AN EPIDEMIC OF ACUTE ENCEPHALITIS IN YOUNG CHILDREN

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This paper is concerned with a small outbreak of illness of an unusual nature occurring in the Children's Unit of the Western General Hospital, Edinburgh. In addition to the clinical interest of the cases, there are features of considerable pathological and epidemiological importance connected with the outbreak.

Clinical Records.

Case 1. I.M.S., female, aged 1 year 7 months, was admitted to the Western General Hospital in March, 1933, at the age of 1 year 3 months. At this time she was noted as being slightly undersized but well nourished and the liver showed moderate enlargement. Prior to admission she had been treated elsewhere for gonococcal vaginitis: during the three succeeding months her health was good and progress uninterrupted, but a positive Wassermann reaction, present on admission, persisted. On the evening of July 22, 1933, the patient was noticed to be less active than usual and generally 'out of sorts': her condition remained unchanged throughout the rest of the day, and on the 23rd she was still quieter and less responsive to all forms of attention and refused food. By the afternoon of the 24th she was definitely dull and apathetic. She lay awake for long periods in her cot but without changing her position or showing response to external stimuli. The expression was heavy and drowsy, the face flushed, the conjunctivae suffused and the eyes dark-ringed and sunken. The tongue was furred and the fauces were injected. Temperature and pulse rate were normal; there was no rash, and examination of the child resulted in only negative findings. At this stage the patient was isolated with three other children (C.B., M.M., E.M.W.) from the same ward who were showing similar but less marked signs in keeping with the prodromal stage of some common infective disease.

At 10.30 p.m. of the same day (July 24) the child's condition became suddenly worse and she looked extremely ill: left undisturbed she lay motionless, staring in front of her without interest, but when examined was excessively fretful. No evidence of organic nervous disease was found. Temperature was still normal. About this time vomiting took place and recurred several times during the night. The motions were loose, but neither foetid nor frequent. There was never any improvement in the child's condition, and at 1.30 a.m. on the morning of July 25

the temperature rose to 103.2° F. This was accompanied by an acceleration of pulse which became increasingly rapid until it was imperceptible. Repeated cerebral cries were noted before the child became comatose and died at 5.30 a.m., sixty hours from the time of onset of the illness.

POST-MORTEM EXAMINATION (12 hours after death).

BRAIN. There was hyperaemia of the meninges at the base, but not elsewhere; no thrombosis of meningeal vessels, nor haemorrhage. The brain substance, both grey and white matter, was markedly congested, especially in the pons. No areas of softening were observed.

FAUCIAL TONSILS were enlarged but not obviously inflamed.

THE LUNGS were congested and there was atelectasis of the left upper lobe.

THE LIVER was slightly enlarged, firm, pale, tough, and showed fine fibrosis.

THE KIDNEYS were healthy.

MICROSCOPIC EXAMINATION. Sections were examined from cerebral cortex, optic thalamus, mid-brain, pons and medulla oblongata. All the parts examined showed considerable hyperaemia, which was accentuated in certain areas and was

FIG. 1. Blood vessel in optic thalamus showing haemorrhage into perivascular space. (Case 1.)
× 150. H. & E.

FIG. 2. Venule in optic thalamus, showing early perivascular infiltration. Small mononuclear cells in perivascular space, arranged in a ring around the vessel. (Case 1.)
× 300. H. & E.

generally more severe in the grey matter than in the white. This was particularly noticeable in mid-brain, pons and medulla where the congestion was greatest in the grey matter beneath the floor of the fourth ventricle and around the Sylvian aqueduct. Haemorrhage into the adventitial space of blood vessels was a noteworthy feature, especially in the optic thalamus (Fig. 1). The extravasated blood was, as a rule, strictly confined within the peri-vascular space, but occasionally it had penetrated to a short distance into the surrounding brain substance. There was oedema of the brain, shown by dilatation of the perivascular spaces, and an increase in the size of the spaces surrounding nerve cells. Perivascular infiltrations of small round cells ('cuffing') were not found in typical form, but evidence of commencing infiltration was forthcoming. A venule in the optic thalamus had a ring of small lymphocyte-like cells, one layer thick, lying in the dilated perivascular space, closely applied to the vessel wall (Fig. 2). A few other vessels showed three or four similar cells in the perivascular space.

Changes indicating injury to nerve cells were conspicuous but not extreme. They were best observed in the large ganglion cells in the floor of the fourth ventricle and central grey matter of the mid-brain; also in the larger nerve cells of the thalamus. The changes included swelling of the cell body, the outline becoming convex, chromatolysis with partial or almost complete disappearance of the Nissl substance, an eccentric position of the nucleus, which sometimes bulged beyond the edge of the cell body, and, in a few of the more gravely injured cells, karyolysis, the nucleus staining so faintly as to be almost indistinguishable. These changes were very variable in degree in different cells and those affected were irregularly distributed. In a single group of ganglion cells some might show severe changes while others appeared quite healthy. Occasional nerve cells had three or four satellite cells, but true neuronophagia was not observed. In the pons and medulla many of the large ganglion cells close to the floor of the fourth ventricle contained small strongly eosinophilic granules in their cytoplasm, either aggregated in a clump or dispersed throughout the cell body (Fig. 3). The

FIG. 3. Large nerve cells in floor of fourth ventricle. Each cell contains a cluster of minute eosinophilic bodies in the cytoplasm. The nuclei are eccentric in position. (Case 1.) $\times 600$. H. & E.

cells which contained these granules often exhibited in relatively severe degree the various degenerative changes described above. Such granules were not found in any other part. Intranuclear inclusion bodies were not found.

