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VIRUS MENINGO-ENCEPHALITIS IN AUSTRIA

2. Clinical Features, Pathology, and Diagnosis

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SYNOPSIS

This paper reports on the clinical and pathological features as well as the diagnosis of 304 cases of virus meningo-encephalitis hospitalized at the Neurological Clinic, Graz, during the 1953 epidemic in Styria, Austria. Of these cases, 175 were of an aparalytic meningeal form, 50 preparalytic, 27 spinal paralytic, 20 bulbospinal or ascending paralytic, 7 bulbar paralytic, 3 radiculitic or transmyelitic, and 22 encephalitic. The case-fatality rate was 4.6%. The clinical course of the disease—usually diphasic—and the changes in the spinal fluid showed a close similarity to those seen in poliomyelitis, but the paralysis preferentially involved the shoulder-girdle and upper arm.

The post-mortem examination showed a picture of acute encephalitis, with changes in the grey matter particularly. Histological findings revealed extensive involvement of the anterior horns of the spinal cord, the medulla oblongata, and the pons, and especially of the Purkinje's cells of the cerebellum.

In making a diagnosis, the possibility of louping-ill, Russian spring-summer encephalitis, Czech tick encephalitis, and, particularly, poliomyelitis must be taken into account. The author points out that it is impossible to distinguish the virus meningo-encephalitis of this epidemic from poliomyelitis on the basis of clinical and post-mortem findings alone; a differential diagnosis must rest on serological and immunological grounds.

Finally, the symptomatic and supporting treatment given is described.

Clinical Features

In the period from 1 April to 1 December 1953, 304 cases of virus meningo-encephalitis (179 men and 125 women) were admitted to the Neurological Clinic at Graz, Austria. When the clinical picture had fully developed, the following forms were distinguishable:

Meningeal forms (cases without paralysis and without clearly detectable encephalitic symptoms); this group is divided into :

(*a*) aparalytic forms; (*b*) preparalytic forms.

Paralytic forms (all cases with clinically detectable motor symptoms, apart from cases with transitory cranial nerve palsy accompanying predominantly encephalitic symptoms); this group is divided into:

(*a*) spinal paralytic forms;

(*b*) bulbospinal forms and ascending forms of the Landry type;

(*c*) bulbar forms;

(*d*) radiculitic and transverse myelitic forms.

Encephalitic forms (cases with predominantly encephalitic symptoms, often with transitory cranial nerve palsy).

Table I shows the distribution of cases according to the various forms.

TABLE I. FORM OF DISEASE IN 304 CLINICAL CASES OF VIRUS MENINGOENCEPHALITIS IN AUSTRIA

Form of disease	Male cases			Female cases			Total cases		
	number	%	fatal	number	%	fatal	number	%	fatal
Meningeal	128	71.5	1	97	77.6	1	225	74.0	2
aparalytic	101	56.4	1	74	59.2	0	175	57.6	1
preparalytic	27	15.1	0	23	18.4	1	50	16.4	1
Paralytic	42	23.5	8	15	12.0	3	57	18.8	11
spinal paralytic	22	12.3	0	5	4.0	0	27	8.9	0
bulbospinal and ascending	16	8.9	7	4	3.2	2	20	6.6	9
bulbar	2	1.1	0	5	4.0	0	7	2.3	0
radiculitic and transmyelitic	2	1.1	1	1	0.8	1	3	1.0	2
Encephalitic	9	5.0	1	13	10.4	0	22	7.2	1
Total	179		10	125		4	304		14

Aparalytic meningeal forms

The description of the 175 cases in this group (58% of the total) corresponds essentially to that of the initial meningitic stage of those cases which later followed a paralytic or encephalitic course.

The patients were generally admitted to the clinic with headache, dizziness, nausea, vomiting, anorexia, and temperatures ranging from subfebrile to 40°C and over. The neurological symptoms were generally quite minor, including nuchal rigidity, meningism, spine sign, and Kernig's and Brudzinski's signs, although these two were sometimes hardly noticeable. There was no significant correlation between the meningism and the gravity of the clinical picture or the state of the cerebrospinal fluid. The

tendon reflexes were usually uniformly decreased although there was an initial hyper-reflexia in some cases. There was frequently a positive Oppenheim reflex for a few days or until shortly after the first lumbar puncture, but a mild Babinski reflex or fan sign might also be found. We interpreted such transitory pyramidal signs, and the very few instances of urine retention, which always ceased after the first lumbar puncture, as being only the result of a general oedema of the brain and spinal cord. In almost all cases there were distinct signs of disturbed diencephalon functions such as sudden perspiration, vasomotor instability, increased dermographism, slight digital tremor, and disturbances in sleep rhythm. At the height of the fever there was occasional herpes labialis. Apart from a few severe cases, the aparalytic meningeal forms appeared to be much milder than, for example, bacterial meningitis. From the purely clinical symptoms, and without lumbar puncture or examination of the spinal fluid, meningitis would probably not have been thought of had the patients not come from regions where a considerable increase in that disease led general practitioners to pay particular attention to it.

The initial cell counts in the spinal fluid varied from 1,500 per mm^3 in a few cases to an average of 100-200 per mm^3, predominantly lymphocytes. In contrast to poliomyelitis, we only occasionally found initial leucocytosis subsequently altering to lymphocytosis. The meningeal involvement was sometimes quite mild, with initial counts of 7-15 cells per mm^3. As the meningitic stage developed, the behaviour of the cell count was completely non-uniform and non-characteristic. In many cases the count fell to 12-18 cells per mm^3 within 2-3 weeks, and the patients were then generally discharged. More usually, however, the cell count took 4-7 weeks, and often two months and more, to fall to normal. It showed no significant relationship either to the objective neurological findings or to the gravity of the clinical picture and the subjective condition of the patient. In many instances the time required for it to fall to normal seemed also to be independent of the initial count, and in a number of cases with a relatively low pleocytosis it took longer than in others with counts originally much higher.

In the great majority of cases, the protein in the spinal fluid was normal at the beginning of the meningitic phase; although in some cases the first lumbar puncture revealed protein values of 70 mg and over per 100 ml, this was probably partly due to the fact that many patients received treatment some days, or even weeks, after the invasion of the central nervous system had begun.

As with the cell counts, the behaviour of the protein values in the spinal fluid varied from case to case. Where they had originally been normal, either they remained within the normal range, or albumino-cytological dissociation took place, the protein increasing in inverse ratio to the fall in the cell count, as is frequently observed in poliomyelitis. Protein which

had at first increased later reverted to normal, but not necessarily simultaneously with the cell count.

The Pandy protein test and the Nonne-Apelt reaction, as well as the mastic and gold-sol curves, gave the results expected in view of the other spinal fluid findings and showed no special characteristics. In almost all cases the sugar content of the spinal fluid was normal (60-80 mg per 100 ml) or slightly increased.

Spinal fluid samples were taken by routine lumbar puncture. In several cases, cisternal and lumbar punctures were made simultaneously for comparison; as expected, the cisternal gave lower cell counts than the lumbar samples, and this difference was particularly marked when the recovery of the spinal fluid was considerably advanced.

Of the other findings, only the blood sedimentation rate was of particular interest; high rates of about 40-70 mm (Westergreen) were found almost without exception in the acute stage. There was a further rise of 10-30 mm in the first hour during the first two weeks, and in many cases values of over 100 mm were reached in the second hour. As the disease developed the sedimentation rate slowly decreased, following irregularly the reversion of the spinal fluid. This behaviour of the sedimentation rate is quite different from that in poliomyelitis. Another striking feature in the aparalytic forms was the height to which the sedimentation rate rose compared to the mildness of the case.

The blood picture repeatedly showed mild leucocytosis in the initial stage with a slight shift to the left. There was no appreciable abnormality in the erythrocyte picture. In a few cases, small quantities of protein were detected in the urine during the acute stage.

The meningism, fever, and subjective disturbances generally disappeared rapidly, often as soon as the first or second day after the initial lumbar puncture. Disturbances of the vegetative nervous system, however, frequently persisted for a long time and in many cases continued, although to a limited extent, after discharge from hospital.

Preparalytic meningeal forms

This group comprised 50 cases, or about 16% of the total. We have divided the meningitic group into aparalytic and preparalytic forms in order to show the resemblance to the different stages of poliomyelitis; the term " preparalytic " was applied to cases with a clinical picture of transitory (lasting usually one day or a few days at most) but distinct changes in the tendon reflexes and weakening of the muscles. The patients usually complained of severe muscular pain. Displacement of the umbilicus, nuchal flaccidity, or a mild motor weakness in an extremity, but without decrease in the range of mobility, were frequently noted.

The preparalytic cases did not differ from the aparalytic in clinical course or duration. The explanation of the neurological symptoms which

distinguished this group is probably that both the nature and the extent of the attack on the motor ganglion cells in the anterior horn of the spinal cord are so mild, relative to the serious nature of the disease, that no paralytic symptoms develop. Collateral oedema around the motor synapses may also be significant.

Spinal paralytic forms (fig. 1-3)

The term " spinal paralytic " was applied to all cases with clear paralysis in one extremity or more, with or without involvement of the trunk, but without cranial nerve palsy. The 27 patients in this group (9% of the total) included 22 men and 5 women, or one man out of 8 and one woman out of 25.

