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Encephalopathy in Acute Leukaemia Associated with Methotrexate Therapy

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Kay, H. E. M., Knapton, P. J., O'Sullivan, J. P., Wells, D. G., Harris, R. F., Innes, E. M., Stuart, J., Schwartz, F. C. M., and Thompson, E. N. (1972). *Archives of Disease in Childhood*, **47**, 344. **Encephalopathy in acute leukaemia associated with methotrexate therapy.** Seven patients are described in whom dementia developed during treatment with methotrexate for meningeal leukaemia. The patients presented with confusion, tremor, ataxia, irritability, and somnolence. There were major epileptic fits in two cases and in one case there was progression to coma and death. Necropsy findings in the latter showed infarcted areas in the temporal and parietal lobes, with no evidence of active leukaemic disease or of viral encephalitis. The condition has not responded to radiotherapy and no positive evidence of viral encephalitis has been obtained. On the other hand, when treated with folinic and folic acid the deterioration has been arrested and there has been some improvement; thus the condition appears to be due to methotrexate. The occurrence of so many cases within the past year of a condition not previously described is probably attributable to the introduction of intensive cytotoxic therapy directed against meningeal leukaemia.

The widespread use of methotrexate, especially in the treatment of acute lymphoblastic leukaemia, has revealed the existence of many toxic effects. These include the frequent occurrence of anorexia, mucosal ulceration, and bone marrow depression, and the less well-known effects of prolonged administration, hepatic fibrosis (Hersh *et al.*, 1966), pulmonary disorders (Clarysse *et al.*, 1969), and osteoporosis (Ragab, Frech, and Vietti, 1970). After intrathecal methotrexate, headache, fever, and vomiting are not uncommon; neurological signs have been noted in a few cases, mostly transient but sometimes permanent; and there have been two fatalities (Naiman *et al.*, 1970; Rosner *et al.*, 1970; Back, 1969; Jacquillat and Weil, 1969; Bagshawe, Magrath, and Golding, 1969; Pasquinucci, Pardini, and Fedi, 1970).

In this paper we describe an encephalopathy in seven patients who were receiving prolonged methotrexate therapy, in part by intrathecal injection. The main features were confusion, somnolence or irritability, ataxia, and dementia, progressing in one case to coma and death; in the six others there has been partial but continuing recovery. A short premonitory account has been published (Kay *et al.*, 1971).

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Case 1

This patient was a man of 22 when he developed acute lymphoblastic leukaemia in May 1968. Remission was induced with 6-mercaptopurine and prednisolone after which he received five 5-day courses of methotrexate combined with 6-mercaptopurine or cyclophosphamide followed by weekly pertussis vaccine (Guyer and Crowther, 1969). Nine months later he relapsed. After reinduction of remission larger doses of methotrexate were given, 40 mg/m^2 intramuscularly 8-hourly for two days followed by folinic acid 23 mg/m^2 intramuscularly 8-hourly for four days. Three similar courses were given over three weeks together with L-asparaginase, 29,000 units/m^2 daily for 28 days, and 5-weekly intrathecal doses of 7·5 mg/m^2 methotrexate. Thereafter he was well for 13 months while taking tablets of methotrexate (7–12 mg/m^2) twice a week. His appetite was good, he ate ample green vegetables, and he had mouth ulcers only once.

On 25 August 1970, he complained of cramps and weakness in both legs for a week (Fig. 1). His CSF

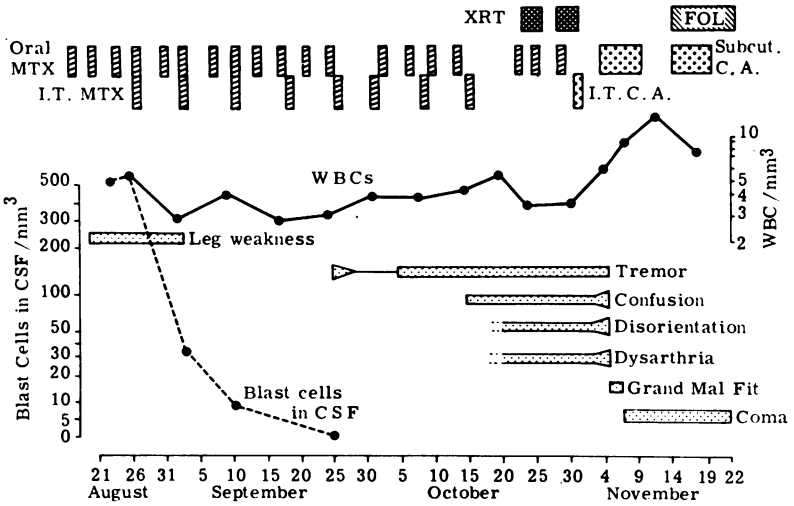

FIG. 1.—*Case 1. Course and treatment from the development of meningeal disease. Oral MTX, oral methotrexate; I.T. MTX, intrathecal methotrexate; XRT, x-ray treatment; I.T.C.A.; intrathecal cytosine arabinoside; FOL, folinic acid; Subcut. C.A., subcutaneous cytosine arabinoside.*