Sections of lung, spleen, kidney and lymph gland showed nothing of pathological significance. Toxic changes were practically absent. In the liver there was an increase of cellular fibrous tissue, infiltrated by lymphocytes, in the portal tracts, and in a few places this tissue had penetrated the lobules. There was also some fatty change in the liver cells. These changes were attributed to congenital syphilis.

Case 2.—C.B., male, aged 1 year and 7 months. He had no illness during infancy other than measles at eight months and occasional attacks of bronchial catarrh. On April 19, 1933, at the age of 1 year and 4 months, he was admitted to the Western General Hospital as a healthy child. He was discharged to the Edinburgh City Hospital with chickenpox on June 4, being readmitted to the Western General Hospital on June 17 in a robust, healthy condition. On July 24, 1933, he was noted to be less active than usual and to have no desire for food.

By evening his face was flushed, his eyes injected and his expression heavy and dull. The tonsils were enlarged and red, the tonsillar glands moderately swollen. Temperature was normal; there was no rash, but, as a precaution, the child was isolated. Temperature was still normal on July 25. The child's condition was one of great agitation which tended to exhaust him so that he was alternately restless and very listless. On being approached he showed intense irritability, and attempts to examine him were resisted with vicious frenzy; he scratched and tore anything within reach, and flung himself about the cot. Pupils were dilated but equal, there was some diminution in arm tendon reflexes, superficial abdominal reflexes were absent, the left knee jerk was increased, and a right extensor toe response was obtained. A true Kernig's sign was not found, but there was definite objection to attempts to elicit it on the left side. Tâche was pronounced. Curious features were the way in which the child screwed up his eyes whenever a hand was brought near his forehead, and a tendency to assume a position of extreme opisthotonus in his endeavour to resist examination. Examination left him extremely exhausted. No localised muscle tenderness was determined. The tongue was moist but heavily coated. Examination of the chest and abdomen was entirely negative. The tuberculin test was positive. The white blood count was 18,000 per c.mm., consisting of polymorphs 57 per cent. and mononuclears 43 per cent. A specimen of stool examined contained no pathogenic organisms. By midnight on the 25th the child looked extremely ill; his expression was dazed, his eyes sunken and ringed; he was definitely drowsy although still able to resist examination violently. The pulse was now very rapid and soft. Lumbar puncture was carried out, and 60 c.c. of clear fluid obtained under pressure. This appeared to result in a slight improvement, but any benefit was only of a temporary nature. By 9 a.m. on July 26 drowsiness had been replaced by a state of intense irritability and restlessness. The patient flung himself about in his cot until, completely exhausted, he lay curled up, his head buried in the pillow. He uttered frequent piercing cries and was obviously in great pain: the lips were ashen, the conjunctivae markedly injected, the right more so than the left, and the pulse continued to become increasingly rapid. Lumbar puncture was again carried out and 10 c.c. of clear fluid obtained under pressure.

At 10 a.m. the child was again examined. Both pupils were contracted, the left more than the right. The eyes were turned upwards and towards the left and blinking was abolished on the left side. A dubious Kernig's sign was elicited on both sides but there was no neck rigidity. The patient continued to utter periodic cries of pain, but these became weaker: he lay continually on his right side, passed into a semi-comatose condition, and died at 12.20 p.m., forty-eight hours from the time of onset of the illness.

POST-MORTEM EXAMINATION (24 hours after death).

BRAIN. There was intense hyperaemia of the meninges over the whole surface; no thrombosis of blood vessels. The brain substance showed intense congestion of both grey and white matter; the grey matter had a pinkish colour and congested vessels were prominent in the white matter. No haemorrhages or areas of softening were visible.

SPINAL CORD showed congestion of the meninges.

FAUCIAL TONSILS were enlarged.

TRACHEO-BRONCHIAL LYMPH GLANDS: one contained a few small tuberculous foci.

LIVER AND KIDNEYS showed very slight toxic changes. No other organ presented anything abnormal.

MICROSCOPIC EXAMINATION. Sections were examined from cerebral cortex, optic thalamus, mid-brain, pons, medulla oblongata and spinal cord. Intense congestion of the brain substance was present in all the parts examined. The adventitial spaces of blood vessels were distended and the pericellular spaces increased in size, indicating oedema of the brain. Haemorrhages into perivascular spaces were numerous in the optic thalamus and present also in pons, medulla and mid-brain; they were not found in cerebral cortex or spinal cord. Typical 'cuffing' of blood vessels with infiltrations of small round cells could not be demonstrated,

but in the dilated perivascular spaces of a few blood vessels in the mid-brain small collections of mononuclear cells were found (Fig. 4). The best examples were in the central grey matter near the aqueduct, and in the region of the substantia nigra. In other parts of the brain and in the spinal cord no such appearance was discovered.