The neurological symptoms were similar to those in poliomyelitis. In the paralysed limbs the tendon reflexes disappeared, and all stages from mild paresis to complete paralysis were seen, although severe paralysis was more frequent than mild. The patients frequently complained of drawing pains in the muscular regions affected; these pains, often occurring before the onset of paralysis, lasted for an average of 3-6 days, that is, for the duration of the acute febrile stage. In many cases the accompanying meningitis was appreciably milder than was usual in the aparalytic forms. However, there was always pronounced vegetative irritation. In several cases, particularly with female patients, there was a long paralytic stage lasting 7 days or more and the onset and development were frequently so insidious that the initial signs of paralysis could hardly be detected on the first clinical examination and developed fully only after one or two weeks. In some cases, involvement of one extremity only—usually the shoulder and upper arm—spread to a second extremity after several days. In a few cases, more or less normal use of the limbs was recovered within 3-4 weeks, but a period of several months was more general. Atrophy was generally comparatively rapid, particularly in the muscular groups preferentially affected—deltoideus, supraspinatus, infraspinatus, trapezius, pectoralis, triceps, and biceps. Residual paresis and atrophy often persisted for some months, the length of time depending on the severity, but showed a renewed tendency to improve after a further six months to one year. There was often complete recovery in such cases. In the light of our experience, virus meningo-encephalitis appears to give a more favourable prognosis for recovery from paralysis than does poliomyelitis. The spinal fluid took as long to revert to normal in the spinal paralytic cases as it did in the meningeal cases.

It is interesting to note that 15 of the 22 men with spinal paralysis were affected in the shoulder girdle and the upper extremities. Both the arms and the legs were involved in two cases, and isolated paralysis of the legs occurred in five cases only. Of the five women in this group, three were paralysed

in the shoulder and arm region, one in the upper extremities and the trunk, and one in the lower extremities. There were thus 19 cases of paralysis of the upper extremities, two of general paralysis, and six of isolated paralysis of the legs. This preferential involvement of the upper extremities provides a useful distinction from poliomyelitis in which the arms are somewhat less frequently involved than the legs. Still more significant is the fact that of the six cases with isolated paralysis of the legs, four occurred in children under 6 years old. Moreover, two of these children gave negative complement-fixation and neutralization tests with the specific virus. Although there may not have been enough time between the onset of the disease and the blood sampling for antibody to have formed, it is nevertheless possible that these two children were suffering from poliomyelitis and therefore did not really belong to the group under consideration.

There is, as is pointed out by Verlinde et al. (see page 565), a certain serological and immunological relationship between the causative virus of this epidemic and the virus of Russian spring-summer encephalitis (RSSE). There is also a clinical resemblance in the site of the paralysis; Smorodintzev [30] reports that flaccid paralysis of the shoulder girdle muscles is indicative of RSSE, and all our cases of paralysis of the upper extremities showed preferential unilateral or bilateral involvement of the shoulder muscles, distinctly less involvement of the proximal upper arm muscles, and even less or no involvement of the muscles of the forearm and hand.

Bulbospinal and ascending forms

This category includes cases of simultaneous spinal paralysis and cranial nerve palsy and cases of paralysis of the Landry type in which initial paralysis of the extremities ascended over a period of from hours to days and involved the bulbopontine centres.

There were 20 cases in this group (16 male and 4 female), 9 of them fatal (7 male and 2 female). This group therefore represents the most severe form in this epidemic, with a case-fatality rate of 45%. In seven of the nine fatal cases there was a distinct ascending paralysis, while in the other two cases bulbar symptoms set in simultaneously with paralysis of the limbs. As in the previously mentioned group, spinal paralysis preferentially involved the proximal segments of the upper extremities; thus paralysis of one arm occurred in three cases, of both arms in two cases, and of one arm and one leg in two cases. In one case there was flaccid tetraplegia, and only once was the spinal involvement restricted to one leg. The bulbar paralysis frequently involved the facial nerve, although sometimes only transitorily and in one case bilaterally. There was occasional paresis of the eye muscles following involvement of the third or sixth nerve nucleus. At least in the terminal stage of every fatal case, there was

involvement of the glossopharyngeal, vagal, and hypoglossal nerves resulting in involvement of the mechanisms of swallowing, breathing, and circulation which represented the immediate cause of death. Disturbances of the bladder and rectum were always present. Encephalitic symptoms were often particularly distinct: some patients were confused and delirious, but protracted psychotic changes were seen only in cases where the course of the disease was itself protracted and were presumably the consequence of damage to the brain by hypoxaemia.

The case-histories did not indicate that in the bulbospinal and ascending forms the disease had followed a diphasic course, although it frequently did so in the other forms. Indeed, with the exception of one patient who suffered from constant fever and headache for 14 days until ascending paralysis finally developed, the onset was always acute, the paralysis appearing not later than the third day after the first signs of illness. In one case the onset of paralysis was almost apoplectiform, the patient having felt perfectly well until the appearance of the first paralytic symptoms.

The paralytic stage can be divided into two categories, according to duration: in five cases the patients died within 48 hours of the appearance of the first paralytic symptoms; in the other four cases the patients died after 6-8 days of paralysis. It should be stressed that no conclusions on prognosis can be drawn from this difference in duration.

In all these fatal cases there was a pronounced increase in the spinal fluid cell count, which varied between 150 cells and 500 cells per mm^3. In the fulminant cases the maximum temperature was always lower than in cases following a more protracted course with a longer paralytic stage. All these patients except one were treated in a respirator.

None of the 11 surviving patients in this category fully recovered, and they were discharged with varying degrees of residual paralysis.

Bulbar forms

This group includes cases with isolated and protracted cranial nerve palsy, without clear clinical symptoms of encephalitis, and without paresis of the trunk or extremities. Whereas in all the other groups the male patients predominated, the bulbar group consisted of 5 women and 2 men.

In six of the seven cases the facial nerve only was affected, on the left side in five cases and on the right in one. Thus apart from one case where there was paresis of the third, eleventh, and twelfth nerves, only one cranial nerve was involved in patients of this group. The bulbar cases were always comparatively mild as regards the accompanying symptoms and the subjective state of the patient. The paresis itself, however, was rather persistent. In one case facial paresis did not appear until the sixth week; the disease had until then followed a purely meningitic course. The bulbar cases showed the least increase in the spinal fluid cell counts, the initial pleocytosis being, on the average, 15-35 cells per mm^3. The rise in

temperature at the beginning of the illness was often slight and of short duration. All these cases recovered completely.

It should be mentioned that at the time of this epidemic a larger number than usual of cases of facial paresis without changes in the spinal fluid were observed at the Graz Neurological Clinic. We have not included these patients (15 women and 5 men) in the epidemic cases described here, although a number of them came from the same regions as cases of virus meningo-encephalitis. Apart from the fact that when the central nervous system is attacked we regard the existence of a pathological change in the spinal fluid as necessary before we can consider cases to be due to virus meningo-encephalitis, we were for various reasons unable to carry out virological tests of the sera of these 20 cases. It is, however, noteworthy that no other cause of facial paralysis, such as aural or dental disease or brain tumours, could be detected in these cases. Consequently we cannot definitely exclude the possibility that some of them were abortive bulbar forms of virus meningo-encephalitis. In addition, many authors consider a complete absence of spinal fluid changes to be possible in the mono-symptomatic bulbopontine form of poliomyelitis, particularly since in that form of disease the cell count is often quite close to normal—as it was in some of our patients with the bulbar form.

Radiculitic and transmyelitic forms

This group includes 2 cases with polyradiculitic symptoms, one of them with a transverse syndrome involving the lower lumbar region of the spinal cord. In one polyradiculitic case the paralysis ascended from the legs, through the trunk muscles, up to the arms. This patient died—without involvement of the cranial nerves—following paralysis of the peripheral respiratory muscles and the diaphragm. The transverse myelitic case also died.

Whereas the existence of radiculitic forms in poliomyelitis is usually denied or at least contested, such forms have been described in RSSE by Panov [22] and in Czech tick encephalitis by Hloucal.[10-12]

Encephalitic forms

We have included in this group all the cases with clinically predominating encephalitic symptoms and with occasional transitory cranial nerve palsy but without spinal paralysis. There were 22 cases in all (9 men and 13 women), amounting to about 7% of the total.

In most cases mental disturbances of a more or less pronounced psychotic type developed at the onset or within the first week of the meningitic stage, but in a few cases they developed later. Fever frequently developed suddenly at a time when the patient felt relatively well, the temperature rising to over 40°C. This was accompanied by mental confusion, disorientation, occasional paranoid attitude, severe excitation, and

anxiety neurosis. One patient made a frustrated attempt at suicide. The mental disturbances were often so serious that the patient had to be transferred to the mental department. In all cases there was very pronounced drowsiness and temporary apathy. In addition, we often noted transitory paresis of the eye muscles, difficulty in swallowing, blurred speech, and temporary facial paralysis. The muscle tonus was often increased, a rigor-like state sometimes developing. A choreiform disturbance of movement occurred occasionally and digital tremor frequently. Slight cerebellar ataxia was very occasionally seen, but nystagmus, hyper-reflexia, and pyramidal signs were frequent. One male patient died with a clinical picture of very severe encephalitis.

