of the mother leading to the production of a non-viable foetus. Such an idea would be supported if it were found that the miscarriages and stillbirths prior to the pregnancy with the mongol tended to accumulate close to this event. With this in mind, the present material was examined to find whether or not there were an unexpectedly large number of conceptions ending in miscarriage in the conception order immediately prior to the mongol. The results are shown in Tables VI and VII. The difference between the observation of 15 and the expectation of 12.72 is clearly not significant.

TABLE VI.—*Positions of Normal Births and Miscarriages in Relation to Mongol in Conception Order*

Position of Conception in Relation to Mongol	No. of Normal Births	No. of Miscarriages
−5	2	1
−4	5	1
−3	8	5
−2	22	7
−1	29	15
+1	18	2
+2	9	1
+3	1	4
+4	0	3
+5	1	1
+6	0	1
+7	1	0
	96	41

N.B.—One miscarriage was counted twice owing to two mongols occurring in one sibship.

TABLE VII.—*Incidence of Miscarriage Immediately Prior to Mongol in Conception Order*

Conception Order of Mongol	Observed Incidence of Miscarriage in Immediately Preceding Conception	Expected
2	5	3·49
3	4	4·57
4	2	1·83
5	2	0·83
6	2	2·00
Total ..	15	12·72

$$\chi^2=\frac{(2\cdot28)^2}{12\cdot72}=0\cdot41.\quad \text{D.F. 1.}\quad P=0\cdot5.$$

Moreover, when all other possible relationships between the conception order of a miscarriage and the conception of a mongol are considered (see Table VII), it is found that no single relationship is favoured at the expense of others: thus there is approximately the same expectation of a miscarriage before as after the birth of a mongol.

Summary

Fifty-five mothers of mongols were examined. The findings failed to confirm earlier reports of thyroid abnormality, including raised serum P.B.I. The body-build of the group as a whole did not differ from normal. When the group, however, was examined according to maternal age at the time of the mongol birth, it was found that the group of mothers bearing a mongol at 27 years of age or younger had a significantly raised mean androgyny score and mean biacromial diameter. A tendency was also observed for the mothers with multiple miscarriages to have a raised androgyny score. Psychological testing and general medical history failed to show deviations from normal. The obstetric histories, however, showed an extremely high rate of miscarriage irrespective of conception order and unrelated to birth order of the mongol.

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INFLUENZAL ENCEPHALOPATHY AND POST-INFLUENZAL ENCEPHALITIS

HISTOLOGICAL AND OTHER OBSERVATIONS

BY

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Cases of neurological disorder associated with influenza have been reported for many years; perhaps it is merely because laboratory investigation has become so much more widely available that more cases have been reported associated with Asian influenza than with previous epidemics or pandemics. We (Flewett and Hoult, 1958) reported 12 such cases. Six of these presented neurological symptoms after the acute attack of clinical influenza had subsided, and all but one recovered; the others were cases of clinical "encephalitis" with convulsions or "fits" proceeding to coma and death, which occurred during the acute phase of an attack of influenza, and which showed a very congested brain at necropsy; we found no obvious histological lesions in a few sections of paraffin-embedded material. This paper describes the results of detailed histological examinations of the brains of five of these patients. The first were children, aged between 5 and 13, who died at intervals of seven to nine days after the onset. The fifth patient was a man aged 44 who died 11 days after the onset.

Methods

Large blocks were taken from the following sites and embedded in celloidin: spinal cord (in some cases only),

medulla, pons, mid-brain, basal ganglia, frontal, occipital, parietal, and temporal lobes, and cerebellum. Sections were stained with cresyl violet, Woelcke's method for myelin, phosphotungstic acid–haematoxylin, and van Gieson. Some sections were also stained with luxol-fast blue and counterstained with cresyl violet.

A virus was isolated or the complement-fixation test on the post-mortem blood was positive in four patients.

