Acute necrotizing encephalitis: a problem in diagnosis

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Acute necrotizing encephalitis is the name given to a type of encephalitis where, in addition to widespread inflammatory changes in the central nervous system, there is severe and extensive neuronal necrosis (Van Bogaert, Radermecker, and Devos, 1955). The latter tends to be most severe in the temporal lobes and one hemisphere is usually more severely affected than the other. The disease appears to be caused by the herpes simplex virus.

Only in the past few years, however, has it been appreciated that cases may present with the clinical and radiological features of an acutely expanding lesion in one temporal lobe (Bennett, ZuRhein, and Roberts, 1962; MacCallum, Potter, and Edwards, 1964; Pierce, Portnoy, Leeds, Morrison, and Wehrle, 1964; Carmon, Behar, and Beller, 1965). In such circumstances these seriously ill patients present considerable diagnostic difficulties and it seems likely that many cases go unrecognized. The present series of seven cases suggests that a diagnosis can sometimes be made in life on the basis of a knowledge of the fairly characteristic clinical picture, the histological appearances of a brain biopsy, or on virological studies. The findings in the brain at necropsy are discussed in relation to this diagnostic problem.

MATERIALS AND METHODS

Seven cases (Table I) of acute necrotizing encephalitis were encountered in the Neurosurgical Unit in the five years 1961-1966; the patients had been admitted to a surgical unit because an expanding intracranial lesion was suspected. Five died within two weeks of admission and in all of these a detailed neuropathological study was undertaken. One patient died in another hospital seven weeks after onset and a limited study was made on sections of the brain subsequently made available.

After the necropsies performed in this hospital, the brain was suspended in 10% formol saline for three weeks before dissection. The fixed brain was first examined for any evidence of raised intracranial pressure. The mid-brain was then transected and the cerebral hemispheres cut in the coronal plane into slices 1 cm. thick. From each brain large blocks of frontal, temporal (at least two levels), parietal, and occipital lobes, and of cerebellum, brain-stem, and spinal cord (where available)

were embedded in nitrocellulose. Sections were stained by Nissl's method using cresyl violet, Woelcke's modification of Heidenhain's method for myelin, phosphotungstic acid haematoxylin (Lieb's), and haemalum and eosin. Smaller representative blocks were embedded in paraffin wax and stained by haemalum and eosin, haemalum and van Gieson's fluid, phosphotungstic acid haematoxylin, and Lendrum's phloxine-tartrazine method for inclusion bodies.

CASE REPORTS

CASE 1 This man of 45 (N.17749, 62/62) developed headache and slight fever, and next day became confused. On the third day of the illness he was admitted to a fever hospital as a case of suspected tuberculous meningitis; he had twitching of the facial muscles and was completely disorientated but there were no signs of meningeal irritation. Cerebrospinal fluid obtained by lumbar puncture contained 64 mg. protein and 84 mg. sugar per 100 ml., and 114 cells per c.mm. Next day (day 4) he was pyrexial and had some basal consolidation in both lungs; for four hours he had profuse salivation. Later that day he developed left-sided limb weakness.

On transfer to the Neurosurgical Unit (day 6) his temperature was 105°F. and neck stiffness was marked; the right limbs now seemed the weaker and consequently left carotid angiography was performed. This was normal. On the same day air ventriculography showed mild ventricular dilatation and a slight shift of the inter-ventricular septum to the right; the ventricular cerebrospinal fluid pressure was greatly raised before ventriculography. On the eighth day he developed a series of major epileptic seizures and died a few hours later without any definite diagnosis being reached.

Necropsy Apart from bronchopneumonia, there were no significant abnormalities outside the nervous system. The principal neuropathological findings are given in the tables and are discussed in greater detail later.

CASE 2 This man of 22 (N.17810, 69/62) was admitted to a fever hospital with a two-day history of pyrexia, headache, and sore throat. His temperature was 103°F. and he was irritable but conscious; his neck was stiff but there were no neurological signs. On the day of admission he had a convulsion and remained confused thereafter. Cerebrospinal fluid obtained by lumbar puncture contained 90 mg. protein and 70 mg. sugar per 100 ml., and 280 cells (mainly lymphocytes) per c.mm. Two days later the protein was 170 mg. and the cell count 165. At this

time the white blood cell count was normal and the E.S.R. 6 mm. in the first hour. Over the next four days his condition fluctuated without his regaining consciousness: he developed pulmonary collapse and a tracheostomy was performed.

On transfer to the Neurosurgical Unit (day 9) he was unconscious, and had some neck stiffness and a definite left hemiparesis. The ventricular cerebrospinal fluid was bloodstained and contained 83 mg. protein per 100 ml. but there was no excess of leucocytes. Air ventriculography revealed a massive shift from right to left, suggestive of a mass in the temporal lobe. The right temporal lobe was then explored with a brain cannula through a burr hole in the expectation of finding an abscess but instead of pus, necrotic brain was aspirated. He died two days later (day 11).

Microscopical examination of the biopsy showed many mononuclear cells in the meninges and around vessels in the cortex and white matter, tissue necrosis with aggregates of lipid phagocytes, and occasional examples of neuronophagia.

In sera taken on the fourth and tenth day of illness the titre of complement-fixing antibodies to herpes simplex virus was 1/16 and 1/512 respectively.

Necropsy There were no significant abnormalities outside the central nervous system.

CASE 3 This highly intelligent and stable woman of 64 (N.19064, 59/63), having been previously well, woke at 3 a.m. one day complaining of headache and began discussing church matters irrelevantly. In the morning she dressed carelessly with her blouse inside out, only one stocking and odd shoes. She improved later in the day, however, but next day complained of tiredness and vomited several times. On the third day she was again confused and was admitted to a mental hospital where her condition fluctuated over several hours between lucidity and incoherent restlessness. The right arm and leg were thought to be spastic, she had retention of urine, and her temperature was 101°F.