The course of the disease in a 31-year-old woman in the fourth month of pregnancy was particularly striking. She was admitted to the clinic in status epilepticus and had 200 fits practically without interruption within three days. Cortical paresis of the left arm also developed, and the cell count was very high. Nevertheless, she recovered completely within eight weeks and gave birth at term to a normal and healthy child.

The urine retention frequently observed in the encephalitic cases often lasted for a relatively long time, sometimes persisting beyond the acute stage into the convalescent period. Apart from the one fatal case mentioned, the encephalitic patients recovered without sequelae.

General survey of cases

Of the 304 cases in all, 225 (74%) were meningeal, 57 (19%) were paralytic, and 22 (7%) were encephalitic; the more serious forms (paralytic and encephalitic) thus amounted to 26% of the total. With 14 deaths, the case-fatality rate in this epidemic was 4.6%—lower than the average for poliomyelitis. Nine of these deaths resulted from the bulbospinal or ascending paralytic form, two from the radiculitic or transmyelitic form, one from the encephalitic form, and two from the purely meningeal form. One of the two fatal cases of the meningeal form occurred in an 80-year-old man who died from pneumonia after the acute phase; in the other case there was concomitant tetanus, which was probably the direct cause of death, although, in view of the long incubation period and the relatively mild course of the disease, it would hardly have been fatal without the accompanying virus infection.

Premonitory symptoms, initial stage, and latent stage

Case-histories showed that in most cases the disease followed a diphasic course, as with poliomyelitis. The first phase, which was not always clearly marked, lasted 2-8 days and was usually accompanied by a slight to moderate increase in temperature, and by general tiredness, anorexia, and pains in the head and limbs similar to those encountered in influenza. This diphasic course was particularly frequent in the purely meningeal forms, in which

many cases also showed gastro-intestinal symptoms with vomiting, nausea, diarrhoea, or constipation in the first phase. As a result of these symptoms patients were repeatedly referred to the infectious diseases department with a diagnosis of suspected typhoid or paratyphoid when the temperature rose again at the onset of the meningeal stage proper, and the meningitis was only detected on examination of the spinal fluid. The symptoms of the first phase were less characteristic at the height of the epidemic: a preliminary anginoid condition was frequently reported, and in many cases this was still present at the time of admission.

This first phase was generally separated from the second, in which invasion of the central nervous system occurred, by a latent stage of from three days to three weeks, but of an average duration of 8-12 days. During this period patients either showed no symptoms or complained of tiredness, malaise, and occasionally pains in the head and muscles. However, in some cases, there was direct transition from the first to the second phase with no latent stage.

The second phase, which began with symptoms similar to but much more severe than those of the minor illness, has already been described in the section dealing with the meningeal forms. Although most patients were admitted to the clinic only at the height of the acute stage of the second phase, we were able to follow its full development in some cases admitted during the first phase. All cases in the first phase which we were able to observe showed normal cell counts and protein in the spinal fluid, pleocytosis only developing with the rise in temperature at the onset of the second phase.

During this epidemic we frequently observed cases showing symptoms of influenza alone, with normal cerebrospinal fluid and no invasion of the central nervous system. In some of these it was possible to demonstrate antibody in the serum by the complement-fixation test with the virus of the meningo-encephalitis epidemic. We therefore regard such cases as abortive meningo-encephalitis ; there is, moreover, epidemiological support for such a view. It is well known that in poliomyelitis contact with the virus may result in an inapparent, symptomless infection or in the disease becoming manifest and either progressing no further than the minor illness or developing to the meningitic, preparalytic, or paralytic stage. It may be supposed that inapparent and abortive infections also exist in virus meningo-encephalitis, the virus not becoming solely neurotropic but remaining pantotropic. This corresponds to Pette's view.[23] The severity of the disease is probably influenced partly by the ability of the body to develop adequate antibody in a sufficiently short time and partly by a variety of predisposing and precipitating factors.

We have not included these abortive cases with a positive complement-fixation test among the 304 epidemic cases, which are restricted to those with symptoms referable to the central nervous system.