Ganglion cells presented variable appearances. Many showed no alteration. Others were profoundly altered, being swollen, showing chromatolysis of varying degree, and having the nucleus displaced to one side of the cell. Sections stained to demonstrate Nissl bodies (cresyl violet) showed in many cells the condition of central chromatolysis, the Nissl substance having disappeared from the central part of the cell body and being collected in a dense mass or ring at the periphery (Fig. 5). The nucleus of such cells might be healthy, but was usually eccentric in position and sometimes showed karyolysis. These changes in nerve cells were more pronounced in the central grey matter and substantia nigra of the mid-brain than elsewhere, but were found in certain cells in the thalamus, pons and medulla. They were not observed in the cerebral cortex nor

FIG. 4. Small blood vessels in central grey matter of midbrain. The perivascular spaces are widely dilated and in them a few small mononuclear cells have collected. (Case 2.) $\times 150$. H. & E.

FIG 5. Degenerate nerve cell in central grey matter of midbrain, showing disappearance of Nissl substance from central part of cell body (central chromatolysis). (Case 2) $\times 580$. Cresyl Violet.

in the cord. No inclusion bodies, either intranuclear or extranuclear were found.

Sections stained by Morgan's method for myelin showed no areas of demyelination.

Sections of liver, spleen and kidney showed no significant changes. Toxic degeneration was very little in evidence. Sections of lung showed nothing except some general hyperaemia.

Case 3.—M.M., female, aged 1 year and 11 months.

Born in the Maternity Ward of the Western General Hospital in August, 1931, she remained in the Hospital until she contracted chickenpox in March, 1933, at the age of 1 year and 7 months. She was readmitted in good health from the City Fever Hospital on May 13, following the attack of chickenpox.

On the morning of July 23, 1933, she was noticed to be less active than usual and without desire for food. Her condition was much the same the next day but her face was flushed and her expression heavy. Temperature was normal, and nothing was found on examination beyond moderate enlargement of the

tonsils and faucial injection. As a precaution the child was removed to the isolation ward.

Complete examination was again carried out on the afternoon of July 25. An extensor plantar response was obtained on the left side; otherwise the superficial and tendon reflexes were normal. The ear drums were healthy in appearance; the urine contained nothing abnormal. The one noticeable change from the previous day was increasing restlessness and irritability. By the afternoon of July 26 this irritability was extreme and made examination difficult. Kernig's sign was not present but the patient resented extension of the legs although there was no apparent muscle tenderness. Superficial abdominal reflexes and the biceps tendon jerks were absent. Sweating of the head was a feature and there was a pronounced *tâche*. A specimen of stools contained no pathogenic organisms. The tuberculin skin test was negative. Towards evening the restlessness was further increased, and lumbar puncture was carried out, 10 c.c. of clear fluid being obtained under slight pressure with resultant relief.

The next day, July 27, the patient's objection to examination was greater. She flung her head back, rigidly arched her spine, uttered piercing cries and tore at anything within her reach. She appeared in terror of having her head touched and screwed her eyes up in a characteristic way when this was attempted. The pupils were widely dilated and there were dark rings around the eyes. Abdominal and tendon reflexes remained unchanged from the previous day. Examination left the patient extremely exhausted. She occasionally sat up and took an interest in her surroundings but soon relapsed into her former drowsy state. A white blood count gave 12,000 cells per c.mm. of which 60 per cent. were polymorphonuclear and 40 per cent. mononuclear.

The next morning, July 28, the child's general condition showed slight improvement and at times she was seen to smile, but still showed the same maniacal frenzy when any attempt was made to examine her. When undisturbed she was still abnormally quiet and unresponsive. Tendon reflexes were unchanged from the previous day. For the first time there was limitation of neck flexion. Lumbar puncture was carried out and 30 c.c. of clear cerebro-spinal fluid obtained under pressure, after which the restlessness was greatly diminished. A few hours later the child was transferred to the City Hospital. The abdominal reflexes reappeared two days after transfer and the pulse rate remained accelerated for almost two weeks. Otherwise there was nothing to note, and recovery was apparently complete. At the present time her condition is excellent and she shows no residual manifestations of her illness.

Case 4.—E.M.W., female, aged 2 years. The child was first admitted to the Western General Hospital in July, 1932, at the age of one year after a severe attack of measles. No other details of the previous history were available. At the time of admission her condition was poor: this improved greatly during the twelve months she was in hospital, despite the fact that she was subject to recurrent attacks of respiratory and alimentary catarrh. The tuberculin reaction was positive.

On the morning of July 24, 1933, she was noticed to be off colour, apathetic and refusing food. By the afternoon her expression had become heavy, the face flushed and the eyes suffused. Usually of a distinctly friendly nature, she was now very peevish. Temperature was normal. There was an occasional short dry cough. Tonsillar glands were palpable; the tonsils were slightly enlarged and injected. Otherwise the findings on examination were negative. Her condition remained unchanged throughout the next day, but by the afternoon of July 26 her lassitude had greatly increased. During examination irritability was extreme; she flung her head back and assumed the position of marked opisthotonus and uttered repeated shrill cries. Absence of the abdominal reflexes and diminution of the biceps and supinator reflexes were noted and there was a pronounced *tâche* cerebrale. There was no nuchal rigidity, Kernig's sign was absent, and there was no ocular paresis. The tongue was furred, and the motions were green and increased in frequency but contained no pathogenic organisms. The urine was

normal. A white blood count was 15,200 per c.mm. and a differential count gave polymorphonuclears 65 per cent. and mononuclears 35 per cent.