On admission to the Neurosurgical Unit (day 4) she was apparently awake but would obey no commands and her speech was incomprehensible; she was considered to be dysphasic but there were no other neurological signs. As her temperature was 104°F. antibiotic therapy was started. On day 7 she was no better: at lumbar puncture the cerebrospinal fluid pressure was 120 mm. H₂O and it contained 66 mg. protein and 88 mg. sugar per 100 ml. and 120 leucocytes per c.mm. To exclude an abscess bilateral carotid angiography was carried out. The left side was examined first because of the suspected dysphasia and this showed a shift of the mid-line vessels to the left. The right carotid angiogram then revealed a large expanding lesion in the right temporal region (Fig. 1). In the belief that this was either an abscess or a tumour, a biopsy was taken from the right temporal lobe through a burr hole on the tenth day. Necrotic material was recovered through the cannula and this was so typical of a malignant glioma to the surgeon's eye that an immediate histological report was not requested. The patient died on the 14th day of her illness and as external examination of the brain showed clear evidence of an expanding

FIG. 1. Case 3. Right carotid angiogram showing temporal lobe mass.

lesion the case was indexed provisionally as a glioblastoma multiforme.

Microscopical examination of the biopsy subsequently showed necrosis, and cuffing of vessels by mononuclear cells, some of which were plasma cells. The appearances were clearly those of an acute encephalitis.

Necropsy There were no significant abnormalities outside the central nervous system.

CASE 4 This girl of 14 (N.20404, K.64086) suffered headaches for 12 days during which she attended school. Vomiting and giddiness, associated with worsening of headache, then developed and she took to bed. She was still bright and reading books but two days later was found unconscious and had a right-sided convulsion. On admission to a general medical ward (day 14) she was in coma with a temperature of 101°F. Neck stiffness developed during the next two days, but examination of the central nervous system was normal. Lumbar cerebrospinal fluid contained 300 lymphocytes per c.mm., and 66 mg. protein and 56 mg. sugar per 100 ml. (day 17); by day 19 the protein level had risen to 132 mg. She was transferred to a fever hospital where she was apyrexial, rousable but disorientated, and still had a stiff neck. Cerebrospinal fluid on day 21 was bloodstained, containing 360 leucocytes per c.mm., and 240 mg. protein and 55 mg. sugar per 100 ml.

On admission to the Neurosurgical Unit on day 22 she was drowsy and irritable, uncooperative, and answering all questions by 'yes'. Her temperature was 102°F. and the neck was stiff; the right limbs seemed spastic at times and the right plantar response was equivocal.

A left carotid angiogram showed an expanding lesion in the temporal lobe: a needle biopsy of this region to exclude abscess yielded only soft brain, which on microscopy (see below) suggested acute viral encephalitis. An E.E.G. on day 32 fluctuated between periods of almost normal activity and runs of theta and delta activity, 2-5 c.p.s., most of the slow activity blocking with visual attention. There were very occasional vertex sharp waves. In each of two sera taken on days 21 and 28, the complement-fixing antibody titre to herpes simplex was 1/2,048.

By day 33 she was improving, alert but dysphasic; on day 47 she was returned to a general medical ward, still very dysphasic. She proved a difficult behavioural problem there and two weeks later was transferred to a mental hospital. The latest report of this child is that she eventually returned to school for the pursuit of relatively non-academic subjects and is now working as a copy typist in an office.

Biopsy from temporal lobe The specimen consisted of small pieces of rather soft cortex. Microscopical examination showed diffuse recent neuronal necrosis and intense reactive changes. There were many hypertrophied microglial cells, lipid phagocytes, and mononuclear cells many of which were clearly of the plasmacytic series. Reactive changes tended to be most severe around small blood vessels many of which were cuffed by mononuclear cells. There were also a few polymorphonuclear leucocytes. Intranuclear inclusion bodies were not seen. The biopsy did not include identifiable meninges or white matter. The appearances were typical of acute necrotizing encephalitis.

CASE 5 This woman of 34 (N.21425, 811/64) developed headache, confusion, and vomiting which failed to improve after two days' treatment at home with chlorpromazine and codeine. On admission to hospital elsewhere she proved to be completely disorientated; she had a minimal right hemiparesis and her temperature

FIG. 2a.

FIG. 2b.

FIG. 2c.

FIG. 2d.

FIG. 2. Case 5. Red blood corpuscles and leucocytes in cerebrospinal fluid; (a) large mononuclear cell with hyperchromatic nucleus; (b) binucleate cell; (c) cell in mitosis; (d) mononuclear cells much larger than small lymphocytes and with a high nuclear/cytoplasmic ratio. Leishman stain a-c $\times 500$, d $\times 1,250$.

was 102°F. Lumbar puncture on two occasions revealed bloodstained cerebrospinal fluid containing more than 100 mg. protein per 100 ml. and 30-50 mononuclear cells per c.mm.: the sugar content was normal. The white blood cell count was also normal and the E.S.R. 15 mm. in the first hour. Tuberculous meningitis was suspected.

On admission to the Neurosurgical Unit (day 5) she was confused and disorientated and her temperature was 103°F.; the right plantar response was extensor but echo-encephalography showed no shift. The E.E.G. was

grossly abnormal, with theta and delta activity and multiple sharp wave foci in all areas. It was decided to examine the leucocytes in the cerebrospinal fluid in greater detail, with the primary intention of excluding tumour cells. The protein level in the fluid at this time was 364 mg. per 100 ml. and the leucocyte count was 34 per c.mm.

Examination of films made from the centrifuged deposit and stained by Leishman's method showed that all of the cells were mononuclear and that several were highly atypical in appearance. These were large, contained hyperchromatic nuclei and had a high nuclear-cytoplasmic ratio (Fig. 2). Occasional mitotic figures were present. The cells appeared to belong to the plasmacyte series and in view of their rather primitive appearance their presence was interpreted as evidence of an unusually severe inflammatory process, probably an acute encephalitis.

Although she subsequently developed a lateral shift on echo-encephalography it was decided on the basis of the cytology of the cerebrospinal fluid not to carry out contrast radiological studies, nor to advise surgical exploration. She died six days later (day 10).

Necropsy There were no significant abnormalities outside the central nervous system.

