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

BY

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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 MCD₅₀ 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 involve-

ment. 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 ..	19	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			

and weakness of the back muscles 24 hours after curettage. She had no parotitis or other swelling of the salivary-glands. The C.S.F. contained 180 leucocytes per c.mm. (49% lymphocytes, 51% polymorphs). Poliomyelitis was suspected but no enteric virus was isolated from the faeces. A serum sample taken on the eighth day of illness was found to have a mumps anti-V antibody titre of 1:64 and anti-S 1:128. Unfortunately a convalescent specimen or serum was not available.

A 6-year-old boy with a three-year history of epilepsy was admitted to hospital with somnolence and ataxia of one week's duration after an attack of mumps three weeks prior to admission. Serum taken on admission showed antibody titres of >1:512 and 1:64 against mumps V and S antigens respectively. Examination showed ataxia, a positive Romberg sign, dysarthria, and nystagmus. The C.S.F. taken 55 days from onset of neurological symptoms contained less than 1 cell per c.mm. and 35 mg. of protein per 100 ml., but an E.E.G. showed deterioration compared with a previous record made one year previously. He was discharged two weeks later after gradual improvement and disappearance of abnormal physical signs. This boy has been readmitted to hospital on two occasions with episodes of vomiting and worsening ataxia and incoordination.

Encephalitis of post-infective type occurred in a boy aged 6 years who developed headache, pyrexia, and neck rigidity three weeks after an attack of mumps. His condition improved and he was free from symptoms within five days. An attempt at lumbar puncture was unsuccessful. On the sixteenth day after the onset of neurological symptoms signs of meningeal irritation reappeared with photophobia, somnolence, and irritability. The C.S.F. was blood-stained but showed no excess of leucocytes; the protein was 240 mg./100 ml., and sugar 72 mg./100 ml. On the nineteenth day of illness he was apyrexial, had mild meningeal signs, and was dull and irritable but well orientated. The C.S.F. contained 64,000 red blood cells per c.mm and 137 white cells (45% polymorphs), protein 242 mg./100 ml., and sugar 74 mg./100 ml. Next day he died, though he appeared brighter, was free from headache, and showed less evidence of meningeal irritation. Serum taken on the twentieth day after onset of neurological symptoms showed anti-V and anti-S antibody titres of 1:32 and 1:64 respectively.

Abdominal symptoms were present in nine patients in the present series.

Oophoritis was diagnosed in a girl aged 18 who had marked tenderness in both iliac fossae. Parotitis, with headache, lethargy, and drowsiness, had begun almost one week before abdominal symptoms. This patient had no definite signs of meningeal irritation and the C.S.F. on the twelfth day of illness was normal (5 cells per c.mm.; protein 24 mg./100 ml.). Serum taken 23 days after onset of illness had anti-V and anti-S antibody titres of 1:256 and 1:64 respectively.

Of considerable interest is the case of a girl aged 9, on whom a laparotomy was performed because of abdominal pain, tenderness, and rigidity, in addition to signs of meningeal irritation. Though enlargement of the left parotid and submandibular salivary glands occurred four days after onset of symptoms, specimens of serum taken on the fourth and twenty-second days of illness had on repeated tests complement-fixing antibody titres of <1:4 against V and S antigens. The C.S.F. on the second day of illness showed pleocytosis with 60% lymphocytes and a raised protein content. This case is not included among the 50 in this series, because the clinical diagnosis was not confirmed by serological tests.

Of the 27 patients with salivary-gland involvement parotitis was present in 11 before the symptoms and signs of meningo-encephalitis, and in six patients neurological manifestations preceded enlargement of the

salivary glands. Parotitis and neurological features occurred more or less simultaneously in seven patients. In the remaining three it was not possible to establish the sequence.

C.S.F. Examinations

Cerebrospinal fluids from 36 of the patients, obtained during the first 12 days of illness, were suitable for examination. The values for cells and protein are presented in the accompanying Chart.

Cell counts and protein estimations in patients with mumps meningo-encephalitis.