On the afternoon of the next day, July 27, Babinski's sign was obtained on the right side, while the response on the other side was dubiously extensor. Nuchal rigidity and Kernig's sign were absent but marked voluntary resistance was encountered in testing for these. The abdominal reflexes were still absent, the pupils were now widely dilated, and the expression one of fear. The child was terrified when a hand was brought near her head. Irritability was still extreme and examination left her greatly exhausted. There was no evidence of localised muscle tenderness. The pulse was rapid.

During the night the child became more restless and walked round her cot until, tired out, she lay down. Early in the morning (July 28) she vomited. Examined again at 10 a.m. she resisted with a maniacal frenzy until exhausted. The abdominal reflexes were absent, Babinski's sign was obtained on both sides, and Kernig's sign was found on the right side but not on the left. Vomiting occurred twice during the course of the morning. Lumbar puncture was performed and 30 c.c. of clear fluid obtained under pressure, giving immediate great relief. Three hours later the patient was transferred to the City Hospital. There her progress was uninterrupted; doubtful neck rigidity persisted for a further forty-eight hours and the pulse, which had become rapid while she was still in the Western General Hospital, did not return to normal until ten days after transfer. The abdominal reflexes reappeared two days after admission to the City Hospital. At the present time the child is in excellent health and shows no evidence of any sequelae.

SUMMARY OF PATHOLOGICAL INVESTIGATIONS

Case number.	Initials.	Date.	C.S.F. Mgrms. per 100 c. c.			Blood.			W.R.	T.R.
			Protein.	Sugar.	Chlorides.	W.B.C.	Polymorpho- nuclears.	Mononuclears.		
1	I.M.S.	January, 1933 25/7/33	...	...	...	per c.mm.	%	%	+	—
			Blood	stained	...	...	...	...	—	—
2	C.B.	January, 1933 25/7/33 26/7/33	...	...	...	...	...	...	—	+
			20	80	737	18,000	57	43	—	—
3	M.M.	13/7/33	...	...	...	...	...	...	—	—
		26/7/33	60	25	735	...	...	...	—	—
		27/7/33	...	...	...	12,000	60	40	—	—
		28/7/33	61	87	584	...	...	...	—	—
4	E.M.W.	August, 1932	...	...	...	...	...	...	—	+
		26/7/33	...	...	...	15,200	65	35	—	—
		28/7/33	22	99	528	...	...	...	—	—

C.S.F. All cases { Cells all lymphocytes, no increase.
Culture sterile; colloidal gold reaction, no precipitate.
(Specimen from Case 1 taken at autopsy).

BLOOD. Cultures made of heart blood at the autopsies on Case 1 and 2, both sterile.

FAECES. All cases; no pathogenic organisms isolated.

URINE. All cases; no microscopical abnormalities.

Clinical summary.

All four children had been in hospital for a prolonged period; two for over three months and two for twelve months. They were all admitted as healthy individuals on the recommendation of the Public Assistance Officer. Three (I.M.S., C.B., and M.M.) were in the same ward, the first two occupying adjacent cots. The fourth child was in a different ward, but was attended by the nurses in charge of the other three cases. Between July 7 and July 11, when the heat was exceptionally great, the four children, along with other inmates of their wards, spent the greater part of each day in the garden adjoining the hospital. Among adult female patients also in the garden were two cases of post-encephalitic Parkinsonism who found a special delight in the companionship of the children. The children I.S. and C.B. were especial favourites and were known to have played for long periods on the knees of one or other of these particular patients. The third child (E.M.W.) was known to have been in similar contact on occasions with the post-encephalitic subjects, but any history of such contact in connection with the fourth child (M.M.) was vague.

The four children fell ill within a period of 36 to 48 hours. The clinical picture presented as the disease ran its course was very similar in all four cases. After an insidious onset extending over a period of some thirty-six hours, characterised by catarrh, lethargy and heaviness of expression, the children became distinctly drowsy but at the same time resisted examination with an almost maniacal frenzy. Nothing abnormal was found on examination of the nervous system five hours prior to death in the first fatal case (I.S.), but in each of the remaining cases Babinski's sign was obtained and the superficial abdominal reflexes were absent. Ready exhaustion, a fear of having the head touched and a pronounced *tâche* were other constant features. The two surviving patients were afebrile throughout, and in the two fatal cases the temperature only rose during the terminal phase, and in one instance (C.B.) this was preceded by an increase in the respiratory rate. In both fatal cases cerebral cries were noted. Vomiting occurred in two patients. Ophthalmoplegia was seen in only one (C.B.), and then only an hour before death. Kernig's sign and neck rigidity, when they occurred, were rather indefinite and showed a tendency to vary from hour to hour. There were no convulsions and no myoclonic movements. The condition of the two children who died became critical with great suddenness; in those who recovered, the improvement following lumbar puncture was dramatic. The three blood examinations carried out all showed a slight relative polymorphonuclear leucocytosis. The cerebro-spinal fluids taken during the stage of active disease all showed a slight increase in the sugar content and a reduction in the chlorides, unaccompanied by any appreciable increase in cell content. Protein in one surviving case was very slightly increased.

Pathological summary.

The outstanding pathological findings in both cases were remarkably similar. Both showed intense congestion of meninges and brain substance, especially the grey matter, oedema of the brain, perivascular haemorrhages, and degenerative changes in nerve cells. Typical cuffing of blood vessels could not be demonstrated, but evidence of the earliest stage of perivascular infiltration was found in the form of collections of a few small mononuclear cells in the adventitial spaces of certain blood vessels. Perivascular demyelination had not occurred.