CASE 6 This woman of 47 (N.21506, K. 64349) was an intelligent working widow who developed a flu-like illness associated with vomiting and diarrhoea. Four days later, having recovered completely from this, she began behaving strangely: she took her son his morning tea in the small hours of the morning. She was rational, however, when the general practitioner came in the morning but by the time she was admitted on the following day to hospital she was reported to be in a state of mumbling incoherence. Her temperature was 102°F. and suspected dysphasia was the only neurological sign then evident. She had a previous history of chronic suppurative otitis media on the left side. Lumbar cerebrospinal fluid contained 272 mg. protein per 100 ml. and 60 lymphocytes per c.mm. Four days later right hemiparesis and homonymous hemianopia were evident and she was transferred to the Neurosurgical Unit as a suspected case of temporal lobe abscess of otitic origin. An emergency left temporal burr hole was performed on admission but needling of the temporal lobe yielded necrotic brain, not pus. Ventriculography next day, however, showed a large temporal lobe mass and the brain was again needled in a search for pus. Again necrotic brain was aspirated, and a pre-suppurative encephalitis was suspected. Examination of the biopsy showed focal neuronal necrosis, slight cuffing of vessels by plasma cells and polymorphs, and an early reactive gliosis. The features were clearly those of an inflammatory process but there was no indication as to its cause. We were by now presuming the diagnosis of acute necrotizing encephalitis, but when, 10 days later, she had further deteriorated with marked hemiplegia, and a gross lateral shift on both angiography and echo-encephalography, we decided to perform a craniotomy to exclude abscess beyond doubt (day 18). The temporal lobe was swollen and on introducing a needle about 20 ml. of almost fluid brain was aspirated, completely collapsing the brain. Examination

of this biopsy showed more severe abnormalities than the earlier one. There was actual necrosis of white matter and the abnormal areas contained numerous lipid phagocytes. There was also more evidence of neuronal necrosis and intense perivascular cuffing by mononuclear cells with plasma cells very numerous. Inclusion bodies were not seen but the appearances were otherwise characteristic of acute necrotizing encephalitis.

She improved after this decompressive procedure, and became well enough to return to her local hospital. She remained hemiplegic, however, and died some two months after the onset of her illness. Virus was not isolated from the second biopsy.

CASE 7 This girl of 17 (N.23659, 56/66) had been vaguely unwell for a week but two days before admission to the Neurosurgical Unit she developed headache and vomiting and became mentally confused. She was restless with marked neck stiffness; the only abnormal neurological sign was an extensor plantar response on the right side. Her temperature was 101°F. on admission and two days later it was 105°F.: it remained above 103°F. until her death. Lumbar cerebrospinal fluid taken at another hospital contained 240 mg. protein and 105 mg. sugar per 100 ml., and 3 lymphocytes per c.mm.: the pressure was 230 mm. H₂O.

Ventriculography showed no abnormality but a brain biopsy of the right temporal lobe taken at this time was reported as showing inflammatory changes of the type often seen near an abscess: herpes simplex virus was subsequently grown from this specimen on human amniotic and on embryonic lung culture. The titre of complement-fixing antibody to herpes simplex on that day was less than 1/8 and she did not survive long enough for a second specimen. An E.E.G. two days later was grossly abnormal with constant irregular slow activity in all areas. In addition there were frequent recurrent vertex sharp waves and although these were stereotyped and repetitive, they were irregular. The patient was deeply unconscious when the recording was made and had been given promazine some hours previously because of restlessness. A left carotid angiogram performed next day was normal.

She died six days after the onset of headache and confusion, 13 days after the first sign of illness.

Necropsy The body was that of an extremely obese girl. Apart from marked adiposity of the myocardium there were no significant abnormalities outside the central nervous system.

DISCUSSION

CLINICAL SYNDROME The patients (Table I) showed a wide range of ages (14-64 years) as in other reports; five were women and two men. All presented with headache, mental confusion, and high pyrexia which had developed rapidly over a few days. Five had hemiplegia of some degree, four had neck stiffness, and three had one or more episodes of epilepsy.

INVESTIGATIONS The cerebrospinal fluid was abnormal in every patient. All showed a raised protein

TABLE I
SUMMARY OF CASES

Case No.	Age	Sex	Time from Onset of Illness until Death	Clinical Features				Cerebrospinal Fluid				Radiological Examination	Suspected Initial Diagnosis	Method of Diagnosis
				Headache	Hemi-paresis	Epilepsy	Stiff Neck	Blood-stained	Protein (mg./100ml.)	Sugar	Leucocytes (c.mm.)			
1	45	M	8 days	+	+	+	+	—	64	84	114	Angiogram (left carotid) normal Ventriculogram, slight shift of interventricular septum to right	Tuberculous meningitis	Necropsy
2	22	M	11 days	+	+	+	+	+	90-170	70	165-280	Ventriculogram, gross shift from right to left suggestive of temporal lobe mass	Abscess	Biopsy and necropsy (serology positive)
3	64	F	14 days	+	+	—	—	—	66	88	120	Angiogram (bilateral carotid), large expanding lesion in right temporal region and gross lateral shift	Glioma	Biopsy and necropsy
4	14	F	Alive 2 yr. later	+	+	+	+	+	66-240	55	300-360	Angiogram (left carotid), expanding lesion in temporal lobe and gross lateral shift	Abscess	Biopsy and positive serology
5	34	F	10 days	+	—	—	—	+	100-364	Normal	30-50	Nil	Tuberculous meningitis	C.S.F. cytology and necropsy
6	47	F	8 wk.	+	+	—	—	—	272		60	Ventriculogram, large left temporal lobe mass Angiogram (left carotid), gross lateral shift and temporal lobe mass	Abscess	Biopsy
7	17	F	13 days	+	—	—	+	—	240	105	3	Ventriculogram and angiogram (left carotid), both normal	Encephalitis	Virus culture and necropsy (biopsy equivocal)

level (64-364 mg. per 100 ml.) and all but one a pleocytosis (30-360 per c.mm.). The white cells were usually reported as lymphocytes or large mononuclears on routine inspection but in one case (case 5) a more detailed cytological study was undertaken. The presence of atypical and primitive cells of inflammatory type (Fig. 2) formed the basis of the diagnosis of acute encephalitis in this case. The cerebrospinal fluid sugar was normal in the six cases in which it was estimated. In three instances the cerebrospinal fluid was bloodstained.

E.E.G. Electroencephalography was carried out in three cases during the acute stage of the illness and we are grateful to Dr. I. D. Melville for the following comments.

Diffuse slow wave activity was seen when the encephalitis had produced coma, but various focal changes were observed against the background of generalized slowing. In two cases these were vertex sharp waves: case 7, who was deeply unconscious, showed frequent repetitive stereotyped but irregular sharp waves at the vertex; case 4, who was conscious but grossly dysphasic, showed similar but infrequent waves. Case 5 showed local sharp waves over areas of the brain subsequently shown to be involved in the

acute inflammatory process. None of these patients showed myoclonic jerking.