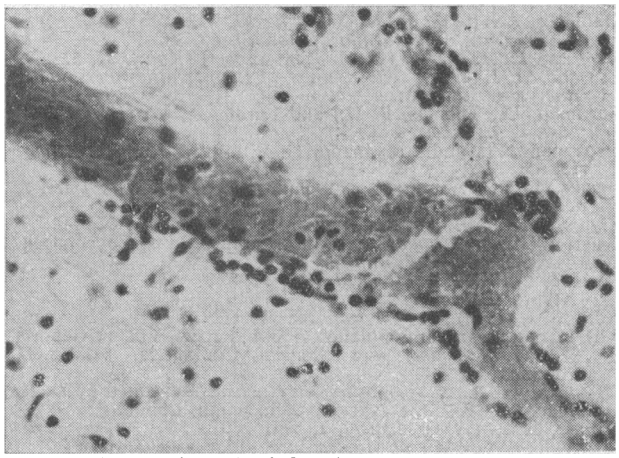

FIG. 1.—Slight perivascular infiltration by lymphocytes. (Cresyl violet. ×90.)

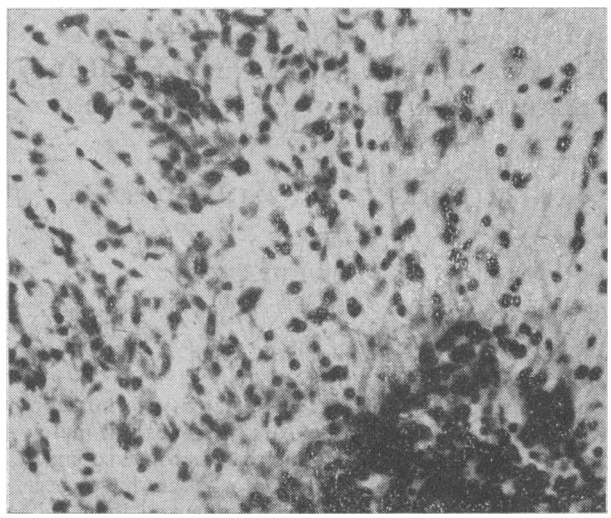

FIG. 2.—Microglial infiltration of cerebellar cortex. (Cresyl violet. ×375.)

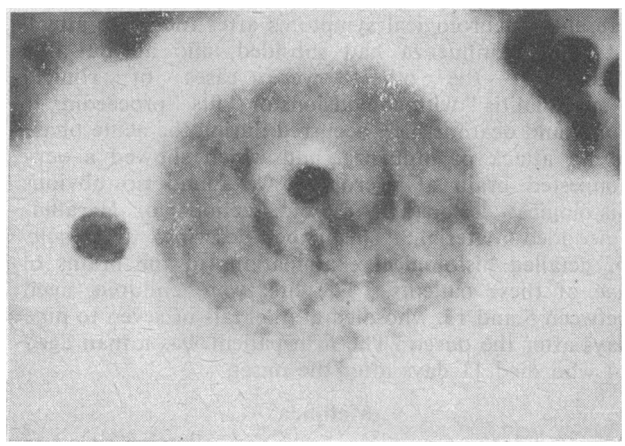

FIG. 3.—Body of a Purkinje cell, showing folding of nuclear membrane. (Cresyl violet. ×1,600.)

No serum was taken or virus isolated from the last case, but the clinical history supported a diagnosis of influenza, and the lung histology was consistent with the history of influenza of 11 days' duration.

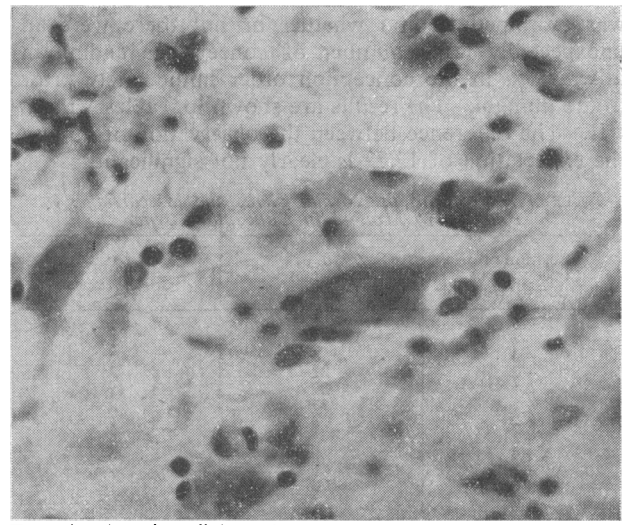

FIG. 4.—A microglial node; grey matter of cervical cord. (Cresyl violet. ×500.)