Caution is necessary in accepting the changes in nerve cells as a genuine effect of disease. Such alterations are admittedly capable of being produced by post-mortem autolysis or by imperfect fixation. The very unequal incidence of the changes in different cells, however, argues in favour of true ante-mortem degeneration. It was remarkable how, in a single small group, certain cells might be profoundly affected and others, close by, present a perfectly healthy appearance. Such a selective effect, while recognized as a common occurrence in true degeneration, is very unlikely in the case of any factor operating after death.

The minute eosinophilic granules observed in the cytoplasm of certain nerve cells in the floor of the fourth ventricle in case 1 were probably merely products of cell degeneration. They do not appear to be of the same nature as the extranuclear granules described by da Fano and others⁶.

The distribution of the lesions is important. This was similar in the two cases. Congestion and oedema were general throughout the brain, but the graver lesions were found only at the lower levels. Perivascular haemorrhages and nerve cell changes were best seen in the thalamus, mid-brain, pons and medulla; they were not found in the cerebral cortex. The early infiltrations were discovered only in the region of the substantia nigra and central grey matter of the mid-brain in one case, and in the thalamus in the other. The spinal cord, in the one case in which it was examined, showed only a degree of congestion.

Attempts to obtain experimental infection in animals by inoculation of cerebro-spinal fluids from cases 1 and 2 were made by Dr. J. M. Alston, who reported as follows:—

CASE 1. Cerebro-spinal fluid was injected intra-cerebrally into two rabbits, two guinea-pigs and six mice. No result was obtained except that one rabbit died seven days after injection. Intra-cerebral injection of two more rabbits from the brain of this animal produced no results.

CASE 2. Intra-cerebral injection of cerebro-spinal fluid into two rabbits, two guinea-pigs and four mice was followed by no result except that one rabbit showed nervous symptoms three days after injection and was killed. Two rabbits injected intra-cerebrally with filtrate of this animal's brain showed no ill effects.

Discussion.

The epidemic nature of the condition is indicated by the almost simultaneous appearance of the initial symptoms, and the occurrence of

all four cases in a single nursing unit. A remarkable feature of the epidemic was the rapidly fatal course of two cases.

Differential diagnosis.—On both clinical and pathological grounds the cases may be regarded as a type of acute encephalitis. Clinically this was suggested by the alternation of marked drowsiness and intense restlessness, amounting at times to frenzy; these occurring in the absence of evidence of meningeal irritation such as nuchal rigidity and Kernig's sign. Ophthalmoplegia occurred in one case; vomiting and cerebral cry were noted in two. Further evidence of organic changes in the central nervous system was afforded by extensor Babinski responses and loss of abdominal reflexes. Changes in other reflexes were variable. The sudden unexpected death in the first case, at a time when other children were showing lethargy and irritability, suggested that the condition might be encephalitis of an epidemic nature. The results of the autopsies on the two fatal cases supported this diagnosis; no significant pathological changes were found anywhere except in the brain, and meningitis was not present.

The absence of a pathological picture completely characteristic of any particular type of encephalitis leaves the question of more exact diagnosis open to discussion, and various possibilities have to be considered.

1. **Food poisoning and alimentary infections.**—The fact that among the fifty-one children in the wards from which the cases were drawn no others were similarly affected although all received food from the same source, virtually rules out the possibility of botulism or other form of food poisoning. In all four cases examination of the stools for pathogenic organisms proved negative.

2. **Heat and sunstroke.**—The epidemic occurred at a time of exceptionally hot weather when all the children in the wards spent the greater part of each day out of doors. They were provided with sun-bonnets and kept in the shade. Neither clinical nor pathological facts support a diagnosis of heat or sunstroke.

3. **Acute toxic encephalitis** has been described occurring as an accompaniment of severe infections^{10, 15}. The possibility of there being any hidden focus of infection in our cases was ruled out by the afebrile course, the results of blood examination, and the failure to discover any source of toxæmia either clinically, or at autopsy on the two fatal cases. Further, the histological changes did not correspond to those described in acute toxic encephalitis by various observers.

Brain, Hunter and Turnbull² described six cases of acute meningo-encephalo-myelitis which they attributed to 'some unknown toxæmia,' without evidence of infection. Clinically, these cases resembled ours in certain particulars, but differed notably in the constancy of evidence

of meningeal involvement and in the presence of fever in five of the six cases. On pathological examination the one fatal case showed congestion, oedema, perivascular haemorrhages and nerve cell changes similar to those found in our cases, though more widely distributed; it differed in the complete absence of any evidence of perivascular infiltration. A further point of difference was the presence of very advanced degenerative changes in the liver and kidneys. The one abortive case in this series (case 3) bears a close resemblance to our two recovered cases, particularly in the rapid improvement following lumbar puncture. This case differed from the others in several important particulars, and it seems to us by no means certain that it was of the same nature.

4. **Varicella encephalitis.**—Two of the children had had an attack of varicella earlier in the year, and had been readmitted from the City Fever Hospital as non-infective, the one ten weeks and the other five weeks before the onset of the illness. The usual interval between the onset of varicella and the appearance of complications involving the nervous system is about nine or ten days²⁹; Winnicott and Gibbs³², reviewing the literature, state that the extremes are four to thirteen days. It is unlikely, therefore, that varicella had any connection with the condition in these two children, and this is further borne out by the fact that, according to Winnicott and Gibbs, no fatal cases of varicella encephalitis have been reported.