contained 560 blast cells/mm^3 and 120 mg/100 ml of protein. Intrathecal methotrexate 10 mg was injected weekly for the next eight weeks while he continued to take oral methotrexate. His symptoms improved after the first injection and the blast cells disappeared after the third. A brainscan (Technetium 99) at this time was normal and a myelogram (RI^{131}SA) indicated normal flow of fluid injected by the lumbar route. Two days after the fourth lumbar puncture he noticed a fine tremor of the hands. This improved during the next two weeks, the oral methotrexate having been stopped because of leucopenia; at the same time he was being treated with prochloperazine maleate. When the oral methotrexate was resumed the tremor became worse within three days and a week later he became confused, disorientated, and slept excessively. He developed dysarthria and increased tendon reflexes. On 14 October 1970, a brainscan and ultrasound examination of the cranium was normal. The EEG one month later showed an unstable, 8–10 c/sec, alpha rhythm postcentrally that was partially attentuated by eye-opening. Intermixed with this was theta, 4–7 c/sec, activity. In addition, episodes of slow waves at 1–2 c/sec were seen bilaterally in the anterior regions and sometimes also posteriorly. His bone marrow (15 October 1971) was in remission and showed a pronounced megaloblastic change. The blood count was Hb 13·7 g/100 ml, white blood cells 4400/mm^3, platelets 130,000/mm^3.

His mental state became steadily worse. Radiotherapy to the brain (1300 rads in six days), given on the assumption that he had intracerebral leukaemic deposits, produced no improvement. Likewise he had one intrathecal injection and two 5-day courses of subcutaneous cytosine arabinoside in case a herpes simplex encephalitis was responsible for his mental state. Later, negative results were obtained from virus cultures of CSF and serum antibody tests. Nine days after the last intrathecal dose of methotrexate he had a grand mal fit from which he never regained consciousness. Folic acid 55 μg/m^2 daily for nine days brought no improvement. He died on 22 November 1970, after being in coma for 16 days.

Necropsy

General findings. The body was that of a slightly-built, cachectic young man. The lungs were congested in all lobes, with purulent bronchitis and bronchopneumonia in the lower lobes. The liver was pale, and histologically the appearances were those of a moderately severe, predominantly centrilobar, fatty change. The portal tracts contained a mild lymphocytic infiltrate, but there was no increased fibrosis. Other organs showed no significant abnormality nor any evidence of residual leukaemia.

Central nervous system. (*i*) *Macroscopical.* The skull and meninges were normal. The brain weighed 1650 g and was of normal external configuration.

After fixation in 10% formol-saline, the organ was sectioned in the coronal plane into slices 5 mm thick. There were a number of lesions with ill-defined boundaries (Fig. 2). These lesions were darker than the surrounding normal tissue and showed numerous pinpoint dark spots, due to congested blood vessels. On the right side, the lesions were at the following sites: (a) prethalamic, in the frontal lobe, 15 × 10 × 10 mm, (b) in the temporal and lower parietal lobes, 60 × 10 × 10 mm, (c) near the surface of the parietal lobe, 20 × 5 × 2·5 mm. On the left side there was only one involved area in the temporal and lower parietal lobes measuring 70 × 10 × 10 mm. There were no other macroscopical lesions in the brain. The spinal cord was normal in appearance. (*ii*) *Microscopical.*

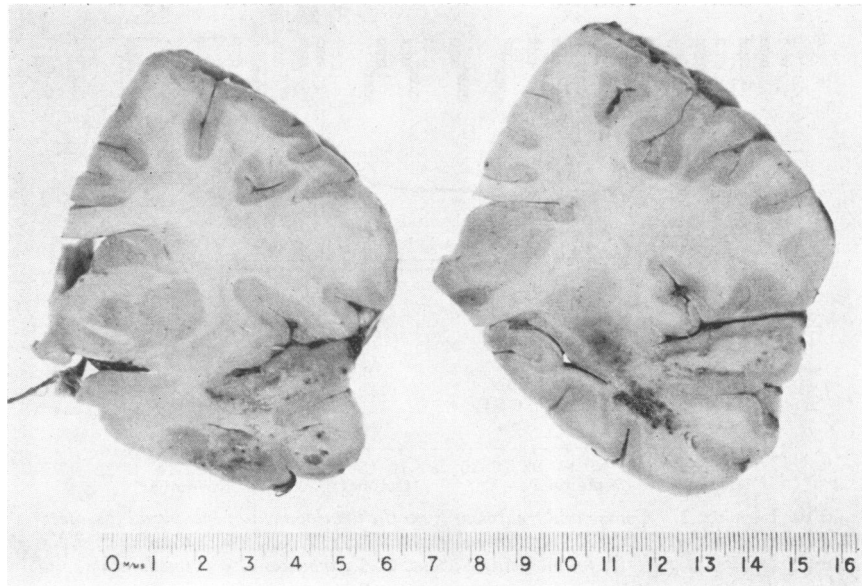

FIG. 2.—*Macroscopical appearance of lesions in the right temporal lobe.*

Multiple blocks were taken from each frontal, temporal, parietal, and occipital lobe, and from the cerebellum, pons, and medulla. The blocks were taken from areas which appeared normal as well as from the macroscopical lesions.