The E.E.G. in this form of encephalitis is therefore of limited diagnostic value. No pathognomonic changes have been reported to compare with the stereotyped repetitive complexes of subacute inclusion body encephalitis (see addendum). Multiple focal abnormalities indicate superficial active brain lesions while gross general slowing usually reflects only the state of coma. A normal or near normal record, on the other hand, virtually excludes the diagnosis of acute encephalitis.

Contrast radiological studies Studies were undertaken in six cases to exclude a space-occupying lesion; in the seventh case (case 5) encephalitis was so strongly suspected that further investigation was deemed unnecessary. Both ventriculography and angiography were carried out in three cases, angiography alone in two, and only ventriculography in one. In four patients a gross lateral shift of the anterior cerebral artery suggested a space-occupying lesion, another showed slight shift, and only one had normal angiography and ventriculography.

Biopsy Brain biopsy was carried out through a temporal burr hole in five patients and in four the

correct diagnosis was reached on the basis of histological examination. In one patient (case 7) the biopsy was equivocal, suggesting a nearby inflammatory lesion; this was the only brain specimen from which virus was isolated in culture, and the only brain in which inclusion bodies were seen after death (three days after the equivocal biopsy).

Virus studies We are indebted to Dr. Constance A. C. Ross, Regional Virus Laboratory, Ruchill Hospital, Glasgow for the following comments on the virus studies undertaken on these patients.

Specimens for virus isolation were taken from cases 2, 5, 6, and 7. The specimens taken during life were faeces from cases 2 and 5, cerebrospinal fluid from cases 2 and 7, and brain biopsy from cases 6 and 7. Necropsy specimens comprised brain and spinal cord from cases 2 and 5. Specimens were examined in tissue cultures and baby mice by the methods described by Grist, Ross, Bell, and Stott (1966).

The only virus isolated was from the brain biopsy of case 7: cytopathic changes characteristic of herpes simplex appeared in human embryonic lung tissue cultures after three days' incubation: this was confirmed as herpes simplex by neutralization tests with specific antiserum.

For serological studies, paired sera were obtained from cases 2 and 4. Acute phase sera only were obtained from cases 3, 5, and 7 as these patients died before a 'convalescent' specimen could be taken. The sera were tested for complement-fixing antibodies to herpes simplex by the method described by Ross, Russell, and Wildy (1964).

The two patients from whom paired sera were obtained both showed serological evidence of active infection with herpes virus: in case 2 there was a rapid rise in antibody titre from 1/16 on the fourth day of illness to 1/152 on the tenth day; in case 4 high, but not rising, antibody titres (1/2,048 and 1/2,048) were obtained on the 21st and 28th days of illness. The three single 'acute' sera from cases 3 (day 8), 5 (day 5), and 7 (day 9) gave titres of 1/16, 1/32, and less than 1/8 respectively. Failure to detect antibody in the case where virus was isolated from the brain biopsy (case 7) suggests that this patient was suffering from a primary herpes simplex infection.

Virological evidence of active infection with herpes simplex virus has therefore been obtained in only three of the present cases, one by virus isolation and two by serology. That only a proportion of cases with acute necrotizing encephalitis yield positive virological evidence of infection with herpes simplex has been reported by other workers (Bennett *et al.*, 1962; Drachman and Adams, 1962; Carmon *et al.*, 1965; Ryden, Moses, Ganote, and Beaver, 1965;

Miller, Hesser, and Tompkins, 1996). There are several possible reasons for failure to demonstrate herpes simplex infection. Virus may not be isolated because herpes simplex is relatively labile and delay in transport of the specimen to the laboratory may kill the virus; collection of the material in transport medium (Grist *et al.*, 1966) may minimize this hazard. Again the minute portion of brain biopsy material may have been collected from an uninfected portion of brain or too late in the illness when virus is no longer viable or antibody present in the material may gain access to virus during the extraction process and prevent its subsequent growth. Similar factors may account for failure to isolate virus from brain tissue obtained after death.

Virus studies can undoubtedly be of considerable value in establishing the diagnosis of acute necrotizing encephalitis (MacCallum *et al.*, 1964) but the practical assistance that the virologist can provide for the clinician tends to be limited by time factors. Growth of herpes simplex virus may be obtained in 24 hours but may take five days, while the main cause of failure of serological tests is death of the patient before a 'convalescent' serum can be collected.

MORTALITY AND TREATMENT Five of the seven patients were dead within 14 days of onset. One lived (but severely disabled) for two months after surgical decompression and was the only patient so treated. Another is alive and, after a long convalescence, is apparently leading a normal life two years later. We know of another local survivor who remains demented and is not included in this series because no question of space-occupying lesion ever arose. All 16 patients referred to by Bennett *et al.* (1962), who presented as cases of space-occupying lesions, were dead within 18 days. However, these authors reported one survivor among their own three cases; he lived four years after surgical decompression though he remained severely disabled. Later Pierce *et al.* (1964) added two survivors both of whom had been operated on: one was disabled but the other had returned to work. Carmon *et al.* (1965) have recently reported three survivors, one without deficit, following 'medical' decompression with urea combined with the administration of steroids. There can be no doubt from the clinical, radiological, and pathological evidence that raised intracranial pressure with brain shift may contribute significantly to the fatal outcome, and it seems that there may be some improved prospect for recovery if the acute inflammatory response can be controlled with steroids while the intracranial hypertension is relieved by surgery or hypertonic solutions.

DIAGNOSIS The diagnosis is most likely to be reached in the patient's life time if histological

examination of a brain biopsy was unequivocal. Virus studies are useful but, because of the rapid tempo of this illness, may allow only of a retrospective diagnosis after the patient's death. The cerebrospinal fluid findings are variable but a lymphocytic reaction with normal sugar is suggestive and blood staining (Miller *et al.*, 1966) adds to the suspicion: the presence of primitive plasmacytic cells may strengthen the diagnosis. Radiological investigations are rather unhelpful in that they tend to show evidence of a space-occupying lesion and so add to the diagnostic difficulties; that the mass is temporal, however, lends weight to suspicions about a diagnosis of this variety of encephalitis.