The C.S.F. findings were similar in the patients with parotitis and those without. There was no obvious relationship between the cell counts or protein levels and the day of illness on which lumbar puncture was done. Lymphocytes were the predominant cells in all but two C.S.F. samples in which only about 50% of the cells were lymphocytes.

Usually C.S.F. cell counts were in the hundreds, but in one case 1,150 lymphocytes per c.mm. were found on the second day after the onset of neurological symptoms. This patient had parotitis and an eightfold rise in mumps anti-V and anti-S antibodies in paired sera.

Protein levels in the C.S.F. were in most cases either normal or slightly raised. The highest level found was 189 mg./100 ml. from a case without salivary-gland involvement; paired sera taken on the second and forty-first days of illness showed a diagnostic rise in mumps antibodies (anti-V, 1:32-1:128; anti-S, <1:8-1:8). There were two cases, one of encephalitis and one with oophoritis, in which the C.S.F. findings were normal.

Epidemiology

The monthly incidence of meningo-encephalitis caused by mumps virus in Northern Ireland during 1957-9 is shown in Table III. Unfortunately it is not possible to give any time relationship between the incidence of meningo-encephalitis due to mumps virus and uncomplicated mumps.

In 33 of the homes where a case of meningo-encephalitis had occurred inquiries were made in order to try to find out (a) if there was any association between cases of meningo-encephalitis due to mumps virus, (b) the order in which parotitis or meningo-encephalitis

TABLE III.—*Monthly Incidence of Mumps Meningo-encephalitis, With and Without Salivary-gland Involvement*

	1957		1958		1959	
	With	Without	With	Without	With	Without
January ..	—	—	2	—	—	—
February ..	—	—	—	1	—	—
March ..	1	1	1	1	—	2
April ..	—	—	2	5	—	1
May ..	1	—	6	1	—	—
June ..	—	—	4	4	1	—
July ..	1	—	2	2	1	—
August ..	—	—	—	2	—	—
September ..	—	—	1	—	—	—
October ..	—	—	—	—	—	—
November ..	—	—	2	3	—	—
December ..	1	—	—	—	—	—

affected other members of the family, and (c) the health of the patient about one year after infection.

In 25 homes there had been no previous cases of mumps or aseptic meningitis in the family and no evidence of the source of infection. In seven families there had been a case of uncomplicated mumps two to three weeks before the patient's illness. In 21 homes in which a case of meningo-encephalitis had occurred there were susceptible siblings—that is, children under 15 years of age who had no previous history of mumps. In 12 of these homes the patient with meningo-encephalitis had parotitis, and further spread occurred in five families. In the other nine homes in which the patient had no salivary-gland involvement there was no spread to susceptible children. One of these "homes" was a residential nursery accommodating 40 children between 2 and 5 years of age. Their contact with the case of meningo-encephalitis was close, yet no other clinical cases of mumps or meningo-encephalitis were observed. These observations suggest a low infectivity in the absence of clinical involvement of the salivary glands.

One young adult and two children aged 5 and 8 years complained of recurrent headaches, and three children were said to be very nervous since their illnesses. One of the latter had been absent from school for three months and was downgraded on his return, but soon regained his normal grade. Physical examination of these patients about one year after infection revealed no abnormalities.

Discussion

Mumps virus can affect many organs, with or without involvement of the salivary glands. The frequency with which the C.N.S. is affected is unknown, and in the absence of notification or of school records of the cause of absenteeism it is not possible to make an estimate. When infection of the C.N.S. occurs it appears to be mainly a meningeal infection, but symptoms of encephalitis with or without meningeal signs were present in about one-third of the cases. Our findings in this respect are very similar to those of Kravis *et al.* (1951). The diagnosis is relatively easy, if there is salivary-gland involvement, but when this is absent an accurate diagnosis can be made only by laboratory tests. Mumps meningo-encephalitis was provisionally diagnosed in a number of patients in 1958 because of the prevalence of uncomplicated mumps or because of definite contact with a known case of mumps. This was, however, unusual, and a variety of provisional diagnoses, including aseptic meningitis, non-paralytic poliomyelitis, tuberculous meningitis, and cerebrospinal fever, were made. In the follow-up it was found that

the illness was vividly remembered by the parents partly because of its alarming onset and partly because of the serious nature of many of the provisional diagnoses.