The material was processed conventionally and stained with the following methods: haematoxylin and eosin, methasol fast blue, Loyez's haematoxylin method, Gram, methenamine silver, periodic acid-Schiff, picro-Mallory, Lendrum's MSB, and chloracetate esterase.

Material from all the lesions showed similar histological appearances. The presence of numerous small infarcts was confirmed (Fig. 3). In each case the most striking changes were those affecting the blood vessel

FIG. 3.—*Microscopical appearance of necrotic lesions.* (*Picro-Mallory* × *60.*)

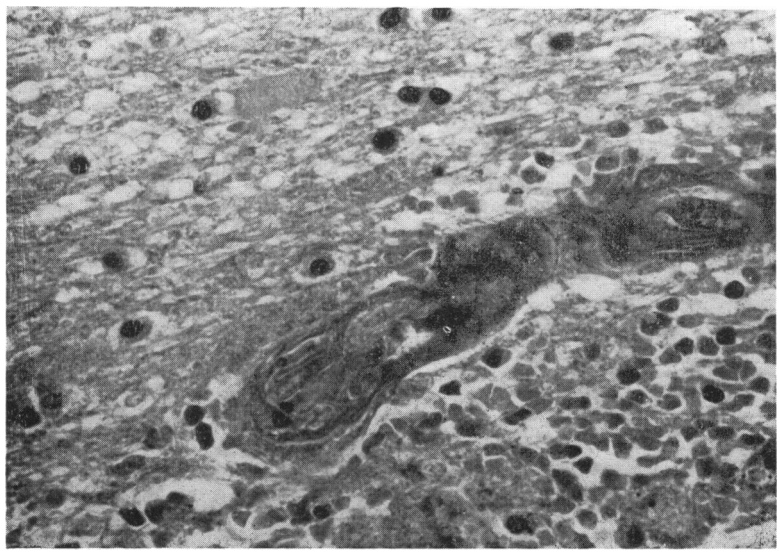

FIG. 4

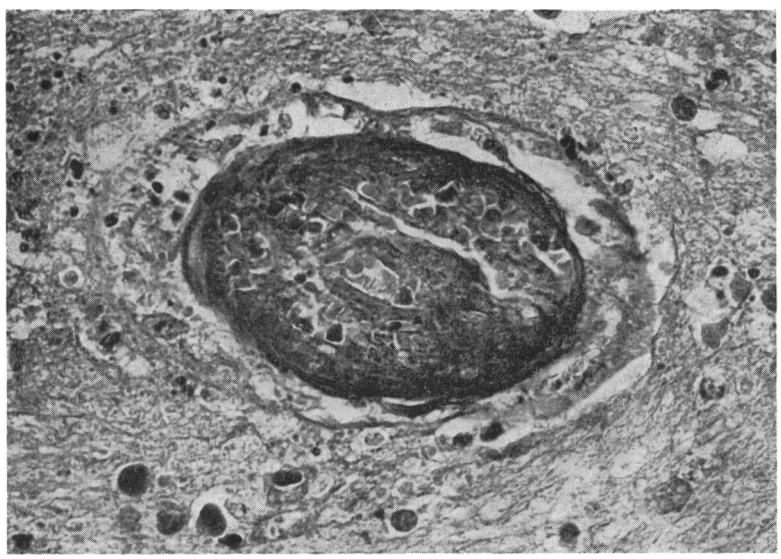

FIG. 5

FIG. 4 and 5.—*Blood vessels in the necrotic lesions showing intravascular thrombosis with fibrinoid necrosis of the vessel walls and extravasation of red cells. (Picro-Mallory × 600.)*

walls (Fig. 4 and 5). Necrosis of the walls was commonly seen, and in a number of cases the blood vessel wall stained positively for fibrin throughout its thickness. Around the damaged blood vessels there was extravasation of erythrocytes. There was a striking paucity of leucocytes, mature and immature, but there was considerable nuclear dusting, possibly indicating disintegrated polymorphs. There were no giant cells, and no fungi or bacteria were shown. Sections from areas of the brain not grossly involved were normal.

Electron microscopy of several blocks failed to reveal the presence of inclusion bodies or viral particles.

Case 2

This patient was a boy of 7 when he presented in October 1968 with pain over the right shin of five

months' duration. Later a swelling appeared in the same area which on biopsy proved to be a lymphosarcoma. Radiotherapy was given at a dose of 500 rads during five weeks with a good response, but in March 1969 he was found to have acute lymphoblastic leukaemia, with *x*-ray evidence of widespread osteoporosis and periostitis along the ribs.

He was treated according to the Medical Research Council 'Concord' protocol (Medical Research Council, Leukaemia Committee and Working Party on Leukaemia in Childhood, 1971) but only three courses and three intrathecal injections of methotrexate were given. Remission was maintained with methotrexate tablets given twice a week at a dose of 20 mg/m^2 for the next 16 months.

He remained well for 12 months until September 1970 when he developed headaches and vomiting. The CSF contained 4600 blast cells/mm^3 confirming the diagnosis of meningeal leukaemia.

He was treated with intrathecal injections of methotrexate given at a dose of 6·3 mg/m^2 on alternate days. This treatment caused severe anorexia and vomiting, and thrombocytopenia; it was, therefore, stopped after six doses had been given. There was symptomatic improvement but following a seventh dose given five days later, there was deterioration though there were no blast cells in the CSF.