In this series three patients were diagnosed initially as cases of cerebral abscess, two as of tuberculous meningitis, and one as of malignant glioma. However, it is encouraging that whereas in the first three cases the diagnosis was made only after death, in the last four cases a diagnosis was reached in life. This was based on the characteristic clinical picture in all four and supported by brain biopsy in one (case 6), by brain biopsy and a rising antibody titre in one case (case 4), by virus culture in one (case 7), and in the remaining case (case 5) by the presence of primitive cells of the plasmacyte series in the cerebrospinal fluid (not diagnostic but in the context highly suggestive).

NEUROPATHOLOGY In all of the five cases available for detailed neuropathological study the findings were typical of acute necrotizing encephalitis (Tables II, III, and IV).

Although the name 'acute necrotizing encephalitis' was not introduced until 1955 (van Bogaert *et al.*, 1955), the characteristic severe involvement of the temporal lobes makes the identification of cases published before 1955 possible, even when details of the histopathology are not available. The relevant literature has been fully documented by Haymaker, Smith, Van Bogaert, and de Chenar (1958) and by

TABLE II
PRINCIPAL MACROSCOPIC ABNORMALITIES IN THE FIVE
BRAINS AVAILABLE FOR NEUROPATHOLOGICAL EXAMINATION

Case No.	Brain Weight (g.)	Macroscopic Abnormality
1	1,500	Anterior third of left temporal lobe and right temporal pole soft. On section, loss of definition between cortex and white matter in these regions and in the posterior orbital gyri (L > R) and insulae. Small haemorrhagic foci in anterior end of left hippocampal gyrus.
2	1,510	Entire right temporal lobe and left temporal pole soft and swollen. On section many small focal haemorrhages in cortex and white matter in the right temporal lobe, insula and posterior orbital gyri. No haemorrhagic foci in left cerebral hemisphere.
3	1,340	Anterior two-thirds of right temporal lobe soft and swollen. On section, many small haemorrhagic foci in cortex and white matter in this region and in the right posterior orbital gyri. Foci extend across genu of corpus callosum into infero-medial part of left frontal lobe.
	1,350	Anterior two-thirds of right temporal lobe and anterior third of left hippocampal gyrus soft and swollen. On section many small haemorrhagic foci in cortex above and below anterior ends of Sylvian fissures.
7	1,470	Abnormalities restricted to slight softening at left temporal pole.

Bennett *et al.* (1962). Other recent reports are the cases of necrotizing encephalitis described at a symposium held in Antwerp (van Bogaert, Radermecker, Hozay, and Lowenthal, 1961) and those of Drachman and Adams (1962), Ryden *et al.* (1965), Zischka-Konorska, Jellinger, and Hohenegger (1965), Miller *et al.* (1966), and Rawls, Dyck, Klass, Greer, and Herrmann (1966). Relatively few cases have been reported from Britain (Greenfield, 1950, case 9¹; Crawford and Robinson, 1957, cases 2¹, 3¹, and 4¹; Grant and McMenemey, 1961, one case; Woolf and Hoult, 1961, case 2¹; Crompton and Teare, 1965,

¹From the information given in the relevant papers, only these cases appear to be examples of acute necrotizing encephalitis.

TABLE III
PRINCIPAL AREAS OF NECROSIS IN THE CORTEX

	Case 1		Case 2		Case 3		Case 5		Case 7	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Hippocampal gyrus	+++	+++	+	+++	+	+++	+++	+++	+++	+
Fusiform gyrus	+++	+++	+++	+++	+	+++	+	+++	+++	+
Inferior temporal gyrus	+++	-	+	+++	+	+++	+	+++	+++	+
Middle temporal gyrus	+++	-	-	+++	-	+++	-	+++	++	-
Superior temporal gyrus	++	+	+	+++	-	+++	+	+++	-	-
Insula	+++	+++	+++	+++	++	+++	+++	+++	+++	++
Posterior orbital gyri	+++	+++	+	++	+	+++	+++	++	+++	+
Cingulate gyrus	+++	++	-	-	+++	+++	++	++	+++	++

+++ = total of almost total necrosis

++ = intermediate between +++ and +

+ = small foci of necrosis

- = no necrosis

TABLE IV
NECROSIS IN BASAL GANGLIA

	Case 1		Case 2		Case 3		Case 5		Case 7	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Caudate nucleus	-	-	-	-	+	+	-	+	-	-
					(R > L)					
Putamen	-	-	-	-	+	+	-	+	-	-
					(R > L)					
Globus pallidus	-	-	-	-	-	-	-	+	-	-
Thalamus										
Anterior complex	+	-	-	+	-	+	-	+	-	-
Lateral complex	-	-	-	+	+	+	-	-	+	-
					(L = R)					
Dorsomedial nucleus	-	-	+	+	-	-	-	-	+	-
			(R > L)							
Amygdaloid nucleus	+	+	+	+	+	+	+	+	+	-
	(L = R)		(L = R)		(R > L)		(L = R)			
Subthalamic nucleus	-	-	-	-	-	+	-	-	-	-
Lateral geniculate body	-	-	-	-	-	-	-	-	-	-
Medial geniculate body	-	-	-	+	-	-	-	-	-	-

+ = presence of well-defined foci of necrosis
- = no significant necrosis

case 2¹; Blackwood, Dudgeon, Newns, and Phillips, 1966, one case) but the two described by MacCallum *et al.* (1964) are probably also cases of acute necrotizing encephalitis and Harriman (1966) has recently observed three cases in Leeds.

The appearances of the brain in acute necrotizing encephalitis are so characteristic that the diagnosis can usually be established by macroscopic examination. In four of the five cases that were available for detailed study there was obvious softening in the temporal lobes and in the posterior orbital gyri (Table II). The softening was always asymmetrical and in the less severely affected hemisphere it tended to be limited to the temporal pole and to the anterior end of the hippocampal gyrus. On the surface of the abnormal areas there were often numerous small haemorrhagic foci and the softened tissue was usually distinctly swollen. One case (case 7) was of particular interest in that although there was widespread and severe neuronal necrosis, the only apparent external abnormality was slight softening of one temporal pole.

