicity. Methotrexate toxicity occurred in 5% of children in this series with ALL: in 13% of those who had had previous CNS leukaemia but in only 2% of those who had not. The spectrum of toxicity ranged from arachnoiditis or one or more convulsions to progressive intellectual deterioration and coma. Arachnoiditis was an infrequent complication, possibly because methotrexate was rarely given intrathecally at less than 7-day intervals; more frequent administration has been shown by others to result in a higher incidence of this complication (Geiser *et al.*, 1975; Jones, 1975). Only one child with severe methotrexate toxicity had not had previous CNS leukaemia but he had received prolonged systemic methotrexate therapy. Meadows and Evans recently (1976) reported evidence of neurological impairment after prolonged systemic methotrexate therapy in nonirradiated children who had not had CNS leukaemia.

The syndrome of methotrexate-radiation toxicity was first described in children with treated CNS leukaemia (Kay *et al.*, 1972; Hendin *et al.*, 1974; Rubinstein *et al.*, 1975), but has recently been recorded in those who receive prophylactic irradiation and subsequent parenteral methotrexate in fairly high dosage (Price and Jamieson, 1975; McIntosh *et al.*, 1976). We have not encountered permanent neurological impairment in children receiving prophylactic irradiation, possibly because the Medical Research Council protocols involve neither high-dose parenteral nor long-continued intrathecal methotrexate.

Administration of cytosine arabinoside has caused CSF pleocytosis and arachnoiditis but has so far caused no long-term complications. L-asparaginase has been reported to cause less toxicity in children than adults (Haskell *et al.*, 1969), and this has certainly been our experience. Vincristine frequently causes peripheral neuropathy but is also known to cause convulsions and coma (Haggard *et al.*, 1968; Whittaker *et al.*, 1973), usually a few days after an intravenous dose. The coma may last for some days; one of our cases was unusual in that coma lasted nearly 3 weeks and full recovery took 3 months. Excess antidiuretic hormone secretion may occur (Whittaker *et al.*, 1973) but has not been noted in our cases. Some patients have been given further vincristine without ill effect, but we have not used it again in our 2 most severely affected cases.

We conclude that there are many causes for neurological abnormality in children being treated for leukaemia; this review may give some guidelines for their differential diagnosis. The most frequently encountered problems have been drug toxicity and viral infections. The risks from drug toxicity must be seen in the context of the widespread use of drugs such as methotrexate and vincristine and seem relatively small, though prolonged follow-up will be necessary to assess the long-term consequences of chemotherapy and cranial irradiation. Preliminary results of neuropsychiatric evaluations of children completing treatment for ALL have been encouraging (Soni *et al.*, 1975; Eiser and Landsdown, 1977).

The problem of viral infections as a cause of death or disability is one for serious concern; children so affected have been most frequently those with 'good risk' ALL (Medical Research Council, 1976). More effective methods of prevention of viral illness and treatment of established infection are urgently needed and the possibility of devising methods of treatment that are less immunosuppressive should be explored.

We thank Drs. J. Wilson and E. Brett for helpful comments and permission to include Cases 9 and 10,

and Dr. M. Erdohazi for reporting the neuropathological findings.

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