In November he developed more headaches, depression, and increased appetite (a gain of 6·5 kg in four weeks). As the CSF contained 100 blast cells per mm^3 a further five doses of intrathecal methotrexate (6·0 mg/m^2) were given on alternate days. After the last injection he developed anorexia, headache, and tinnitus in the right ear, though his CSF contained no blast cells. In order to reduce the likelihood of meningeal relapse, he was given 10 more weekly intrathecal injections without any worsening of his symptoms. Towards the end of this course marrow examination showed he had relapsed.

Treatment was changed to vincristine, prednisone, and later 6-mercaptopurine. Within two weeks headache and vomiting recurred and two further doses of methotrexate were given intrathecally, though CSF blast cells were absent and there was no excess of protein.

There was a rapid deterioration in his condition with vomiting, drowsiness, slurred speech, and confusion, followed by a *grand mal* fit and coma on 17 February 1971. He became conscious three days after the convulsion but remained dysphasic, ataxic, drooling, and incontinent. The tone in his legs was increased suggesting damage to the pyramidal system. EEG showed large, generalized slow activity at 2–3 c/sec of larger amplitude over the left than right central and posterior regions. Over the right hemisphere there was a considerable amount of 5–6 c/sec activity which attentuated on eye opening.

Bone marrow aspiration at this time (18 February 1971) showed a remission pattern with very slight megaloblastic change only. It was considered that his symptoms were probably due to intracerebral leukaemic deposits and radiotherapy was given twice weekly to the brain for two weeks (total dose 500 rads). During the next 10 days (2–12 March) there was little change and therefore he received a further 945 rads to the brain, bringing the total dose to 1445 rads, without improvement. Treatment with 6-mercaptopurine at this time produced slight myelodepression—Hb 9·4 g, leucocytes 300/mm^3 (17 March)—but by mid-April the count was back to normal.

On 16 April 1971, CSF folate was 4·2 mg/ml (normal 12·6–67 mg/ml) and red cell folate 186 mg/ml (normal 100–640 mg/ml). Serum B_{12} was 780 pg/ml (normal 150–1000 pg/ml). (He had never enjoyed green vegetables and probably had had a folate-poor diet over a long period.) From 16–18 April folinic acid 21 mg/m^2 t.i.d. was given intravenously along with vitamin B12 and tablets of the B complex.

During the next four weeks his condition improved slightly and folinic acid was then restarted at a dose of 21 mg/m^2 i.v. on alternate days. Since that time he has shown slow but sustained improvement. He is sociable, his intellect is returning, and he can read again. The drooling has stopped, he can feed himself, complete simple jigsaw puzzles, and play dominoes. There is still some ataxia but he can walk with assistance and write a few words. The dysphasia has improved to the extent that he can speak short sentences.

Case 3

This patient was a boy aged 3 when acute lymphoblastic leukaemia was diagnosed in January 1968. Cytotoxic drug treatment similar to that in Case 1 was followed by prophylactic cranial irradiation (1615 rads) and then weekly pertussis vaccine. After the first relapse (February 1969) six 'Concord'-type methotrexate plus folinic acid courses were given followed by BCG until second relapse in March 1970. His third remission, induced by prednisone, vincristine, and asparaginase was maintained by 5-day courses of oral methotrexate but in November 1970 he developed meningeal leukaemia. Weekly injections of intrathecal methotrexate (7·5 mg) were given for seven weeks with a good response and disappearance of blast cells. He then became drowsy, unsteady on his legs, dysarthric, and incontinent. These symptoms progressed during the next three weeks until he was severely demented. There was ataxia, bilateral nystagmus, and slight increase in the tendon reflexes. A brain scan with Technetium 99 was normal. His EEG was reported as follows: 'A considerable amount of large amplitude 3–7 c/sec activity was seen over both hemispheres together with occasional slower waves. The slowest components were more marked over the right than left frontocentral and temporal regions. A little fast activity was present and there were occasional sharp waves over the right frontocentral region.'

All methotrexate was stopped and folinic acid tablets 15 mg daily started. There was no improvement for two weeks during which time he showed signs of cerebral irritation with screaming. He had episodes when the

head would be turned violently to one side with twitching of the limbs.

The second EEG showed a generalized increase in slow wave activity which remained more marked over the right than left frontocentral and temporal regions, but more posteriorly was most prominent on the left.

He then began to improve and in two weeks was continent and rational though still unsteady on his feet. Treatment was changed to folic acid 140 $\mu g/m^2$ twice a day. He also received 6 M-P 70 mg/m^2 and dexamethasone 6 mg/m^2. Four months after the start of his mental symptoms his mother considered him normal and he is back to school. No viruses were cultured from CSF, throat swab, or faeces, and virus antibody levels did not rise. The EEG showed an improvement with a decrease in the amount of slow activity, but there was still an excessive amount of 4–7 c/sec activity particularly over the right hemisphere. Alpha rhythm was recognizable on eye closure. A considerable amount of 20–24 c/sec activity was present over both hemispheres though the child was not receiving any drugs known to induce this type of rhythm. Another EEG two months later showed further improvement, but there was still an excess of theta and fast activity and some asymmetry between the activities of the two hemispheres anteriorly. A further EEG (26 August 1971) showed more improvement, but was still not quite normal.