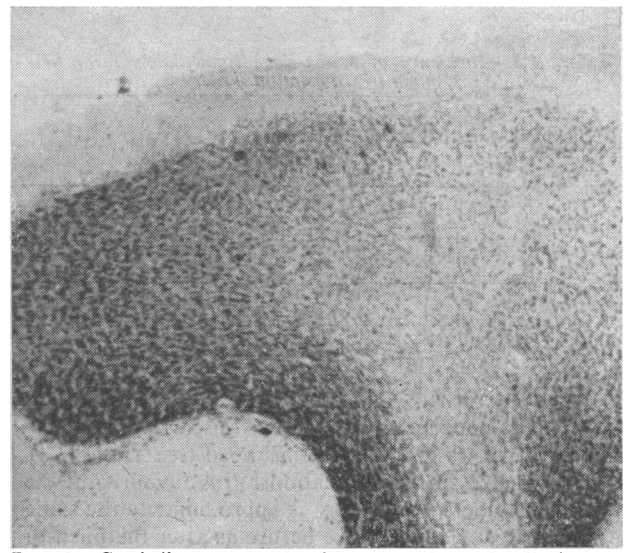

FIG. 5.—Cerebellar cortex, showing severe loss of cells in the granular layer. (Cresyl violet. ×75.)

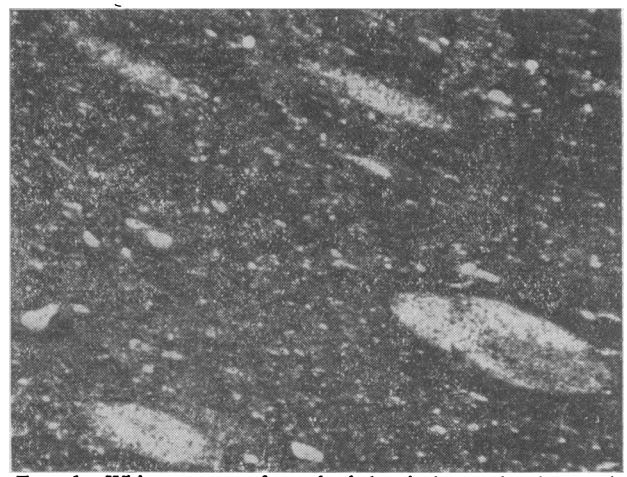

FIG. 6.—White matter of cerebral hemisphere, showing perivascular demyelination. (Woelcke's stain. ×45.)

Results

No gross histological abnormalities were found in the brain except in Case 5. Such changes as were found had to be patiently sought over many sections, and might well have been missed in the small routine paraffin sections. The changes found consisted in: (1) Scanty and patchy lymphocytic infiltration of meninges and perivascular spaces. These were found chiefly over, in, and just beneath occipital, temporal, and cerebral cortex, except in one case in which no histological abnormality could be found at all (Cases 1, 2, 3, and 5) (Fig. 1). (2) Microglial proliferation and formation of microglial nodes in the cerebellar cortex, together with patchy loss of Purkinje cells; some of these cells also showed a folding of the nuclear membrane (Figs. 2, 3, and 4). The distribution of the microglial lesion in Fig. 2 suggests a reaction to the death of a Purkinje cell. Several such lesions were found in the cerebellum of this patient; but no cells were found in an early stage of degeneration such as might throw light on its cause.

It is of interest that Fraser *et al.* (1959) observed, by marking infected cells with fluorescent antibody, that Purkinje cells of both infant and adult mice were infected by neurotropic strains of influenza virus, and in infant mice could be infected with non-neurotropic virus also. The lesion in Fig. 4 also suggests a reaction to the destruction of a neurone in the spinal cord; the adjacent neurone has lost its Nissl substance. Another case showed a more extensive lesion in which many of the dwarf neurones of the granular layer appeared to have undergone autolysis without giving rise to any obvious inflammatory reaction (Fig. 5).

The fifth case resembled histologically that described by Henson and Russell (1942) and Russell (1955) as acute haemorrhagic leuco-encephalitis. The lesions appeared to be of recent origin in that there was some infiltration with microglia and an occasional polymorph; but new gliofibrils had not been laid down around the affected blood-vessels, and the erythrocytes in the "ring haemorrhages" still showed normal morphology and staining reaction. The lesions were widely distributed in the white matter of the cerebral hemispheres; not all showed gross haemorrhage, though a few erythrocytes could almost always be found in the zone of perivascular damage; the zone of demyelination did not extend far from the vessels (Fig. 6: lesions with little haemorrhage were selected for illustration to show the extent of demyelination).