FIG. 1. RESIDUAL PARALYSIS OF LEFT ARM, PECTORALIS, AND SHOULDER OF 32-YEAR-OLD WOMAN

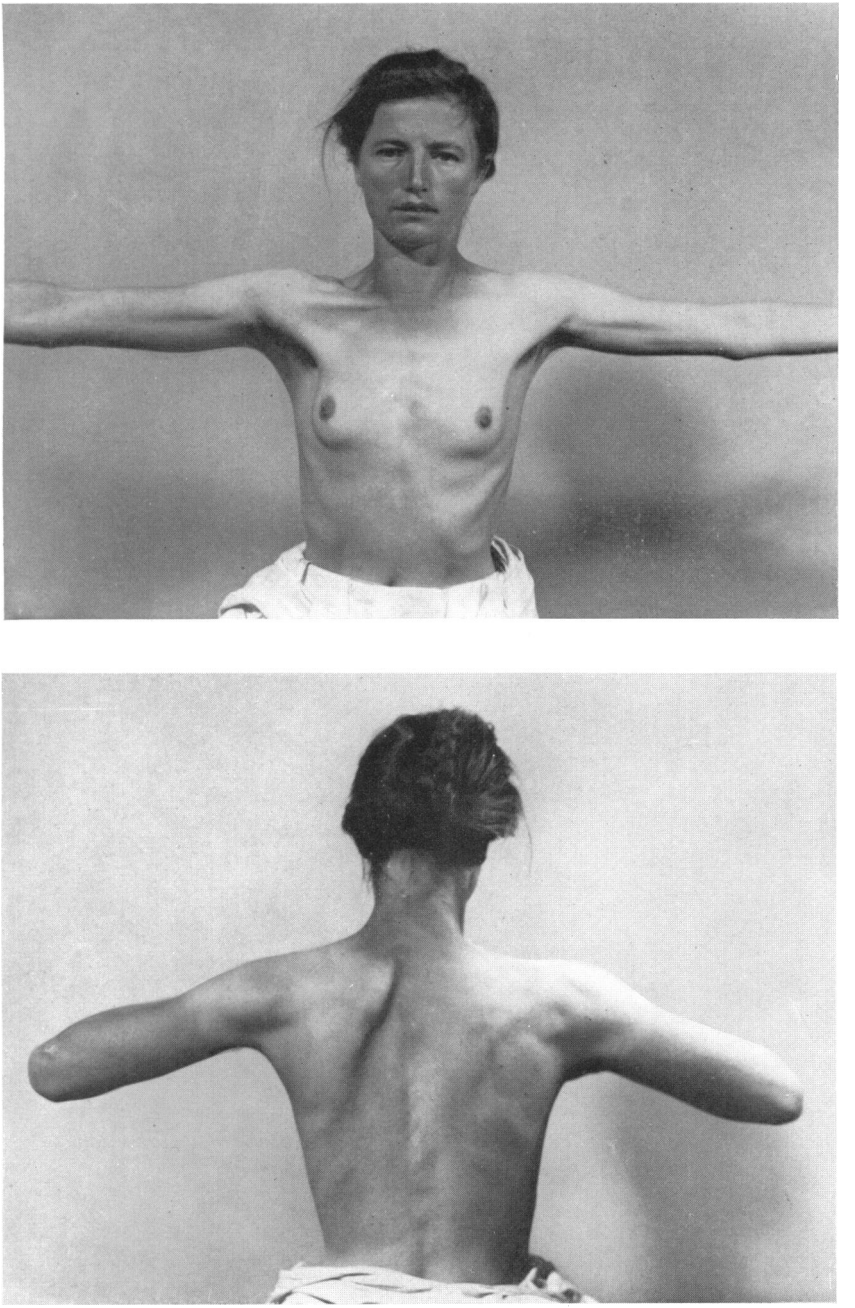


FIG. 2. PARALYSIS OF SHOULDER GIRDLE AND BOTH UPPER ARMS OF 58-YEAR-OLD MAN—FRONT

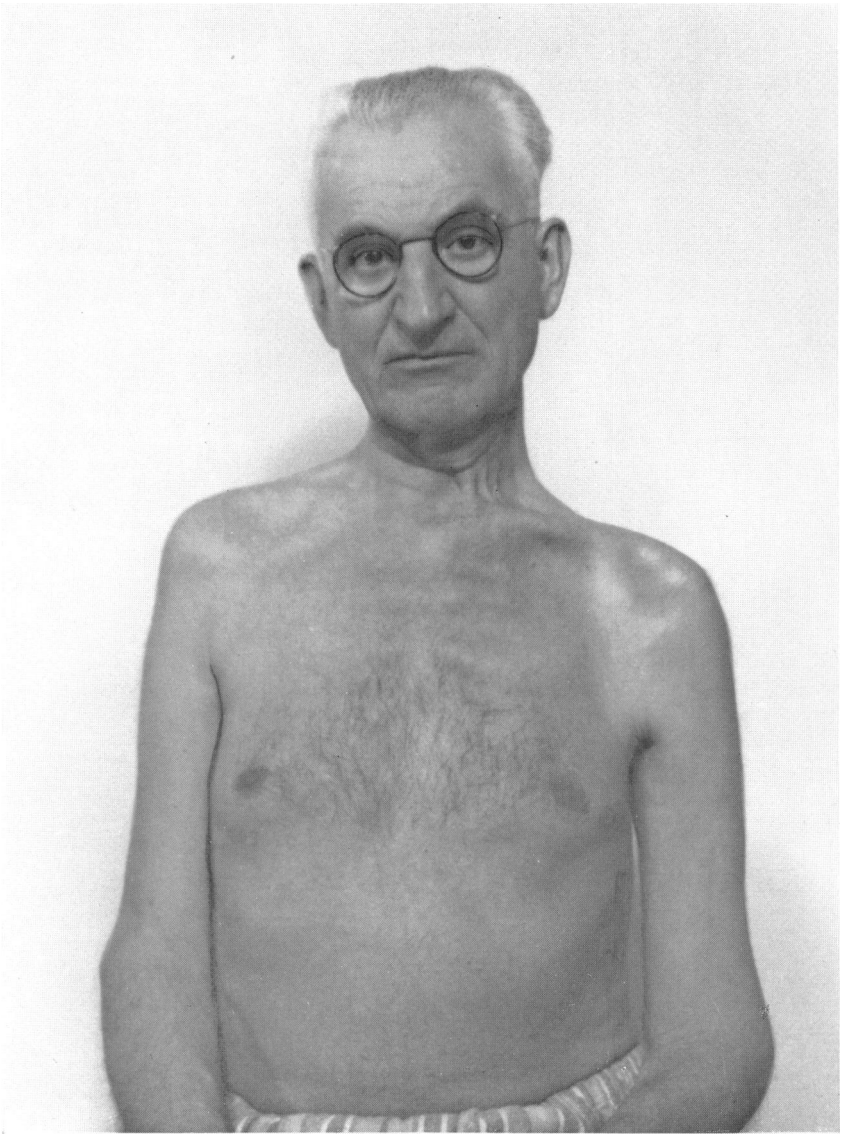


FIG. 2. PARALYSIS OF SHOULDER GIRDLE AND BOTH UPPER ARMS OF 58-YEAR-OLD MAN—BACK

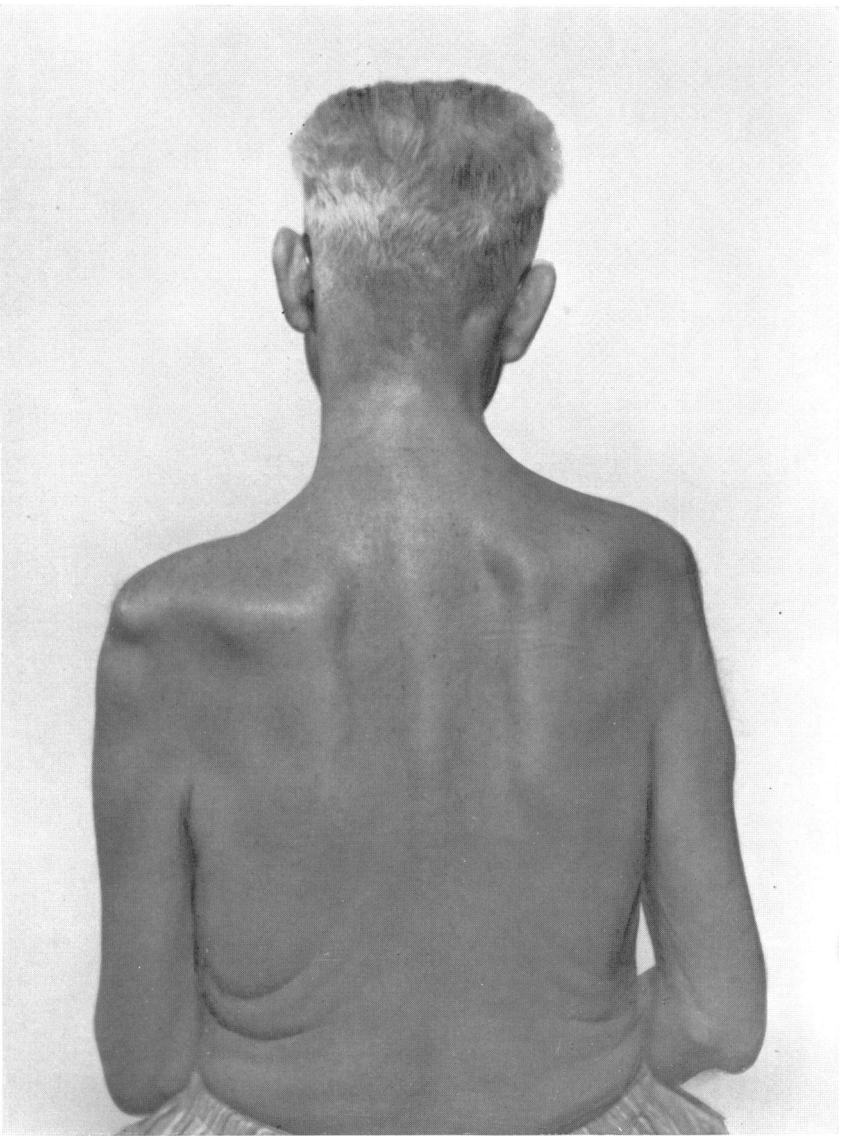


FIG. 3. RESIDUAL PARALYSIS OF LEFT ARM AND SHOULDER OF 28-YEAR-OLD WOMAN

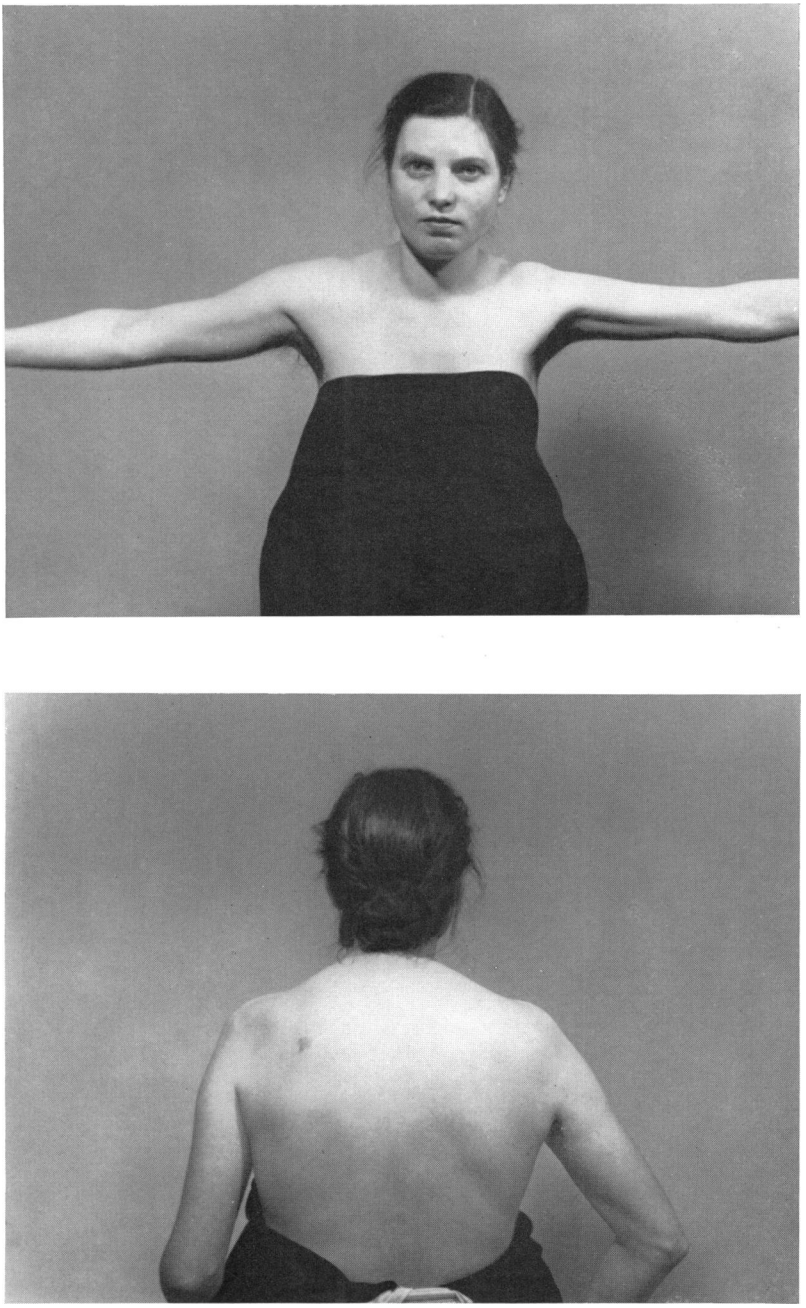
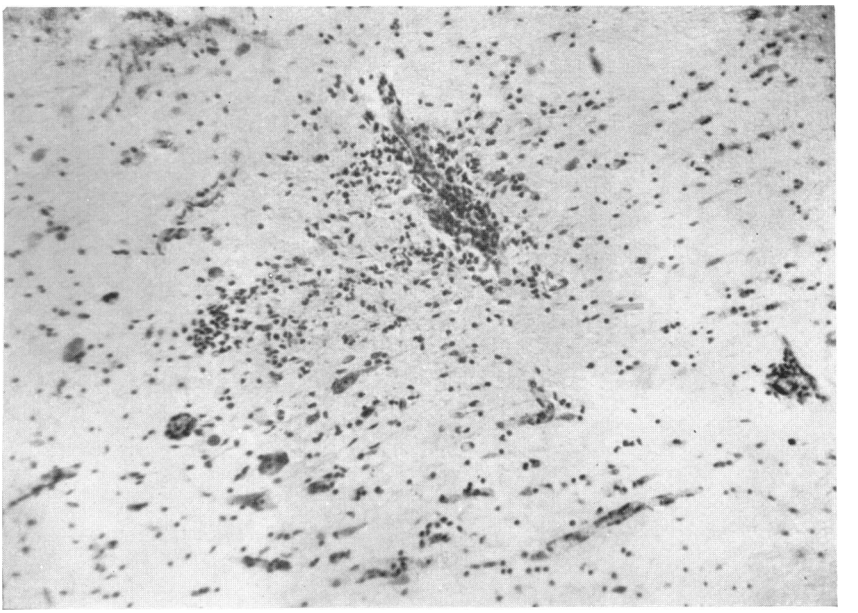
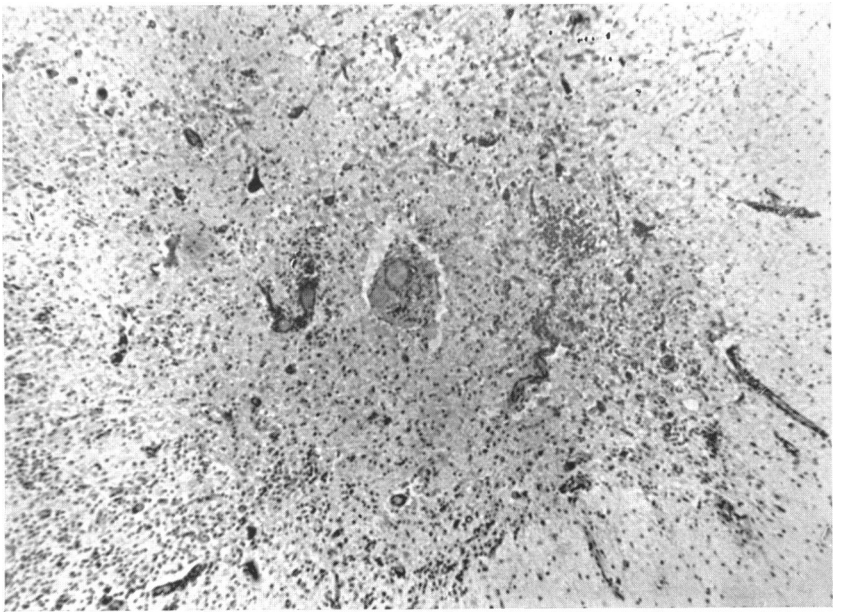