The protein and cellular content of the C.S.F., while assisting in the diagnosis, will not necessarily distinguish mumps infection of the C.N.S. from infection with polioviruses, Coxsackie and Echo viruses, Weil's disease, or irritative meningo-encephalitis due to a brain tumour or abscess. In one of the patients in this series ventriculography to exclude a space-occupying lesion might have been avoided if serological tests had first been done. The diagnosis depends on complement-fixation tests, and if viral (V) and soluble (S) antigens are used a presumptive diagnosis may be made in the first week of illness in some cases. Serology is used in preference to attempts at virus isolation because of the irregularity with which the latter can be accomplished.

Complete recovery usually occurs, but 18% of the present series who were followed up were found to be complaining of headache or "nervousness" when seen a year later. In none were any severe sequelae observed. Residual disabilities such as diverse eye and ear symptoms or mental symptoms of a neurasthenic nature both with or without headaches, though relatively uncommon, have been recorded by Oldfelt (1949), Kravis *et al.* (1951), Ritter (1958), and others. Such sequelae, as might be expected, appear to be more common when signs of encephalitis have been present. Nothing is known of the lesions which mumps virus produces in the C.N.S., and there is no evidence that demyelinating lesions occur in mumps infection of the C.N.S. except in the very rare post-infective type of encephalitis. In general it was concluded from our follow-up that a good prognosis can be made in mumps meningo-encephalitis.

Our own observations and those of others, including Enders, Cohen, and Kane (1945), Kilham (1949), and Kravis *et al.* (1951), have shown that mumps meningo-encephalitis is more common in boys than in girls. There is no obvious explanation for this sex difference.

Of the patients with mumps meningo-encephalitis in Northern Ireland, 46% had no salivary-gland involvement. This is remarkably similar to what was observed by Kravis *et al.* (1951) and Ritter (1958), who found no salivary-gland involvement in 49% and 43% of infections respectively. Ritter has reported that he found a predominance of meningo-encephalitis *with* parotitis in the spring and of meningo-encephalitis *without* parotitis in the summer. (His conclusion was based on 30 patients over a period of five years.)

Our findings do not support this, as may be seen from Table III, for the peak incidence of mumps meningo-encephalitis cases both with and without parotitis occurred in the late spring and early summer months. But, as already noted, we do not know whether the peak incidence of meningo-encephalitis and of uncomplicated salivary-gland infection coincided. Russell and Donald (1958) described an epidemic of mumps in Gurkha troops in Malaya and noted that all the meningo-encephalitis cases occurred in the course of a few weeks towards the latter part of the epidemic. They suggested that the virus might have acquired an increased neuro-tropism during the epidemic and that separate strains with increased affinity for the C.N.S. might have arisen. Our observations suggest that cases of mumps meningo-encephalitis without parotitis are more or less "dead-end" infections in that patients with meningo-encephalitis *without* parotitis are, as might be expected, less infectious than patients *with* parotitis. We have no

evidence which suggests that patients with meningo-encephalitis give rise to cases of meningo-encephalitis or that meningo-encephalitis cases are caused by a "separate" neurotropic strain. The prevalence of mumps meningo-encephalitis in Northern Ireland in 1958 may have been due to a mumps virus of increased neurotropism, or may simply have been the reflection of a large epidemic of mumps and an available viral diagnostic laboratory whereby infection of the C.N.S. with mumps virus could be differentiated from non-paralytic poliomyelitis and other causes of aseptic meningitis and encephalitis.

Summary

The clinical, laboratory, and epidemiological features of 50 cases of mumps meningo-encephalitis are described. 39 of these occurred during 1958, when there was a mumps epidemic in Northern Ireland. The diagnosis in all cases was confirmed by complement-fixation tests using V (viral) and S (soluble) antigens. The C.S.F. findings in 36 cases are presented. Males were more commonly affected than females, and 84% of the cases occurred in children under 15 years of age.