5. **Vaccinia.**—None of the four patients, none of the other children in the wards, and none of their attendants had been vaccinated during the year.

6. **Acute disseminated encephalo-myelitis.**—Boyd¹ describes under this title a form of encephalitis quite distinct from the lethargic encephalitis of von Economo. He includes in this category post-vaccinal and post-infectious encephalitis and also a spontaneous type, which forms much the largest group. The clinical picture of this condition, as described by Boyd, shows little resemblance to that observed in our cases. According to him, the essential histological lesion is the presence of areas of perivascular demyelination scattered widely throughout the brain and spinal cord. Nothing at all resembling this was found in our cases.

7. Other epidemic forms of encephalitis.—

A. 'TYPE B-ENCEPHALITIS' AND 'X-DISEASE.'—Type B-encephalitis has occurred in epidemic form in Japan on many occasions during the last sixty years³³. X-disease was met with in Australia in 1918 and 1918^{33, 4, 29}. Pathologically these conditions show many features in common with the encephalitis lethargica of von Economo, but at the present time authorities are still inclined to regard them as separate diseases³³. Clinically they closely resemble each other. They appear to be virus infections of the central nervous system tending to occur during

exceptionally hot weather, but otherwise the clinical picture they present does not resemble that of our cases.

B. THE EPIDEMIC IN ST. LOUIS, U.S.A. (1933).—This has been regarded as a type of encephalitis distinct from the lethargic form¹. The distinction is based upon both clinical and pathological grounds. Paresis when it occurred was only transient, ocular palsies were notably absent, and, so far as can as yet be ascertained, there were no sequelae. The pathological lesions occurred at higher levels, without special localisation in the mid-brain or basal ganglia¹⁴, and cellular infiltrations occurred with no relation to vessels¹⁶. Although our cases resembled this type in the initial catarrhal phenomena and in certain features during the later stages, they differed markedly in the absence of fever, the occurrence of ophthalmoplegia and the distinct localisation of the graver pathological changes, including early infiltration, in the bulbar region and basal ganglia.

C. ACUTE SEROUS ENCEPHALITIS.—Under this name Brown and Symmers³ described ten cases which resembled ours in both clinical and pathological features. Their cases all occurred in children during the summer, ran a rapidly fatal course, and showed catarrhal phenomena and signs of general nervous involvement. They differed from our cases in their febrile nature, in the occurrence of convulsions and in the presence of other localising signs. The pathological data set forth in their paper are scanty, but the changes described, including engorgement of blood vessels of the brain, oedema, perivascular haemorrhages and focal collections of cells, resemble those found in our cases. There is no reference to the exact distribution of these lesions. It is doubtful whether the cases described by Brown and Symmers represent, as they claim, a separate entity.

D. POLIO-ENCEPHALITIS.—In the literature there is general agreement that differentiation between the encephalitic form of polio-myelitis and epidemic encephalitis is uncertain. It has even been suggested that cases hitherto regarded as of the former type should rather be classed as epidemic encephalitis¹³. This view is supported by the fact that the virus of polio-myelitis has not been isolated from a case in which the clinical diagnosis of polio-encephalitis has been made¹³.

The fact that polio-myelitis was not prevalent in epidemic form in the district at the time is in itself an argument against regarding our cases as examples of that disease. The absence of fever, the nature of the changes in the reflexes and the predominance of females among the patients are all facts contrary to those usually associated with polio-myelitis. Another important argument is the bizarre character^{34, 12} of the clinical picture and the lack of evidence pointing to cord lesions.

Pathologically there appears to be no criterion by which certain distinction can be made in all cases between epidemic encephalitis and the bulbar form of polio-myelitis. In the Report of the International Committee for the Study of Infantile Paralysis¹³ the statement is made

that 'the histological lesions (in poliomyelitis) cannot be differentiated with certainty from those of epidemic encephalitis.' More recently Freeman⁸ also has emphasised the similarity of the lesions in the two conditions. Points against the diagnosis of polio-encephalitis in our cases are the relatively slight damage to the nerve cells, and the absence of lesions in the spinal cord in the one case in which it was examined, and the completely inconclusive results of the attempts to transmit the infection to animals. McIntosh¹⁷ considers that these three points are sufficient to distinguish encephalitis lethargica from cerebral polio-myelitis. Kinnear Wilson³¹ emphasizes the prominence of haemorrhage in encephalitis as a distinguishing feature in differential diagnosis.