FIG. 4. CERVICAL SPINAL CORD OF HUMAN CASE. 1



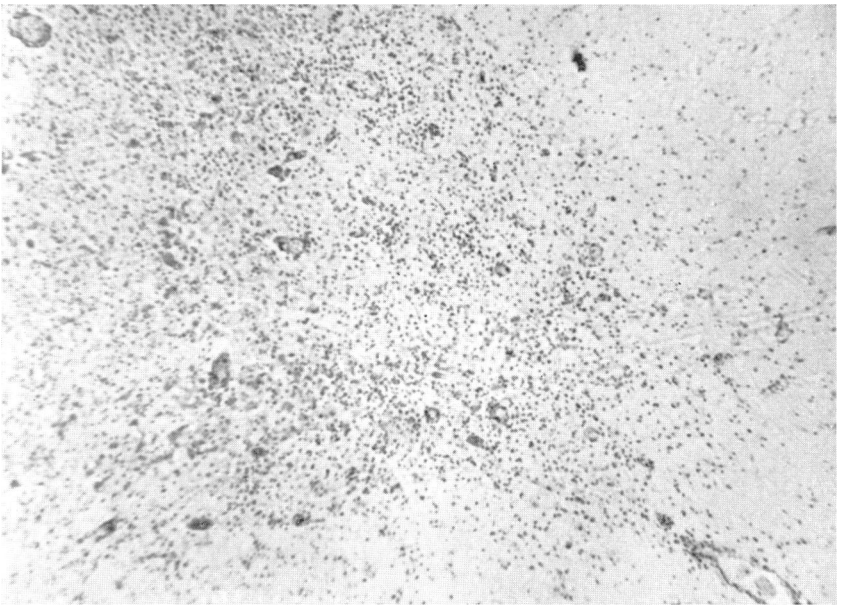
Inflammatory reaction in the anterior horn, perivascular infiltration, and onset of motoneuron destruction (Nissl stain ; magnification × 75)

FIG. 5. CERVICAL SPINAL CORD OF HUMAN CASE. 2



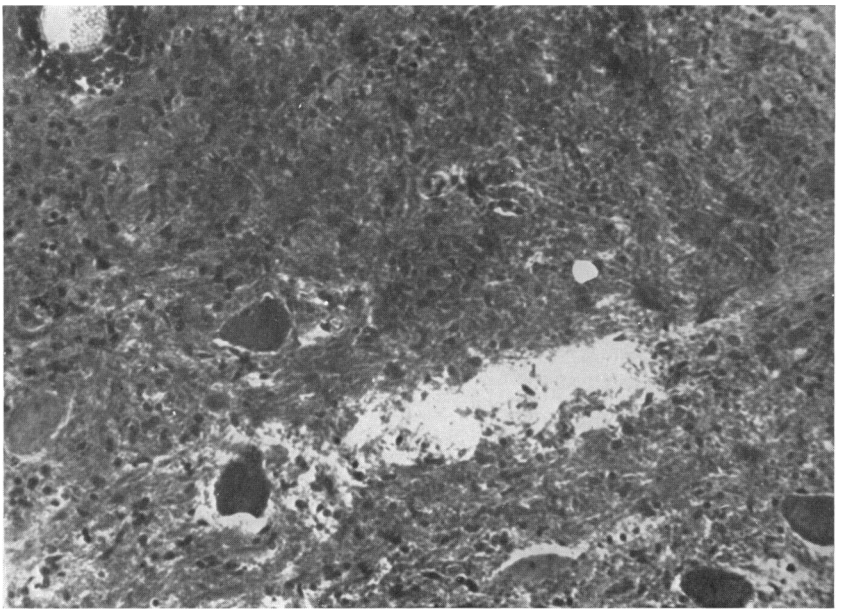
Extensive vascular reaction, with the majority of cells affected (Nissl stain; magnification × 40)

FIG. 6. CERVICAL SPINAL CORD OF HUMAN CASE. 3



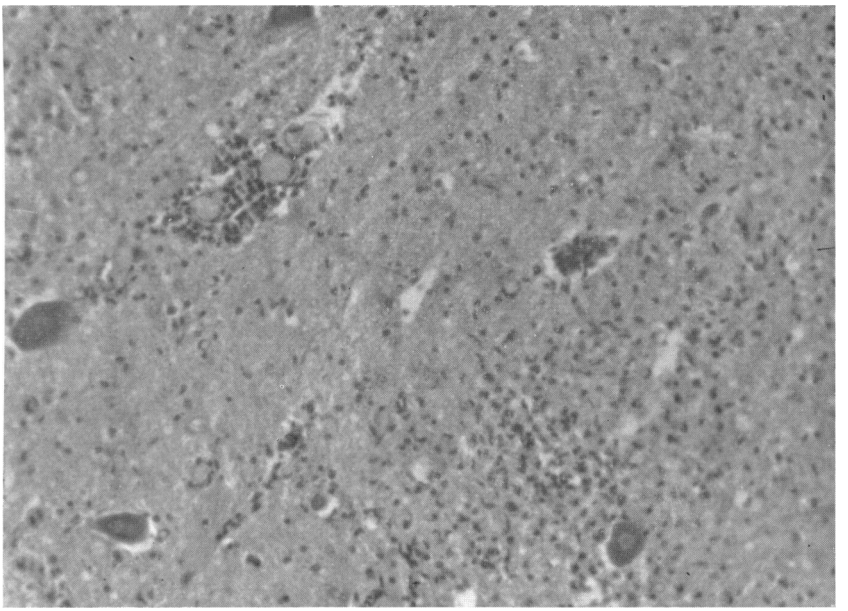
Later stage than fig. 5, with severe destruction of motoneurons in the anterior horn (Nissl stain; magnification × 40)