The principal clinical features were fever, headache, neck rigidity, and vomiting with or without salivary-gland involvement, which occurred in only 54% of the cases. About one-third of the patients showed signs of encephalitis, one of which was of the post-infective type.

The peak incidence of mumps meningo-encephalitis occurred in the late spring and early summer months, and there was no difference in the seasonal incidence of mumps meningo-encephalitis with parotitis and mumps meningo-encephalitis without parotitis. Mumps virus infection appears to have been more readily transmitted by patients with parotitis than by patients without enlarged salivary glands.

A follow-up study of a number of patients was done, and the absence of serious sequelae in this series suggests that a good prognosis may usually be given in mumps meningo-encephalitis.

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The Australian Director-General of Medical Services for the Army, Major-General W. D. REFSHAUGE, is to become Australia's Director-General of Health. The present permanent head of the Department of Health, Dr. A. J. METCALFE, will retire later this year. Major-General Refshaug, who is 47, is a graduate of Melbourne University, and is at present engaged in work for the Department of Defence.

SERUM INSULIN IN A CASE OF SEVERE DIABETES MELLITUS SHOWING REMISSION

BY

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Increasing interest has latterly been shown in cases of severe diabetes showing remission (Goadby, 1943; Harwood, 1957; Phillips, 1957; Peck, Kirtley, and Peck, 1958; Stutman and Hayes, 1959), and some recent correspondence in the *British Medical Journal* has emphasized that clinical remission in the more severe forms of the disease may be commoner than is perhaps realized (Waddell, 1959; Wolff, 1959; Paton, 1959).

Serum insulin studies in a case in which spontaneous remission took place from a state of severe diabetic ketosis are described below. While this case was less severe than some of those reported by the authors above, and even in clinical remission an impairment of glucose tolerance remained, observations on serum insulin and insulin antagonists have not hitherto been reported in this type of patient. In view of current interest in this aspect of diabetes, it seemed worth while to give a detailed account of these studies for the light they may throw on serum insulin in early diabetes.

Case Report

A married professional man, aged 33, attended the out-patient department in May, 1959, with a one-month history of increasing thirst, polyuria, and lassitude, and during this time his weight had decreased from 9 st. 7 lb. to 8 st. 11 lb. (60.3 to 55.8 kg.). Until this period he had been well, without significant earlier illness, nor was there any family history of diabetes. Detailed examination did not reveal any abnormal physical findings, apart from evidence of early dehydration, though his breath smelt strongly of acetone. Intercurrent infection appeared to be absent. The urine then contained over 2% of sugar and gave a strong positive ferric-chloride reaction for acetoacetic acid. The blood-sugar at the time of examination was 352 mg./100 ml. The patient was admitted for stabilization of his diabetes, and after an uneventful period in hospital was discharged on a dose of 20 units of soluble insulin in the morning, 14 units in the evening, and a suitable diet containing 200 g. of carbohydrate.

After severe hypoglycaemia his insulin dosage was reduced to 12 units in the morning and 10 units in the evening and he was instructed to reduce the dosage still further if hypoglycaemia continued. In July, 1959, as a result of increasingly severe hypoglycaemic episodes, he was taken off insulin entirely, and has remained without insulin until the time of writing (January, 1960). During this period he has remained symptom-free, with blood-sugars, taken at an afternoon clinic which he was attending at six-weekly intervals, ranging from 84 to 134 mg./100 ml. His weight has increased to and has remained at 9 st. 4 lb. (59 kg.). An oral glucose-tolerance test, performed in September, 1959, was, however, definitely diabetic in type. Thus, after 50 g. of glucose the blood-sugar rose from a fasting level of 125 mg. to 177 mg./100 ml. at half an hour, and 245 mg. at one hour, falling to 217 mg. at two hours after the glucose. It is clear, therefore, that diabetes in this patient remains quiescent, and that remission is in no sense complete.

Methods

Serum Samples.—Samples of blood were drawn from an antecubital vein into a clean dry syringe. After allowing

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