With the exception of the last case, the cellular lesions, irregularly distributed as they were, might perhaps be explained as the consequences of small infarcts due to emboli from pneumonic lungs; and the scanty round-cell infiltration of the pia-arachnoid and the perivascular spaces might be a reflection of small lesions of this kind in the neighbouring brain substance; it seems unnecessary to postulate intracerebral multiplication of virus or any specific toxic effect of the virus, though of course this could not be excluded.

Discussion

All the cases we have described here, with the exception of the fifth case, were mentioned in our last paper. It so happened that only two patients showing a picture of perivascular demyelination and in whom a firm diagnosis of epidemic influenza could be made came to necropsy—the last case described above and the one previously described that presented with acute ascending paralysis. It is quite likely that the cases described by us that developed encephalitic symptoms with abnormal cerebrospinal fluids some days after recovering from influenza may have had lesions of this type. They recovered, so histological evidence is not available. Presumably the fatal cases encountered by McGill and Goodbody (1958) and Goodbody and McGill (1958) were all of this type. Post-influenzal encephalitis is so rare that probably no one pathologist will see enough cases to find all the varieties of histological picture described by others.

Furthermore, because this form of encephalitis is so rare, it is almost impossible to be sure that its association with influenza is significant; cases of encephalitis do occur from time to time, and may be expected to continue to occur during any epidemic. However, Kapila *et al.* (1958), describing a number of cases of neurological disorder associated with influenza in India, estimated that the normal incidence of encephalitis in two stations from which patients were admitted was two or three cases a year, whereas during the influenza epidemic 21 cases occurred within a month; we know of no other series in which such a comparison has been made. Furthermore, Kapila *et al.* were able in four of their cases to exclude by serological means infection by arthropod-borne viruses of groups A and B. Their paper thus affords the best evidence so far that the association is not a chance one.

When the symptoms come on some days after the acute attack of influenza, it is probably not valid to make a distinction between the encephalitic variety (shown by Case 5, described above) and the spinal variety, resembling clinically the Guillain–Barré syndrome (as shown in Case 4, described in our last paper), since the lesions were essentially of the same nature—namely, perivascular demyelination—though the distribution in the central nervous system was different. The nosological identity of such conditions has been supported by Russell (1955). If this identity be accepted, then from our experience it appears that there are two principal forms of major neurological disturbance associated with influenza: (1) an acute encephalopathic variety, with minimal histological lesions, occurring early in the attack of influenza, and (2) the perivascular demyelinating leuco-encephalitis of the type described as a post-infective sequel to a number of other acute virus infections—measles, varicella, etc.

A third type of encephalomyelitis, closely resembling acute paralytic poliomyelitis, both clinically and histologically, was associated with the Asian influenza pandemic in Italy (Battaglia *et al.*, 1959), but these authors do not mention any attempt to exclude infection with polio virus.

It is tempting to speculate, in accordance with modern immunological concepts, that damage occurs in the acute phase, whether by a toxin or by actual virus multiplication, that products of such damage are liberated into the blood, giving rise to anti-brain antibodies, and that these, becoming fixed in brain substance around blood-vessels, somehow cause disintegration of the myelin. This may be so; but there is, unfortunately, no evidence to support it, other than the demonstration that similar lesions can be provoked in guinea-pigs or rabbits, and occasionally in man, by injecting suspensions or extracts of nervous tissue.

Summary

Histological examination of brains of four children and one man dying with encephalitic symptoms within a few days of an attack of Asian influenza showed, in the children, scanty microglial infiltrations principally in the cerebellar cortex and also in the spinal cord; in the man, an acute haemorrhagic leuco-encephalitis. In one brain no abnormality other than congestion could be found. The remainder showed also slight lymphocytic infiltration of the perivascular spaces and meninges.

We are indebted to those physicians named in our last paper who allowed us to report their cases and supplied us with clinical details; to Professor Stuart-Harris for reading our draft, and especially to Dr. A. L. Woolf for his helpful comments and criticisms, and for drawing our attention to the nuclear changes in the Purkinje cells.