FIG. 7. CERVICAL SPINAL CORD OF HUMAN CASE. 4



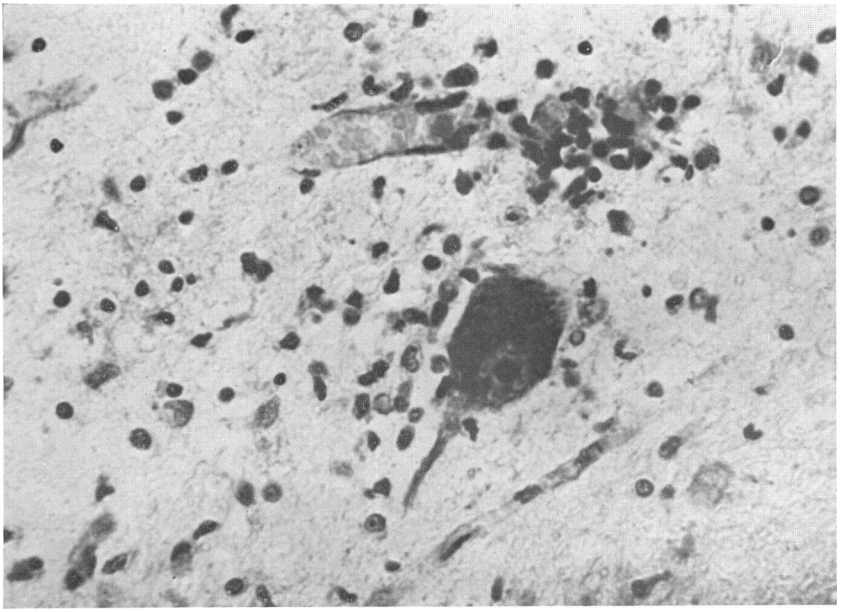
Perivascular infiltration and degeneration of anterior horn cells (haematoxylin-eosin stain; magnification × 180)

FIG. 8. CERVICAL SPINAL CORD OF HUMAN CASE. 5



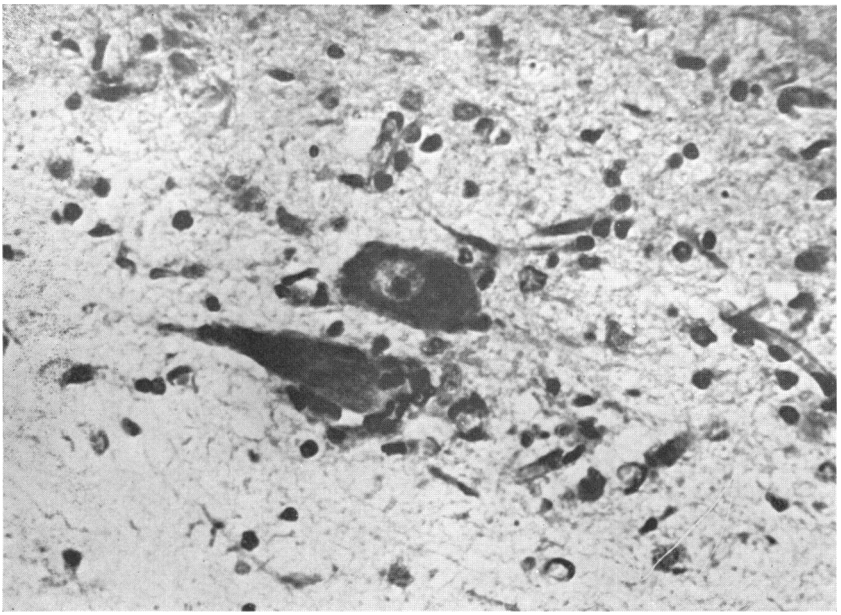
Inflammatory reaction, chromatolysis, and onset of neuronophagia (haematoxylin-eosin stain; magnification × 150)

FIG. 9. CERVICAL SPINAL CORD OF HUMAN CASE. 6



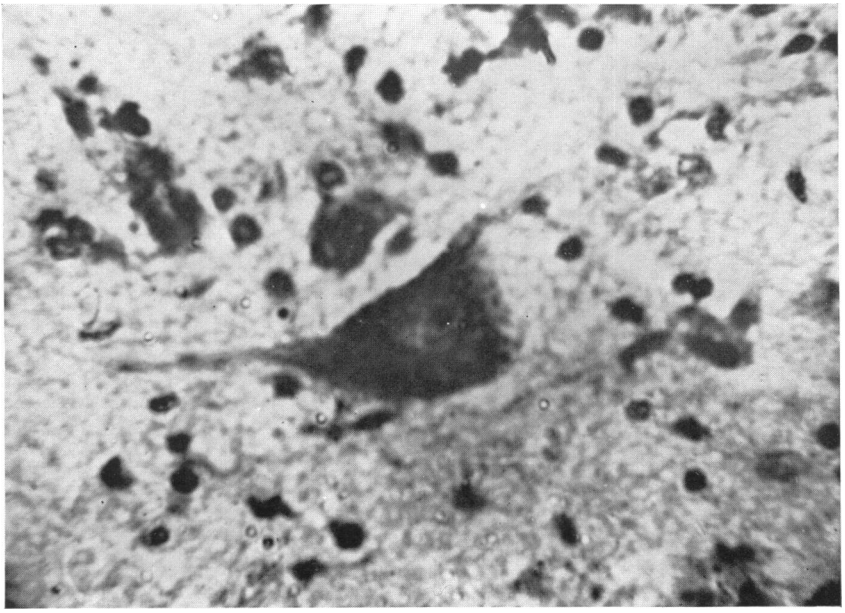
Infected anterior horn cell, dissolution of Nissl bodies, and leucocytic infiltration from neighbouring vessel (Nissl stain; magnification × 300)

FIG. 10. CERVICAL SPINAL CORD OF HUMAN CASE. 7



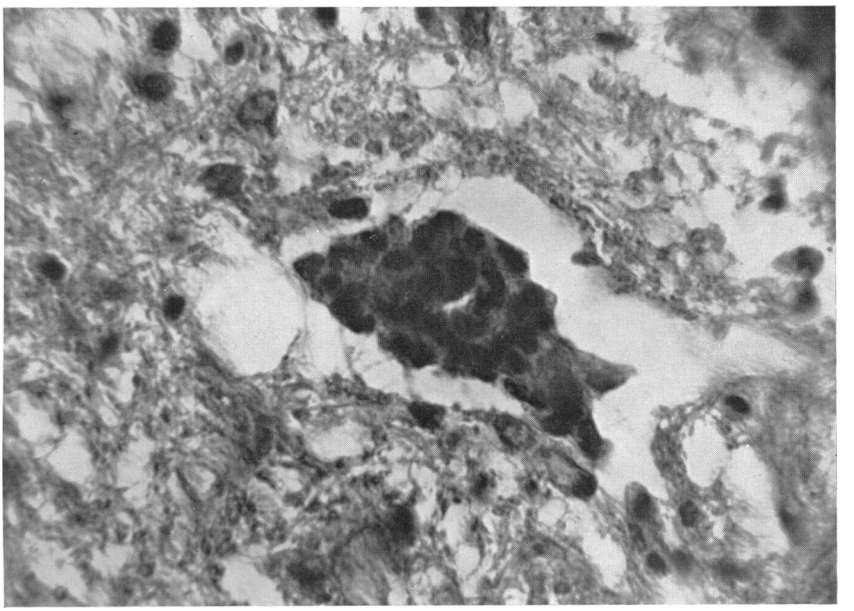
Top: Chromatolytic anterior horn cell with intact nucleus and eccentric nucleolus
Bottom: Shrunken hyperchromatic anterior horn cell; onset of phagocytosis (Nissl stain; magnification × 300)

FIG. 11. CERVICAL SPINAL CORD OF HUMAN CASE. 8



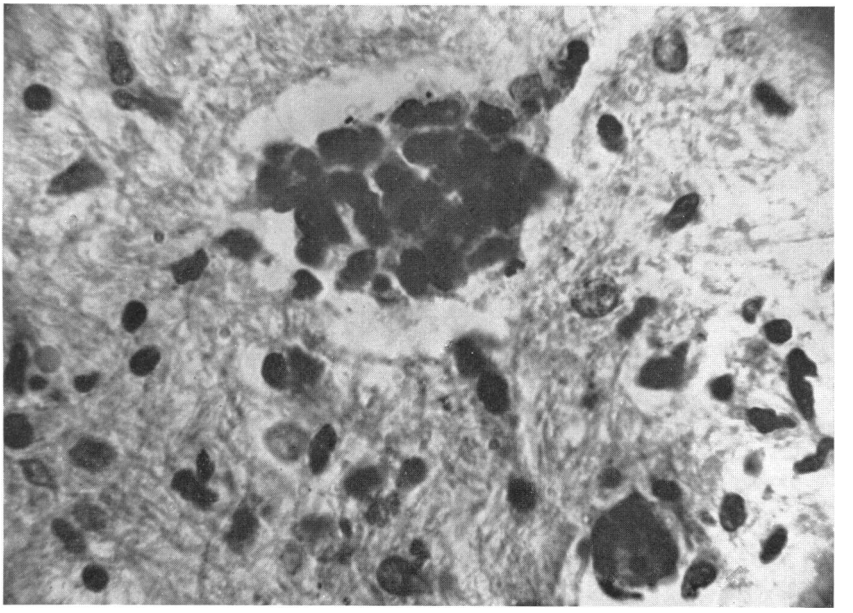
Severely damaged anterior horn cell, with disintegrating nucleus (Nissl stain; magnification × 450)