Case 4

This patient, a boy, was 4 years old when acute lymphoblastic leukaemia was diagnosed in August 1969. He was treated in accordance with the MRC 'Concord' protocol but two weeks after the last lumbar puncture (a remarkably short interval), he developed headache and vomiting and was found to have meningeal leukaemia with 100 lymphoblasts/mm^3 in the CSF, with 10 mg/100 ml of protein. A Technetium-99 brainscan was normal. Virus studies were all negative. He responded to further weekly injections of intrathecal methotrexate, eight doses each of 5 mg being given (February–April 1970). During the next eight months he had two more episodes of meningeal leukaemia in which methotrexate was given intrathecally with good response. There was a haematological relapse (25 March 1970) during the first attack of meningeal leukaemia and after reinduction of remission he was maintained on methotrexate 7·5 to 10 mg (9–12 mg/m^2) twice a week for nine months (April 1970–January 1971). One month after his last intrathecal injection and while still taking oral methotrexate twice a week he became bad-tempered and had difficulty in concentrating at school. There were no abnormal physical signs. The EEG showed a little alpha rhythm but there was a considerable amount of large amplitude generalized 3–7 c/sec activity together with even slower waves and small amplitude fast activity. The slow waves were more conspicuous over the left than right hemisphere anteriorly, and multifocal sharp waves were seen.

Methotrexate was stopped and folic acid tablets 17·5 $\mu g/m^2$ daily prescribed, together with 6 M-P 60 mg/m^2. Within a week he began to improve though he then developed difficulty in sleeping due to motor restlessness lasting about six weeks. Six weeks later his mother considered him normal and treatment was changed to folic acid 120 $\mu g/m^2$, twice a day. He had previously eaten normal quantities of green vegetables.

Subsequent EEGs showed a decrease in slow activity but in a record taken three months after the first there were generalized bursts of irregular slow waves mixed with spikes.

An EEG nine months later (27 September 1971) continued to show improvement but there remained a moderate increase of slow components.

Case 5

A 2-year-old boy was diagnosed in April 1970 as having acute lymphoblastic leukaemia. The patient was treated with the standard MRC 'Concord' protocol followed by oral twice-weekly methotrexate (10–20 mg/m^2) for a total period of six months before meningeal leukaemia was diagnosed (March 1971). The patient was in haematological remission at this stage.

The meningeal leukaemia was treated by intrathecal methotrexate 7·5 mg weekly for three weeks with disappearance of cells from the CSF. Subsequently, methotrexate 7·5 mg and cytosine arabinoside 15 mg were given intrathecally at 7- or 14-day intervals for 10 weeks, together with oral 6-mercaptopurine.

Between 22 June and 4 July he was given radiotherapy (1000 rads) to the brain. At this stage he was noted to be very irritable and difficult to manage. Further radiotherapy was stopped when he was found to have relapsed haematologically and reinduction of remission was attempted with prednisone 20 mg daily and vincristine 1 mg i.v. weekly for three weeks. A further bone marrow showed little improvement. Meanwhile the child became very excitable, agitated, disorientated, and confused. He was a little unsteady on his feet but no long tract signs were evident. Folic acid 100 μg daily was started and after a fortnight some improvement had been noted though he was still far from normal.

In this case the first EEG (Fig. 6), taken before the onset of symptoms, showed rhythmic activity at 6–7 c/sec which was diminished over the posterior part of the head on eye opening. There was a minimal excess of 4–7 c/sec activity present over both hemispheres. The second record showed a severe deterioration with large amplitude generalized 2–7 c/sec activity together with even slower waves. The amplitude and amount of slow activity was more marked over the right than over the left hemisphere, especially anteriorly.

Case 6

A girl was 3 years old when acute lymphoblastic leukaemia was diagnosed in April 1970. She was treated according to the 'Concord' protocol but one course of methotrexate was omitted. Twice-weekly oral methotrexate therapy (10–20 mg/m^2) maintained remission for a further 32 weeks. At this time (April 1971) though the patient had no headache or papilloedema, the CSF contained 650 lymphoblasts/lympho-