In coronal slices small haemorrhagic foci were frequently seen in the cortex and adjacent white matter and in one (case 3, Fig. 3) they extended across the genu of the corpus callosum into the inferomedial part of the frontal lobe of the less severely affected hemisphere. In another (case 5) they were restricted to the cortex. The presence of numerous haemorrhagic foci above and below the anterior end of the Sylvian fissure was particularly characteristic. There was always some loss of definition of the boundary between cortex and white matter not only in the temporal and orbital gyri but also in some cases in the insulae and in the cingulate gyri. The very considerable neuronal necrosis

subsequently found in the other cortical regions and in basal ganglia was not apparent macroscopically. In the case of longer survival (case 6) there was obvious softening, shrinkage, and brown discoloration of the residual temporal lobe tissue, particularly in the left cerebral hemisphere.

Histological examination showed a diffuse encephalitis and selective necrosis in grey matter but with spread of the necrotizing process into the white matter adjacent to the most severely affected cortex. The encephalitic features were similar to those seen in any diffuse encephalitis caused by a virus. In the present cases there were many large mononuclear

FIG. 3. Case 3. There is loss of definition between cortex and white matter at the right temporal pole. Numerous small haemorrhagic foci are seen. The pericallosal arteries are displaced to the left and there is a supracallosal hernia. $\times 0.7$.

cells, lymphocytes, and plasma cells in the subarachnoid space and around vessels in the cortex and white matter. Many of the plasma cells were large and binucleate forms were frequent. The meningeal cellular exudate and perivascular cuffing were seen in all parts of the central nervous system but they tended to be most intense in the regions where necrosis was severe and only slight in the cerebellum. Polymorphonuclear leucocytes were not prominent in any case. Neuronophagia was common in the cerebral cortex, basal ganglia, brainstem, and spinal cord; gliomesenchymal nodules were frequent in the white matter of all parts of the central nervous system; and there was often diffuse hypertrophy of microglial cells in the grey matter. There was no increase of mononuclear cells in the choroid plexus or on the ependyma.

The most striking histological feature, however, was intense and widespread necrosis in the cortex (Table III). In every case the temporal and orbital gyri and the insulae were involved and in four of the five cases the cingulate gyri were affected. The necrosis was always bilateral and asymmetrical. In some gyri necrosis was total, in others only some layers (particularly the outer three) were affected while in others the necrosis was focal and often perivascular. Where necrosis was total, the adjacent white matter was often necrotic. In the less affected gyri there was an occasional tendency for the cortex in the depths of sulci to be more severely affected than that on the crests but a classical laminar necrosis was never seen. The necrotic areas in the cortex tended to be relatively well demarcated from other areas where abnormalities were limited to inflammatory changes. This sharp transition was often particularly clear on either side of the insula. In addition, well-defined zones where there was no obvious neuronal loss sometimes remained in otherwise devastated gyri (Fig. 4). In these zones, however, ischaemic cell change was seen in a few of the residual neurones.

The intensity of reactive changes varied not only from case to case but also between different regions of total cortical necrosis in any one case. Furthermore it was rarely possible to relate the intensity of reactive changes to the duration of the illness (compare Fig. 5, 14-day illness, with Fig. 6, 13-day illness). At one extreme the cortex was completely replaced by dense sheets of lipid phagocytes and there was intense vascular proliferation and a diffuse infiltration by plasma cells (Fig. 5). At the other the cortex was extremely pale in cresyl violet preparations (Fig. 6). At a more intermediate stage, one that was commonly seen, the deeper layers of the cortex were pale while there was a dense sheet of lipid phagocytes in the outer layers (Fig. 4). In

FIG. 4. Case 5. Right posterior orbital gyri. In the zones of necrosis there is a dense subpial band of lipid phagocytes and mononuclear inflammatory cells. The deeper cortical layers are still at the stage of rarefaction necrosis. A sharply defined segment of the cortex is not affected by the necrotizing process. The inferior surface of the frontal lobe is on the right of the photomicrograph. Cresyl violet $\times 5$.

the necrotic areas, cells of inflammatory type were always conspicuous in the meninges and around vessels in the cortex and in the subjacent white matter. As reactive changes became more pronounced cells of the plasmacyte series infiltrated diffusely into the necrotic tissue.

Necrosis of cortical neurones was not restricted to the regions given in Table III. Smaller foci were commonly seen in the medial aspects of the frontal lobes and in the parietal and occipital lobes. These smaller foci, which usually contained numerous lipid phagocytes, were always sharply circumscribed and occurred both on the crests of gyri as well as in the depths of sulci. The Ammon's horns were always implicated. Total necrosis was present bilaterally in two cases and unilaterally in three, but the other Ammon's horn was completely normal in only one of the latter.

FIG. 5. Case 3. Right superior temporal gyrus. Although necrosis is total, the cortex is dark because of its greatly increased cellularity, reactive changes being well advanced. Perivascular cuffing by inflammatory cells is prominent. The Sylvian fissure is on the right of the photomicrograph. Cresyl violet $\times 21$.

FIG. 6. Case 7. Left middle temporal gyrus. Rarefaction necrosis in the cortex and inflammatory cells in the meninges and around vessels. Despite the duration of the illness (13 days), reactive changes in the cortex are slight. Cresyl violet $\times 13$.

As indicated in Table IV, there were also foci of necrosis with intense reactive changes in the basal ganglia. The amygdaloid nuclei and the various thalamic nuclei were mainly affected but in two cases the necrosis in the posterior orbital gyri spread to involve the inferior parts of the putamen and caudate nucleus. Apart from the one case where there was a mild loss of Purkinje cells (case 7), necrosis was not seen in the cerebellum, brain-stem, or spinal cord (except where there were haemorrhagic foci in the brain-stem secondary to raised intracranial pressure).

The cause of the neuronal necrosis in acute necrotizing encephalitis has not been established. One suggestion is that the swelling of the temporal lobe may impede the circulation through it and that secondary anoxic or ischaemic factors might be the main cause of the necrosis in this location (Grant and McMenemy, 1961; Woolf and Houlst, 1961).