FIG. 12. LUMBAR SPINAL CORD OF HUMAN CASE. 1



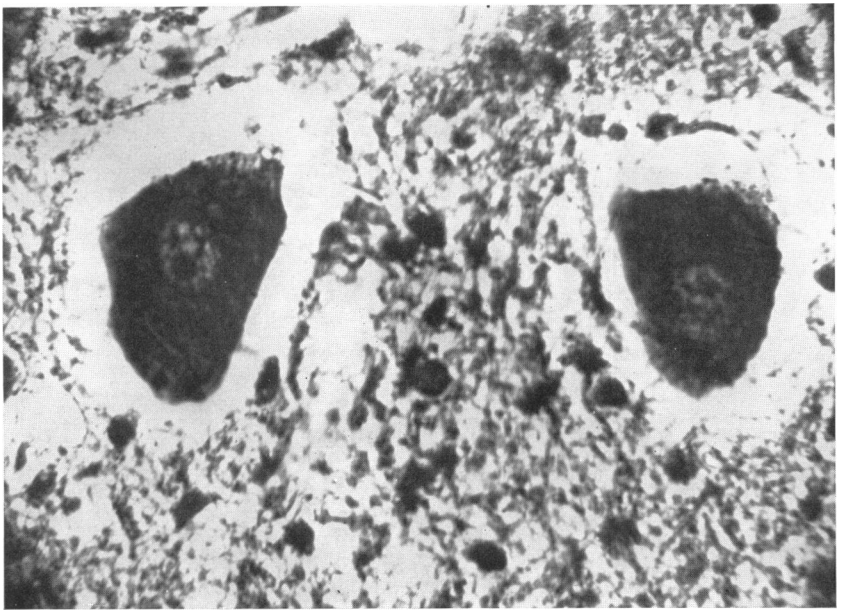
Active neuronophagia of necrotic anterior horn cell with collateral oedema (haematoxylin-eosin stain; magnification × 450)

FIG. 13. LUMBAR SPINAL CORD OF HUMAN CASE. 2



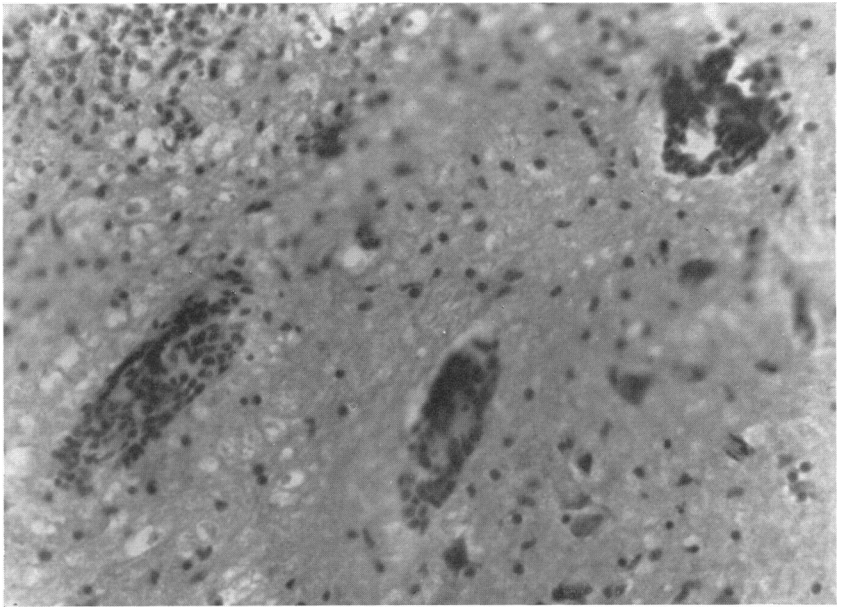
Complete neuronophagia of anterior horn cell, with macrophages and glial cells and collateral oedema (Nissl stain; magnification × 450)

FIG. 14. LUMBAR SPINAL CORD OF HUMAN CASE. 3



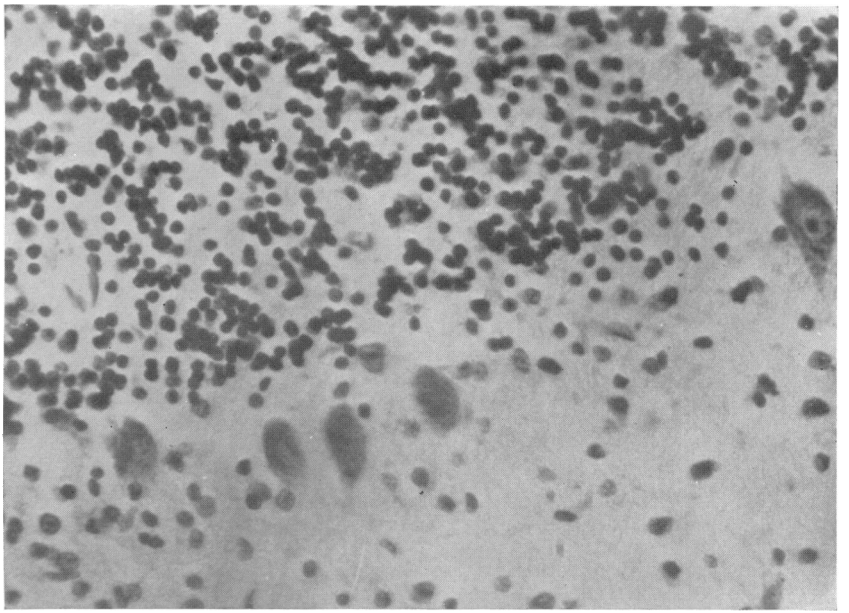
Cytolysis of anterior horn cells (haematoxylin-eosin stain; magnification × 450)
Left: Almost intact nucleus Right: Disintegrated nucleus

FIG. 15. MEDULLA OBLONGATA OF HUMAN CASE



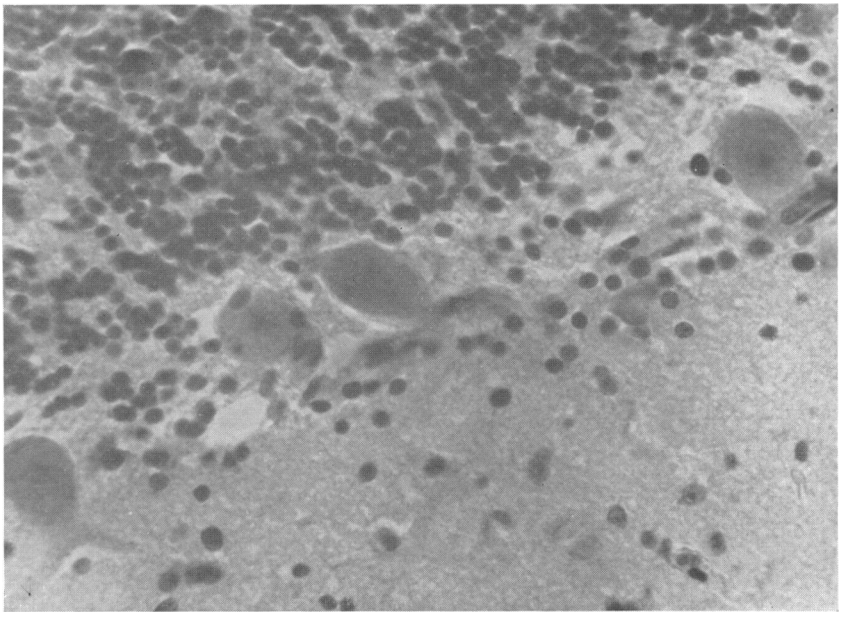
Perivascular lymphocytic infiltration (haematoxylin-eosin stain; magnification × 180)

FIG. 16. PURKINJE LAYER OF CEREBELLUM OF HUMAN CASE. 1



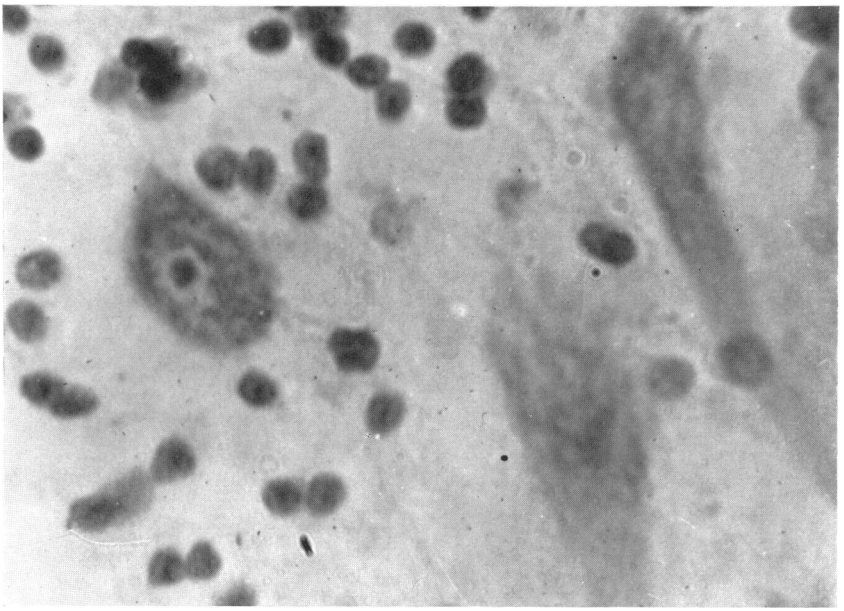
One intact Purkinje's cell (right) and complete necrosis of cells (left); no alteration in the granular layer (Nissl stain; magnification × 250)