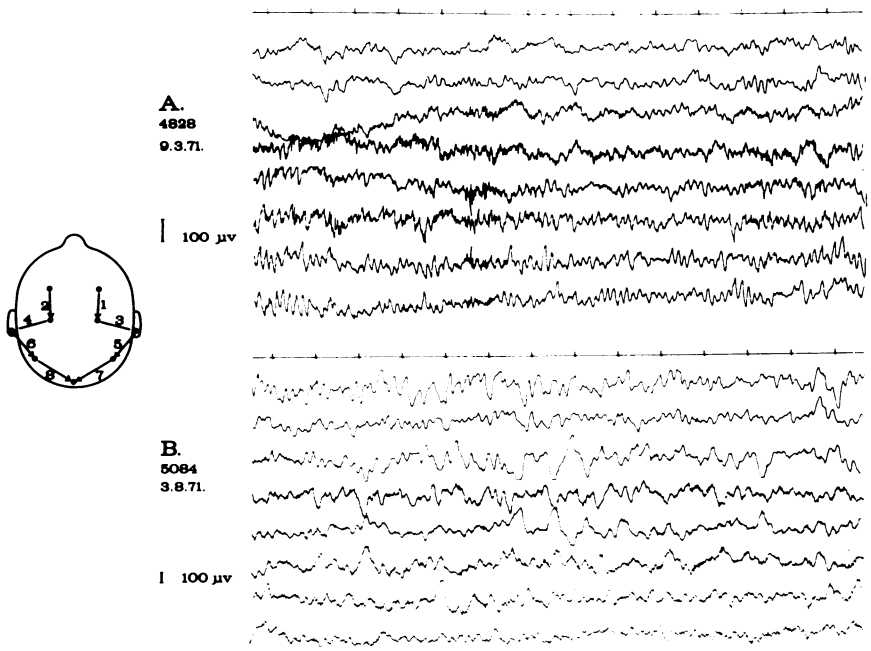

FIG. 6.—*EEG Case 5. Before and after development of encephalopathy. (A) Lying quietly with eyes closed. The record shows rhythmic activity at 6–7 c/sec and only a minimal excess of slow components. (B) Restless and with eyes open. There is a marked increase in slow wave activity particularly over the right hemisphere.*

cytes per mm^3, and a diagnosis of meningeal leukaemia was made. She was treated with three intrathecal injections of methotrexate 8 mg at weekly intervals, at the same time continuing to receive twice-weekly oral methotrexate 10 mg. Her symptoms improved rapidly and the CSF became clear of cells.

Weekly intrathecal injections of methotrexate 8 mg were continued to which cytosine arabinoside 16 mg was added. After two such injections the patient became unwell with irritability, nausea, and vomiting. The CSF was found to be free of cells, and the symptoms were thought to be once again due to methotrexate toxicity. Accordingly, the oral methotrexate was reduced to a single weekly dose of 10 mg given midway between her intrathecal injections.

She now developed measles (19 May 1971) complicated by a pneumonia which was successfully treated with ampicillin and tetracycline. At no time during the course of the measles was there alteration of consciousness or any other indication of encephalitis.

After recovery from measles, the patient was given one further intrathecal injection of methotrexate and cytosine arabinoside (11 June). When next seen a week later her mother reported that she had been unwell, irritable, and lethargic. She spent most of the day lying curled up on her side, and was becoming progressively more withdrawn and noncommunicative. Her gait was unsteady on a broad base, and though she had previously been well able to manage a knife and fork, she now had great difficulty in getting food to her mouth. She also had difficulty in initiating micturition, and on admission her bladder was found to be greatly distended. Neurological investigation revealed generalized hypotonia with sluggish reflexes, but no localizing signs. The CSF remained cell-free. Blood and marrow were found to be normal, and in particular there was no megaloblastic change or other evidence of folate deficiency in the marrow.

Because of the suspicion that the progressive dementia might be attributable to methotrexate, all methotrexate therapy was now stopped. Daily oral 6-mercaptopurine was started, and two further weekly intrathecal injections of cytosine arabinoside alone were given. In view of the progressive mental deterioration which occurred during this time, however, intrathecal therapy was thereafter abandoned. An EEG at this point showed dominant 4–6 c/sec activity with delta components of high voltage in the posterior regions and an increase in fast activity.

Intramuscular folinic acid 3 mg daily was given daily for a week with no evident improvement, and then, at the parents' request, the child was discharged home. Treatment now consisted of 6-mercaptopurine 50 mg and folic acid 500 μg daily.

Since her return home, the patient has improved remarkably. She lives on a farm, and within two weeks she was riding on the tractor and 'helping' with the haymaking. Speech has returned to a considerable

extent, and she is clearly once again enjoying life. Her behaviour, however, remains infantile, and she has to be prevented constantly from getting herself into dangerous situations.

Case 7

An 8-year-old girl was first seen in June 1969, when a diagnosis of acute lymphoblastic leukaemia was made. Treatment was according to the MRC 'Concord' protocol with no maintenance treatment. She relapsed 6 months later (April 1970). A further remission was maintained with oral methotrexate 10–20 mg/m^2 twice weekly for 11 months. A third remission was induced (March 1971) and maintained by cytosine arabinoside and cyclophosphamide.

The first episode of meningeal leukaemia occurred 17 months after diagnosis (November 1970) and was treated successfully with intrathecal methotrexate 10 mg/m^2 given at weekly intervals for 14 weeks, and was tolerated well. She was on maintenance oral methotrexate at the time and apart from a moderate degree of buccal ulceration, which cleared when the dose of methotrexate was reduced to 10 mg/m^2 twice weekly, no untoward effects were noted, though bone marrow samples showed marked megaloblastic changes. A second episode of meningeal involvement occurred eight months after the first and again was treated with intrathecal methotrexate, in a similar dose; maintenance chemotherapy at this time was cytosine arabinoside and cyclophosphamide. The symptoms of headache and vomiting cleared rapidly after the first intrathecal dose but after the second dose (5 days later), an alteration in mood was noted. Within three days she was completely irrational, disorientated in time and space, and unable to co-operate in any way. Apart from the dementia, the only abnormal neurological sign was a right 6th nerve palsy. However, in view of her mental state, assessment of vision and hearing were impossible at that time. Repeat lumbar puncture showed that the cell count had fallen from 735 to 12/mm^3, protein and sugar determinations were normal, the fluid was not xanthochromic and the pressure normal. EEG showed a moderate diffuse abnormality with excessive slow activity bilaterally but predominantly over the frontal lobes. Intravenous folinic acid was given during the recording, but no alteration in pattern was observed. A brainscan with Technetium 99 was normal. In view of the remarkable progression of dementia after the second dose of intrathecal methotrexate, she was given 72 mg intravenous folinic acid in 3 divided doses. A rapid improvement in her mental status occurred and within three days she was fully orientated and co-operative. However, it was now apparent she was blind in both eyes, only able to appreciate hand movements. The pupils were moderately dilated and reacted sluggishly to light; fundi were within normal limits. A moderate degree of nerve deafness on the right side was noted. The right 6th nerve palsy has persisted but no other neurological signs developed. At no time was there evidence of peripheral neuritis. Oral cyanocobalamin was given in a dosage of 100 μg but no improvement in the neurological signs occurred. At the time of the present neurological disturbance, no oral methotrexate had been given for nearly five months.