E. EPIDEMIC LETHARGIC ENCEPHALITIS.—As our cases resembled this condition in many features it is necessary to consider these in detail.

a. Epidemic form. It is recognized that it may occur in the form of limited outbreaks in institutions. McNalty and Hall^{20, 11} have collected a number of reports of such outbreaks in this country, and Duzar and Balo⁵ recorded an institutional epidemic in Budapest.

b. Season. Although epidemic encephalitis has its maximum incidence in the colder months, outbreaks have occurred during hot weather²⁰. Hall¹¹ draws attention to the fact that most of the few outbreaks of encephalitis lethargica of a definitely contagious character have occurred at periods of the year when the disease was not present in epidemic form.

c. Age. Although encephalitis lethargica is generally regarded as a disease which affects adults more often than children, its occurrence in newborn infants, of which several well authenticated cases have been reported²², proves that even the youngest are not immune. Furthermore McNalty²⁰ reported a fatal case occurring in a child aged one year nine months; Netter²⁵ described a case occurring in an infant of two months; and the eleven cases in the Budapest epidemic were all in infants a few months old.⁵

d. Predisposition. Syllaba and Henner³⁰ emphasize the importance of predisposition towards infection. Such predisposition was met with in children of unhealthy parentage and they particularly mention that many patients were children of syphilitic parents. Our four children were all poor-law patients; one was a congenital syphilitic and two gave positive reactions to the tuberculin skin test.

e. Result. Our two fatal cases correspond exactly in the matter of age and duration with the case described by McNalty²⁰ in a female child aged one year and nine months who died after two days' illness. The same authority²⁰ has recorded improvement following lumbar puncture similar to that which occurred in our two recovered cases.

f. Clinical features. Certain features of the clinical picture already described have been stressed by other observers. Among these are the following :—

Duration of the prodromal period. McNalty¹⁹ states that the prodromal period is commonly one to seven days and that, particularly in children, it tends to be brief. In our case signs of active disease were present within 24 to 36 hours of the appearance of initial signs of illness.

Early catarrhal phenomena. These occurring in relation to the throat, conjunctivae and intestine have been particularly emphasized by McNalty¹⁹, Riley²⁸, Duzar and Baló⁵ and others¹⁸.

Absence of fever. Fever was present only during the terminal stages in the two fatal cases, the other two being afebrile throughout. Kinnear Wilson³¹ and Hall¹¹ remark upon the frequent absence of fever throughout the course of the illness; McNalty¹⁹ considers that afebrile cases do not exist but believes that a rise in temperature may be a late event. Syllaba and Henner³⁰ in a review of a thousand cases encountered a number which ran afebrile courses and concluded that the elevation of temperature paralleled the patient's general condition.

General symptoms and signs. The symptoms in our cases were admittedly vague and the findings noticeably variable. The protean character of epidemic encephalitis is frequently mentioned in the literature^{34, 28, 12} and has been emphasized as an observation of especial value in differential diagnosis¹³. Among the few constant findings in our cases was the absence of abdominal reflexes. Raimist²⁷ and Price²⁶ consider this phenomenon to be of diagnostic importance and emphasize that these reflexes return with recovery. The indefinite way in which the prodromal period merged into the stage of active disease corresponds with what McNalty¹⁹ has described as a typical history of encephalitis lethargica. The alternation of irritability and lethargy, so prominent in our cases, is emphasized by Kinnear Wilson³¹ and others. Ophthalmoplegia, which occurred in one of the cases, is a frequent and important finding in lethargic encephalitis.

g. The blood and cerebro-spinal fluid. In two of three of our cases in which an examination of the blood was carried out there was a slight leucocytosis; in all three there was a small relative increase in the number of polymorphonuclear cells. These findings are in agreement with those of Holt¹² and Riley²⁸ in connection with encephalitis lethargica.

According to McNalty¹⁹ and Wilson³¹ the cerebrospinal fluid shows no characteristic changes in encephalitis lethargica. Boyd¹ is in agreement with these authorities but states that the fluid may show a moderate lymphocytosis. Holt¹² maintains that the fluid may be normal during the acute stage but commonly shows an excess of mononuclear cells at a later period. Syllaba and Henner³⁰ and Riley²⁸ consider that sugar is often present in excess. The changes present in the fluids obtained from our patients (see table) were in keeping with those recognized by these observers as occurring in epidemic encephalitis lethargica.

h. Pathological features. In certain respects the pathological changes resemble those of encephalitis lethargica:—

The distribution of the lesions. There is general agreement among observers that while congestion and oedema may be universal throughout the brain in encephalitis lethargica, the perivascular lesions and nerve cell changes have a characteristic distribution. The parts most affected are the region of the substantia nigra and central grey matter of the mid-brain, the pons and medulla oblongata, and the basal ganglia, especially the optic thalamus; the cerebral cortex is spared and the spinal cord little involved. This distribution is claimed by McIntosh¹⁷ as one of the most striking features of the lesions. The same fact is emphasized by Zinsser³⁴ and Freeman⁸. This characteristic distribution of the graver pathological changes was found in both our fatal cases.

The nature of the pathological changes. i. The perivascular infiltrations. The paucity of perivascular infiltrations is perhaps the chief objection to a diagnosis of epidemic lethargic encephalitis. These infiltrations are generally recognized as the most characteristic of the lesions. There is, however, to be found in the literature considerable support for the contention that the infiltrations are relatively slow in developing and consequently absent in the early stage of the disease. McIntosh¹⁷ is of this opinion on account of the histological appearance of the lesions and states that 'several acute cases where death has occurred within a week after the onset of the disease have shown only slight lesions in the brain.' Gay⁹ suggests that 'perivascular infiltration (cuffing) of mononuclear cells probably does not occur in the earliest stages.' Michels and Globus²³ observe that 'in cases of epidemic encephalitis that have run a stormy course with a sudden termination, the predominant histologic picture is that of numerous haemorrhages with an unusual sparsity of typical small round cell infiltrations.' McNalty²¹, referring to rapidly fatal cases, draws attention to the almost completely negative histological findings and the absence of perivascular infiltrations, which he attributes to the fatal issue having occurred before characteristic lesions had time to declare themselves. Duzar and Balo⁵, basing their opinion on post-mortem findings in the Budapest epidemic, express the view that characteristic infiltrations are found only in cases of relatively long duration. Kinnear Wilson³¹ describes perivascular infiltration consisting of only a few cells—'less than one complete layer round'—a description which aptly applies to the venule illustrated from case 1 of our series (fig. 2). In our cases the duration of the illness was very short, and perivascular infiltration was at an early stage of development.