In three cases (Table V) there was evidence of raised intracranial pressure after death but in two (cases 1 and 7) there was no evidence of a significant increase of intracranial pressure. It seems, therefore, that the characteristic neuronal necrosis can occur in the absence of raised intracranial pressure. A further significant point is that in the one case (case 3) where there was infarction of the medial occipital cortex in association with an ipsilateral tentorial hernia, the pathology of the calcarine neuronal necrosis was different from that seen elsewhere in that brain or in any of the other brains. Furthermore, the presence of numerous necrotic foci in other cortical regions and in the basal ganglia, and the absence of laminar necrosis or of a significant tendency for necrosis to be most severe in the depths of sulci, all tend to militate against a local ischaemic or anoxic pathogenesis. It has been shown by Adams, Brierley, Connor, and Treip (1966) that a reduction

TABLE V
POST-MORTEM EVIDENCE OF EXPANDING LESION AND/OR
INCREASED INTRACRANIAL PRESSURE

	Case 1	Case 2	Case 3	Case 5	Case 7
Tight dura	—	+	+	+	—
Convolutional flattening	—	+	+	+	—
Tentorial hernia	—	—	+	—	—
Tonsillar hernia	—	—	—	+	—
Small ventricles	—	+	+	+	+
Mid-line shift	—	+	+	—	—
Supracallosal hernia	—	—	+	—	—
Asymmetry of Sylvian fissures	—	—	+	+	—
Calcarine infarction	—	—	+	—	—
Brain stem infarction	—	—	+	+	—

+ = present — = absent

in total cerebral blood flow can produce foci of necrosis in the cortex and basal ganglia but there was no evidence to suggest that any of the present cases had suffered any episode of acute cardiovascular failure in the course of the disease.

Various authors (Haymaker *et al.*, 1958; Harri-man, 1966) have observed necrosis in the walls of small vessels in the necrotic areas in the cortex. As vascular changes of this type, although carefully sought for, were not found in the present cases it seems unlikely that necrosis is always secondary to vascular damage.

A further possibility is that the regions where necrosis is severe are particularly susceptible to direct invasion by the causal virus. Necrosis was never seen in the absence of inflammatory changes; indeed these tended to be accentuated and this suggests a direct association between the distribution of the virus and the production of necrosis.

Typical intranuclear inclusions were found in only one case (case 7, Fig. 7) where they were widely distributed throughout the brain although they were most numerous immediately adjacent to the areas of necrosis. They were not seen in the biopsy taken three days earlier although this was the specimen from which herpes simplex virus was isolated. In the other four cases, however, many astrocytic nuclei were swollen and there was obvious margination of chromatin, appearances at least consistent with the presence of virus. Intranuclear inclusion bodies have been found in many previously reported cases (Haymaker *et al.*, 1958; Drachman and Adams, 1962; Bennett *et al.*, 1962; Carmon *et al.*, 1965; Ryden *et al.*, 1965) but in others they have not been identified (see Haymaker *et al.*, 1958; Grant and McMenemey, 1961; Drachman and Adams, 1962; Pierce *et al.*, 1964; Carmon *et al.*, 1965; Miller *et al.*, 1966).

As a result of viral, serological and histological studies, there is therefore a great deal of evidence to suggest that herpes simplex virus is the causal agent

FIG. 7. Case 7. Right cingulate gyrus. Three swollen astrocytic nuclei contain inclusion bodies. Haematoxylin and eosin $\times 1,250$.

of acute necrotizing encephalitis. Further support has been provided by the electron microscopic observations of Ryden *et al.* (1965), Itabashi, Bass, and McCulloch (1966), and Vanderhaeghen, Périer, and Bossaert (1966) who have found unequivocal particles of characteristic herpes morphology in areas of the brain where light microscopy had shown intranuclear inclusion bodies. There is, however, considerable speculation as to the route of entry and mode of spread in the nervous system (Haymaker *et al.*, 1958). An interesting observation has recently been made by Yamamoto, Otani, and Shiraki (1965), who found that when the herpes simplex virus is administered intraperitoneally to mice, more virus antigen can be demonstrated in the temporal lobes and in the diencephalon than in other parts of the cerebral hemispheres. They attribute this finding to an inherent susceptibility of these regions to the virus but the possible relationship of this to a similar state existing in man that might be responsible for selective neuronal necrosis remains in doubt, since there was considerably more virus antigen in the spinal cord and brain-stem than in the cerebrum in these experimental animals. Because of the frequent tendency for one hemisphere to be more severely affected than the other in man it has been argued that there may be a local portal of entry for the

virus (Haymaker *et al.*, 1958), probably by way of an olfactory tract. These tracts, however, were not particularly severely affected in any of the present cases.

However, whatever the route of entry and the mode of spread of the virus, the fact that the intensity of the reactive changes in the most severely affected areas of the cortex varies strikingly not only from case to case but also between different regions in any one case supports the views of Krücke (1957) and Haymaker *et al.* (1958) that neuronal necrosis does not all occur at the one time but that there are multiple episodes. This is compatible with the concept of periodic spread of virus through the central nervous system.

CONCLUSIONS

Acute necrotizing encephalitis is being recognized with increasing frequency but is still readily overlooked. It presents as an acute pyrexial illness associated with headache, confusion, and sometimes convulsions. Local swelling of the temporal lobe may produce increased intracranial pressure and localizing signs so that distinction from tumour or abscess is difficult. Contrast radiology may add to the confusion by showing all the features of an expanding lesion in the temporal lobe.

The diagnosis can be made in life if the possibility is considered soon enough on the basis of the clinical syndrome and if full use is then made of the various diagnostic procedures available. Brain biopsy (through a temporal burr hole) is the most useful because histological examination can provide a rapid answer and isolation of virus from the biopsy may confirm the diagnosis. Serial serological estimations of complement-fixing antibodies to herpes simplex are useful if the patient survives long enough. Examination of the cerebrospinal fluid may demonstrate atypical inflammatory cells.

The most remarkable feature about the pathology is intense neuronal necrosis in the temporal, posterior orbital and cingulate gyri, and in the insulae. The severity and asymmetry of the necrosis in the temporal gyri often leads to considerable enlargement of one temporal lobe. Foci of necrosis occur irregularly in the basal nuclei. There are also diffuse inflammatory changes of the type associated with a primary viral encephalitis. So far the only agent known to cause acute necrotizing encephalitis is the herpes simplex virus.

While the outlook in recognized cases is almost uniformly bad, with a fatal outcome within two weeks, satisfactory recovery is possible. Treatment of raised intracranial pressure may increase the chance of survival.

ADDENDUM

Since this paper was accepted for publication, we have encountered another fatal case of acute necrotizing encephalitis in this Institute.