It seems likely that these neurological complications are related to the methotrexate in view of the time relation and also the rapid improvement of the dementia following folinic acid. However, the possibility of other factors such as intracranial leukaemic deposits or a haemorrhage cannot be excluded, though this seems unlikely. Cranial irradiation was started seven days after the onset of these symptoms, but no dramatic change in the neurological deficit has resulted.

Discussion

The 7 patients described all developed neurological signs and dementia after long periods of oral methotrexate treatment to which were added multiple intrathecal injections of methotrexate when meningeal leukaemia occurred (Table). At the onset of the disorder other diagnoses were considered—intracerebral leukaemic deposits, subdural haematoma, and chronic fungal or viral encephalitis—but investigation and the lack of response to radiotherapy provided no support for any of these. It is, of course, difficult to exclude the possibility of a 'slow' virus infection of the central nervous system but the absence of serological, cultural, and histological evidence makes

TABLE

Details of Methotrexate Therapy

Case No.	Age (yr)	Surface Area m^2	Parenteral Methotrexate		Oral Methotrexate		Intrathecal Methotrexate		Total Dose Methotrexate (mg)
			Total Dose (mg)	Period (wk)	Total Dose (mg)	Period (wk)	Total Dose (mg.)	Period (wk)	
1	24	1·84	1332	10+3	1980	65	150	5+8	3462
2	9	1·04	765	3	3480	71	213	3+19	4458
3	5	0·70	1123	10+6	326	26	87	5+7	1536
4	5	0·85	1188	5	750	36	200	15+4+10	2138
5	3	0·60	432	6	430	23	82	5+14	944
6	4	0·73	900	5	1200	40	78	5+8	2178
7	10	1·00	1440	6	1120	78	200	5+14+1	2760

this explanation less likely, while the improvement that followed cessation of methotrexate treatment and the response to folinic and folic acids seems to incriminate methotrexate. The history of measles in two cases suggests an alternative cause, but the lesions in Case 1 are not those of subacute sclerosing panencephalitis and no serological evidence against the measles virus was obtained. The EEG in this case showed none of the typical changes described in this condition (Cobb and Hill, 1950).

With one possible exception (Pinkel *et al.*, 1971) such a condition has not been previously recorded, though the cerebral disturbances associated with B_{12} deficiency are well known and dementia due to folate deficiency and responding to folate therapy has been observed in two patients (Strachan and Henderson, 1967). A similar condition has also been described in patients receiving anticonvulsant therapy with folate antagonists (Dow, 1971). The similarity between the latter and the cases we have described includes some of the EEG changes (though the increase in slow waves was not so severe) and the occurrence of a period of hyperexcitability when treatment with folic or folinic acid was first begun. The latter was noticeable in three of our cases and was reported by Reynolds (1967) during the correction of folate deficiency induced by anticonvulsants. The exact role of folates in cerebral metabolism is uncertain, but the high concentration in CSF (two to three times greater than in serum) may indicate its importance (Herbert and Zalusky, 1961). Though in the mature brain there is little DNA synthesis, Richter (1965) has drawn attention to the high rate of protein synthesis. N^{10} formyl tetra-hydrofolate is known to be required for the formation of methionyl t-RNA which is needed to initiate peptide synthesis, and this could represent one requirement for folate in the metabolism of nerve cells.

The histological findings in the one fatal case strongly suggest a vascular basis for the lesions, despite the absence of thrombosis, haemorrhage, or blood vessel changes elsewhere in the body, though it is possible that the lesions are secondary to brain necrosis via some other mechanism. Vascular damage is not one of the established consequences of methotrexate poisoning but experience has shown that many different tissues are susceptible, not only those with a high rate of cellular proliferation. The cells of the small cerebral blood vessels may be in an unusually vulnerable position, where they traverse the subarachnoid space, to relatively high concentrations of surrounding methotrexate, and it is possible that local ependymal reactions or loculation may be subsidiary factors.

Perhaps one should also consider the possibility of a local hypersensitivity type of reaction though there does not appear to be any single factor in dosage, timing, or route of administration (Fig. 7) which would distinguish these cases from some others treated by methotrexate.