ii. Haemorrhage. Reference has already been made (p. 165) to the importance of haemorrhages as a feature distinguishing encephalitis lethargica from poliomyelitis. Zinsser³⁴ describes them as perhaps the most striking element and states that some pathologists suspect haemorrhages to be the primary lesion.

iii. Changes in the nerve cells. The degenerative changes in the nerve cells found in our cases correspond closely to those described by McIntosh¹⁷ and others. The focal distribution of these changes which was so conspicuous is a characteristic already emphasized by Freeman⁸.

Experiments on animals. The results of Dr. Alston's attempts to transmit infection to animals of various species were negative. This is similar to the experience of the majority of those who have attempted experimental transmission of the virus of epidemic encephalitis. McIntosh and Turnbull¹⁷ succeeded in infecting a monkey with material from one of McNalty's cases, and Levaditi¹⁷ claimed success with rabbits, but his results were criticized on account of the likelihood of contamination of the inoculated material with herpes virus. Zinsser³⁴ even goes so far as to suggest that the successful transmission of infection in McNalty's case throws doubt upon the diagnosis.

Diagnosis.—From the clinical point of view these cases almost certainly represented an outbreak of acute encephalitis of epidemic nature. In such an isolated epidemic it was not possible to classify the cases as of any one particular form. Even pathologically, although the condition was clearly acute encephalitis, the findings were not absolutely conclusive as to type. Both clinically and pathologically these cases had many points of resemblance to several of the recorded types of acute encephalitis occurring as epidemics. These types have so much in common with each other that it is possible that they do not in reality represent separate entities, but are rather different manifestations of a single disease process. In the present state of knowledge, our findings would appear to indicate that our cases most closely resembled the lethargic type of epidemic encephalitis (von Economo) in an early stage.

Source of infection.—The almost simultaneous occurrence of the four cases seems to indicate a common source of infection rather than case to case transmission. No member of the staff in attendance on the four children reported sick at any time during the month of July. There were no other recognized cases of epidemic encephalitis in the wards. Apart from the possible presence of an unrecognized carrier there is little likelihood that infection was derived from any member of the staff or patient in the wards.

A possible source of infection existed in adult patients with post-encephalitic Parkinsonism with whom the children had associated. The possibility of infection arising from contact with cases of chronic encephalitis has been considered by several authorities. Both Netter²⁴ and Freeman⁷ favour the view that the later manifestations of the disease are due to the continued presence of the infective agent. Hall¹¹ considers that the occurrence of recrudescence at long and varying intervals provides clinical evidence of persistent infection. There is general agreement that the disease may be contagious in the initial acute stage. Netter and Freeman are definitely of this opinion. According to Hall, although proof is rare 'contagion may occur to a marked degree.' If it be recognized that the infective agent persists during the later chronic stage, the possibility of the disease being still contagious must be admitted. Netter recorded several cases in support of this view. These cases have been included in a review of the subject

by Freeman⁷, who collected seven cases of acute encephalitis which had developed in individuals who had been in close association with patients suffering from the disease in its chronic stage. These observers are inclined to relate the contagion in these cases to exacerbations occurring long after the original attack.

The infection in the cases of our two adult patients with chronic encephalitis dated from acute attacks nine and eleven years before. There was no history of any exacerbation in either case, but it may be mentioned that one of the patients had suffered from an attack of unexplained vomiting shortly before the outbreak among the children. The intimate contact occurring between these patients and the affected children has already been emphasized. On the assumption that the cases of chronic encephalitis lethargica were still infective, the risk of the children contracting infection could hardly have been greater.

If these chronic cases were the source of infection it can be definitely stated that the incubation period in the children was not more than two weeks, as there was no contact between the parties prior to July 7, 1933. McNalty²⁰, basing his estimate on records at the Ministry of Health, considers that the incubation period of encephalitis lethargica varies from two days to over two weeks.

It is not possible to dogmatize regarding the probable route of infection, but the presence of faucial and pharyngeal catarrh in every case suggests that the virus gained entry through the mucous membrane of those regions. There is considerable evidence favouring the view that the salivary secretion of patients suffering from chronic encephalitis is infective.¹¹ The condition of our adult patients was characterized by excessive salivation. As already mentioned, these women frequently fondled the children and actually kissed them. Under these circumstances it seems probable that infection entered by the fauces.

Summary.

The subject of the paper is a small outbreak of acute encephalitis in a hospital, affecting four young children, with two deaths. Clinical details are given, together with the results of examination of the blood and cerebro-spinal fluid. Autopsies were performed on the two fatal cases and full histological examination was carried out. Attempts were made to transmit the infection to animals. Various possibilities in connection with diagnosis are considered. The findings appear to indicate that the cases most closely resembled the lethargic type of epidemic encephalitis. The children had been in close contact with cases of post-encephalitic Parkinsonism. The possibility of infection from this source is discussed.

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