The patient was a man of 18 (N. 24994, K. 7/67) who developed mental confusion and pyrexia. On day 1 meningism and a right extensor plantar response were the only abnormal signs. An E.E.G. showed recurring slow wave complexes suggestive of encephalitis. A left carotid angiogram was normal. Herpes simplex virus was isolated from a left frontal biopsy taken on day 2. He became progressively more drowsy and was akinetic and mute by day 4. He died on day 7. The titre of complement fixing antibodies to herpes simplex rose from 1/16 to 1/512. Lumbar cerebrospinal fluid was blood-stained and contained 370 leucocytes per c. mm. and 25 mg. protein per 100 ml. At necropsy the right temporal lobe was soft and swollen, and there was a tonsillar hernia and bilateral calcarine infarction. Preliminary histological studies showed features similar to those seen in the cases described above.

We wish to thank Mr. J. Sloan Robertson, Mr. A. Paterson, and Mr. Robert Tym for access to the clinical records of patients under their care. Dr. Bruce Woodger kindly provided sections from the brain of case 6.

REFERENCES

- Adams, J. H., Brierley, J. B., Connor, R. C. R., and Treip, C. S. (1966). The effects of systemic hypotension upon the human brain. *Brain*, **89**, 235-268.
- Bennett, D. R., ZuRhein, G. M., and Roberts, T. S. (1962). Acute necrotizing encephalitis. A diagnostic problem in temporal lobe disease: report of three cases. *Arch. Neurol. (Chic.)*, **6**, 96-113.
- Blackwood, W., Dudgeon, J. A., Newns, G. H., and Phillips, B. M. (1966). Case of encephalitis due to herpes simplex. *Brit. med. J.*, **1**, 1519-1521.
- Carmon, A., Behar, A., and Beller, A. J. (1965). Acute necrotizing haemorrhagic encephalitis presenting clinically as a space-occupying lesion. A clinico-pathological study of six cases. *J. neurol. Sci.*, **2**, 328-343.
- Crawford, A. R., and Robinson, F. L. J. (1957). Necrotizing encephalitis. *Brain*, **80**, 209-221.
- Crompton, M. R., and Teare, R. D. (1965). Encephalitis after the reduction of steroid maintenance therapy. *Lancet*, **2**, 1318-1320.
- Drachman, D. A., and Adams, R. D. (1962). Herpes simplex and acute inclusion-body encephalitis. *Arch. Neurol. (Chic.)*, **7**, 45-63.
- Grant, H. G., and McMenemey, W. H. (1961). A case of necrotizing encephalitis. In *Encephalitis*, edited by L. van Bogaert, J. Radermecker, J. Hozay, and A. Lowenthal, pp. 227-229. Elsevier, Amsterdam.
- Greenfield, J. G. (1950). Encephalitis and encephalomyelitis in England and Wales during the last decade. *Brain*, **73**, 141-166.
- Grist, N. R., Ross, C. A. C., Bell, E. J., and Stott, E. J. (1966). In *Diagnostic Methods in Clinical Virology*. Blackwell, Oxford.
- Harriman, D. (1966). Personal communication.
- Haymaker, W., Smith, M. G., van Bogaert, L., and de Chenar, C. (1958). Pathology of viral disease in man characterized by nuclear inclusions. In *Viral Encephalitis (Fifth Annual Scientific Meeting of the Houston Neurological Society, Texas)* edited by W. S. Fields and R. J. Blattner, pp. 95-204. Thomas, Springfield, Illinois.
- Itabashi, H. H., Bass, D. M., and McCulloch, J. R. (1966). Inclusion body of acute inclusion encephalitis. *Arch. Neurol. (Chic.)*, **14**, 493-505.

- Krücke, W. (1957). Über eine besondere Form der spontanen Encephalitis. *Nervenarzt*, 28, 289-301.
- MacCallum, F. O., Potter, J. M., and Edwards, D. H. (1964). Early diagnosis of herpes-simplex encephalitis by brain biopsy. *Lancet*, 2, 332-334.
- Miller, K. J., Hesser, F., and Tompkins, V. N. (1966). Herpes simplex encephalitis. Report of 20 cases. *Ann. intern. Med.*, 64, 92-103.
- Pierce, N. F., Portnoy, B., Leeds, N. E., Morrison, R. L., and Wehrle, P. F. (1964). Encephalitis associated with herpes simplex infection presenting as a temporal-lobe mass. *Neurology (Minneapolis)*, 14, 708-713.
- Rawls, W. E., Dyck, P. J., Klass, D. W., Greer, H. D., and Herrmann, E. C. (1966). Encephalitis associated with herpes simplex virus. *Ann. intern. Med.*, 64, 104-115.
- Ross, C. A. C., Russell, W. C., and Wildy, P. (1964). Herpes antigens from hamster kidney cell-cultures in the diagnosis of primary and recurrent infections. *Arch. ges. Virusforsch.*, 15, 58-66.
- Ryden, F. W., Moses, H. L., Ganote, C. E., and Beaver, D. L. (1965). Herpetic (inclusion-body) encephalitis. *Sth. med. J. (Bgham, Ala.)*, 58, 903-913.
- Van Bogaert, L., Radermecker, J., and Devos, J. (1955). Sur une observation mortelle d'encéphalite aiguë nécrosante. *Rev. neurol.*, 92, 329-356.
- , Hozay, J., and Lowenthal, A. (ed.) (1961). Necrotizing encephalitis. In *Encephalitis*, pp. 203-282. Elsevier, Amsterdam.
- Vanderhaeghen, J. J., Périer, O., and Bossaert, Y. (1966). Acute necrotizing encephalitis. Observations of herpes-like particles by electron microscopy. *Path. europ.*, 1, 29-49.
- Woolf, A. L., and Hoult, J. G. (1961). Atypical encephalitides. In *Encephalitides*, edited by L. van Bogaert, J. Radermecker, J. Hozay, and A. Lowenthal, pp. 315-324. Elsevier, Amsterdam.
- Yamamoto, T., Otani, S., and Shiraki, H. (1965). A study of the evolution of viral infection in experimental herpes simplex encephalitis and rabies by means of fluorescent antibody. *Acta neuropath. (Berl.)*, 5, 288-306.
- Zischka-Konorsa, W., Jellinger, K., and Hohenegger, M. (1965). Zur Pathogenese von Herpesvirus-Erkrankungen mit besonderer Berücksichtigung der nekrotisierenden Herpes simplex—Encephalitis. *Ibid.*, 5, 252-274.