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MUMPS MENINGO-ENCEPHALITIS

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During 1958 there was an epidemic of mumps in Northern Ireland which was associated with an increased prevalence of mumps meningo-encephalitis. It is the purpose of this paper to present the clinical, laboratory, and epidemiological finding in 50 cases of mumps meningo-encephalitis. Five occurred in 1957, 39 in 1958, and six in 1959.

Laboratory Diagnosis

Where possible, two samples of serum from each patient were obtained for determination of complement fixation antibody titres. The first, "acute," serum was taken as soon as possible after the onset of illness. The second, "convalescent," serum was usually taken about three weeks after onset. These are together referred to as "paired sera." V and S mumps antigens (see Kravis, Sigel and Henle, 1951), 2½ MCD_{50} of complement, and overnight fixation were used in the tests. The diagnosis in 42 cases was based on the demonstration of a fourfold or greater rise in complement fixation antibody in paired sera. In one case the sera were taken three weeks (anti-V = >1:512; anti-S = 1:64) and five weeks (anti-V = 1:256; anti-S = 1:16) after the onset of mumps, so that the antibody titres were on the wane. Six out of seven cases in which only single samples of serum were tested had clinical salivary-gland involvement. In all but one the anti-V antibody titre was 1:128 or higher. The single exception in which the serum was taken approximately six weeks after onset of parotitis had anti-V and anti-S antibody titres of 1:32 and 1:64 respectively.

Of 40 sera taken within seven days of onset of symptoms of mumps meningo-encephalitis, sixteen had an antibody titre of <1:8 against V and S antigens, and 5 were tested against V antigen only. Of the remaining 19 the anti-V was higher than the anti-S antibody titre in 11 cases, in one case they were equal, and in seven cases the anti-S exceeded the anti-V antibody titre, thus allowing a presumptive diagnosis of mumps virus infection to be made within the first week of illness in these cases (Kravis *et al.*, 1951). Of the 49 serum samples taken after the seventh day of illness which were tested against V and S antigens, four showed an anti-S > anti-V antibody pattern.

Clinical Findings

The age and sex of the patients are summarized in Table I. It will be seen that 84% of the cases occurred in children under 15 years of age and that males were more commonly affected than females in a ratio of more than 2:1.

Twenty-seven of the patients had parotitis and/or other salivary-gland involvement, but in 23 there was no evidence of salivary-gland involvement.

Apart from the presence or absence of parotitis the clinical findings were essentially the same in the two groups, and these are summarized in Table II. The principal features were fever, neck rigidity, vomiting, and headache. Somnolence was present in 14 patients. Two patients were delirious.

One child, a girl of 6½ years, without salivary-gland involvement, developed complete ophthalmoplegia and was subjected to ventriculography. This patient was apyrexial throughout her illness, and the C.S.F. on the third day of illness showed no abnormality. Sera taken on the third and nineteenth days of illness had anti-V and anti-S antibody titres of 1:64 and 1:8, and 1:256 and 1:16 respectively.

A woman aged 26, who aborted after seven weeks' amenorrhoea, developed pyrexia, neck stiffness, vomiting,

TABLE I.—*Age Distribution of Mumps Meningo-encephalitis*

Age	Salivary-gland Involvement				Total
	Present		Absent		
	Male	Female	Male	Female	
0–4	4	1	5	2	12
5–9	17	1	8	2	28
10–14	1	0	1	0	2
15 and over	0	3	0	5	8

TABLE II.—*Frequency of Clinical Features in Patients with Mumps Meningo-encephalitis*

Clinical Features	Salivary-gland Involvement		Clinical Features	Salivary-gland Involvement	
	Yes	No		Yes	No
Fever	24	20	Sore throat	2	2
Neck rigidity	20	18	Vertigo	2	2
Vomiting	20	18	Photophobia	1	3
Headache	19	17	Listlessness	2	1
Somnolence	9	5	Urinary symptoms	1	1
Lucid and alert	6	4	Delirium	2	0
Irritability	6	3	Ataxia	1	0
Abdominal pain	5	3	Dysarthria	1	0
Anorexia	4	4	Paresis	0	1
Constipation	1	5	Upper respiratory symptoms	0	1
Nausea	2	4	Aches and pains	0	1
Eye signs	1	5			