The effects are clearly different from the immediate and mostly spinal lesions referred to in the introductory paragraph. Whatever the mechanism, either methotrexate itself or the preservative mixture (methylhydroxybenzoate and propylhydroxynemzoate) could be the responsible agent, though there is no particular reason to suspect the latter.

The marked EEG abnormalities found in these patients are in keeping with some kind of diffuse encephalopathy. The asymmetry in the distribution of the excessive slow wave activities over the various regions of the two hemispheres which occurred, particularly in the children, is in keeping with a somewhat patchy involvement of the cerebral hemispheres. In a severe toxic encephalopathy it is difficult to know how much irreversible cerebral damage may have occurred in addition to the metabolic disturbance, and in the two children with serial records (Cases 3 and 4) there were persistent abnormalities over a period of a few months in spite of a general slow trend towards EEG recovery. Methotrexate therapy, unaccompanied by any clinical complications is not necessarily associated with any EEG abnormalities; three other children (aged 4, 5, and 11 years) had normal records after long periods of treatment. Case 5 also had an unremarkable EEG while on treatment, but before the onset of symptoms: the appearance of the EEG abnormality in this child coincided with the clinical deterioration.

EEG abnormalities may occur during the course of acute lymphoblastic leukaemia due to a variety of factors such as cerebral haemorrhages, leukaemic infiltrations, ischaemic lesions, toxic effects of drugs, and intercurrent illness (Butcher *et al.*, 1970). A sudden gross global deterioration in the EEG is, however, most likely to be due to some form of toxic encephalopathy.

It is perhaps remarkable that other signs of induced folate deficiency, e.g. in the bone marrow or mucous membranes, were mostly slight or absent, but the same is true of other chronic manifestations of methotrexate toxicity, e.g. pulmonary and hepatic changes. Their absence does not exclude the emerging probability that the combination of prolonged oral and multiple

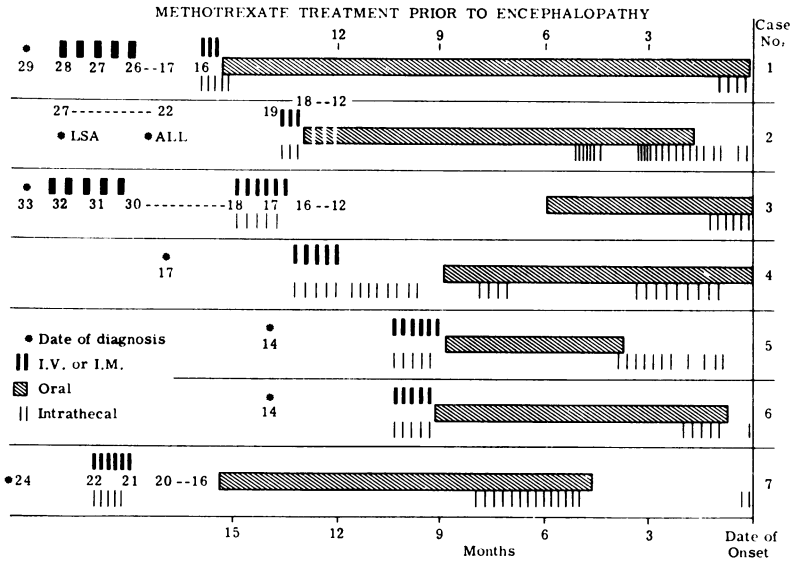

FIG. 7.—*Time and route of methotrexate treatment before the onset of the first symptoms of encephalopathy. In each case the upper rank indicates parenteral treatment (i.v. or i.m.) usually in 5-day or 2-day courses. The middle rank shows oral therapy, almost always twice weekly. The lowest rank indicates each dose of intrathecal methotrexate. All the figures indicate time in months before encephalopathy.*

intrathecal doses was the determinant factor, with possibly a cumulative effect through the anorexia and reduced folate intake resulting from the methotrexate itself.

It is curious that the condition has not been noted elsewhere since methotrexate has been the standard treatment for meningeal leukaemia for many years. Possibly some cases have been misdiagnosed and the manifestations attributed to cerebral leukaemia. More probably it is the intensity of the treatment which has now brought to light a new effect of methotrexate. This intensive treatment has been motivated by the chance of eradicating meningeal leukaemia. The arguments, as set out by Selawry and Odom (1968), rest upon the assumption that if two or three doses of intrathecal methotrexate are enough to reduce the CSF cell concentration to less than 1/mm^3 then the remaining undetected cells in the meninges could be eradicated by 8 to 10 further doses. Remission lengths of over 225 days have been obtained by such dose schedules and eradication may have been achieved in 1 or 2 cases (Pinkel *et al.*, 1971). Multiple intrathecal methotrexate injections should not, therefore, be immediately abandoned especially as the toxic effects, if diagnosed early, seem to be largely reversible though this may be a slow process. Further study is clearly needed.

Meanwhile it seems prudent to discontinue oral methotrexate in all patients having multiple intrathecal injections of the same drug. If the condition is suspected, an EEG may provide useful confirmatory evidence, and prompt treatment with adequate doses of folinic acid may prevent the worst effects of this distressing complication. Such treatment should not in these cases induce leukaemic relapse as it is usually possible, as in the present cases, to substitute other cytotoxic drugs.

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