FIG. 17. PURKINJE LAYER OF CEREBELLUM OF HUMAN CASE. 2



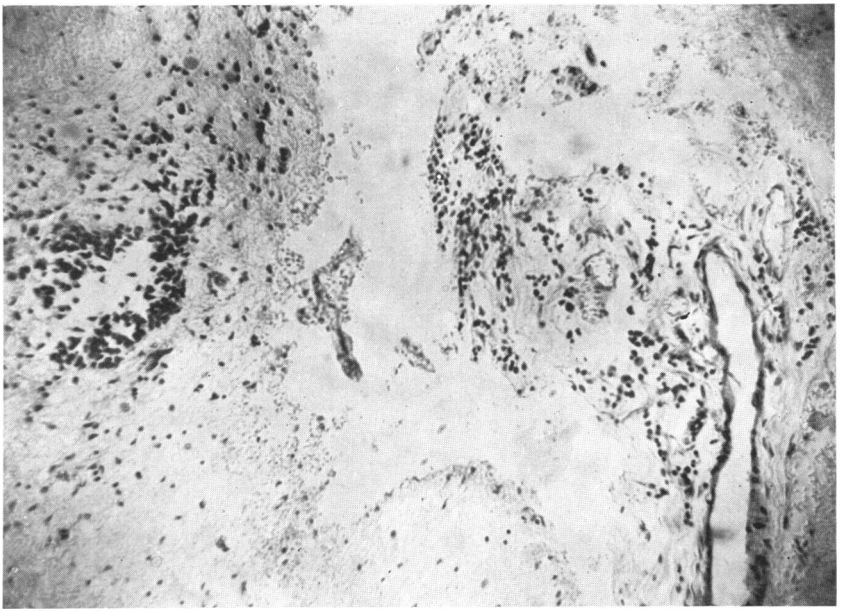
Shadow cells and empty spaces (Nissl stain; magnification × 300)

FIG. 18. PURKINJE LAYER OF CEREBELLUM OF HUMAN CASE. 3



Different stages of necrosis of Purkinje's cells, with mild glial reaction (Nissl stain; magnification × 750)

FIG. 19. CERVICAL SPINAL CORD OF HUMAN CASE. 9



Inflammatory meningeal reaction in the pia mater (Nissl stain; magnification × 75)

Pathology

Post-mortem examination [a] reveals a picture of acute encephalitis, with changes in the grey matter particularly. The dura mater is tense and the brain oedematous and hyperaemic. The meningeal vessels over the hemispheres are congested. There is frequently a distinct swelling of the pons, medulla oblongata, and cervical region of the spinal cord. Part of the spinal cord acquires a soft consistency with the result that the medullary matter flows out at the cut surface. The spinal grey matter is sunken and indistinct of outline. The cut surfaces are often reddish, and small punctate haemorrhages are visible. The extent of the changes varies from case to case.

The histological findings described below were observed by ourselves, using our own preparations of brain matter. There are pronounced changes, with infiltration and ganglion cell damage, in the region of the spinal cord, medulla oblongata, pons, mesencephalon, diencephalon, and cortex, particularly in the anterior central region of the latter. The pathological process is particularly pronounced in the cervical medulla, where the anterior horns are severely affected. The general picture is dominated by extensive vascular reactions, foci of inflamation, perivascular cuffing, and degenerative changes in the ganglion cells, consisting of chromatolysis, fragmentation, pyknosis, and complete destruction with neuronophagia (fig. 4-11). The findings are similar in the lumbar region of the spinal cord, although occasionally somewhat less pronounced, with the Nissl bodies in the ganglion cells in the course of disintegration, the nucleolus eccentric, the cells staining more deeply than normal, the nucleus disintegrating, and the cell body distended or shrunken. The necrotic cell shows collateral oedema and there is leucocytic and lymphocytic infiltration. Finally, macrophages and microphages accumulate, and microglial proliferation follows complete neuronophagia (fig. 12-14). Similar cell necrosis is found in the posterior horns but to a considerably lesser extent. Severe neuron damage can be seen in the regions of the medulla oblongata and in the basal cranial nerve nuclei in the pons. In the white matter, the gliomesodermal reaction is often slight, but in the more heavily damaged areas of the grey matter there is extensive perivascular cuffing, infiltration of leucocytes and lymphocytes (fig. 15) with glial elements, and the formation of microglial nodules.

The Purkinje layer in the cerebellum is particularly severely affected; frequently, no intact Purkinje's cells can be seen in the microscope field and there is a picture of complete cell destruction, although some indistinct

[a] Post-mortem examinations were carried out at the Institute of Morbid Anatomy, Graz University—Director, Professor T. Konschegg.

shadow cells can occasionally be observed (fig. 16-18). The granular layer of the cerebellum remains unchanged. Less pronounced changes also occur in the cerebellar nuclei. Infiltration and rarefaction of cells are also noted in the mesencephalon and diencephalon. Changes in the cerebral cortex are almost invariably restricted to the motor area, with degeneration and necrosis of the pyramidal cells and lymphocytic accumulation and glial proliferation near the surface. There is dense infiltration in the leptomeninges over the brain and spinal cord, leading in many places to swelling of the pia mater and to formation of glial nodules in the underlying nervous tissue (fig. 19).

Involvement of the cerebellum is characteristic of post-mortem findings in louping-ill [15, 27] and RSSE; [16, 29, 32] this provides another analogy between the virus meningo-encephalitis in this epidemic and these two closely related arthropod-borne diseases. However, we now know that the poliomyelitis virus also attacks the cerebellum, although the cerebellar nuclei [14] are more affected than the Purkinje layer.[17, 24] Baker & Cornwell [1] examined the cerebellum in 75 fatal cases of bulbospinal poliomyelitis and in over 75% of them found inflammatory changes in the nerve cells, particularly the ganglion cells in the nucleus dentatus and the Purkinje's cells of the vermis. Nevertheless, in poliomyelitis the damage to the Purkinje's cells of the cerebellum is appreciably less both in extent and in severity than in this virus meningo-encephalitis. However, this difference is not absolutely characteristic and cannot be used as a criterion for a differential diagnosis after death. If account is also taken of the fact that the extent of the changes varies considerably from case to case, it may be said that in practice the post-mortem and neuro-histological findings cannot be distinguished with certainty from those of poliomyelitis.

Differential Diagnosis

Although certain clinical and post-mortem characteristics observed in the course of an epidemic of virus meningo-encephalitis give some indication of the causative agent, a specific diagnosis can in fact only be made on serological and immunological grounds. There are two different ways of approach: the isolation of the virus early in the course of the disease or from brain and spinal cord material taken from fatal cases, and demonstration of antibodies by the complement-fixation or neutralization test with the specific virus later in the disease.

Virological investigations were carried out on patients in the 1953 epidemic by Verlinde et al. (see page 565) and by Vesenjak et al. (see page 513). In August 1953, Verlinde et al. succeeded for the first time in isolating a virus from a sample of brain matter taken from a fatal bulbospinal case; this virus was of a new immunological type of the arthropod-

borne group and was shown to be serologically closer to the causative agent of RSSE than to that of louping-ill. Later, we also succeeded in isolating the virus from other cases by intracerebral inoculation of mice. Whereas, in demonstrating antibody, Verlinde et al. used an antigen prepared from a virus demonstrated from cases in the Austrian epidemic, Vesenjak et al. used a virus isolated from a case in the Slovenian epidemic; this proved identical to our virus.

Of the 304 cases in the Austrian epidemic, 75 (25%) were investigated virologically. A virus was isolated from the brain and spinal cord of three of the four fatal cases in this group, and blood from the remaining 71 patients, suffering from all forms of the disease, was examined for complement-fixing and neutralizing antibodies. In 54 cases the serological and immunological tests were positive, and in one group of cases serum samples were taken at various intervals so that the rise and fall in the complement-fixation titre could be followed. In five cases on which the complement-fixation test only was done the titres were such that the test was regarded as doubtful. In 12 cases the results were negative in all tests carried out; however, in some of these the interval between onset of the disease and blood sampling may have been too short for the formation of antibody, while in others it may have been so long that complement-fixing antibodies would no longer be demonstrable. Bearing this in mind and taking into account the three fatal cases from which virus was isolated, 57 of the 75 cases were positive, five were doubtful positive, seven might have been positive if the blood sample had been taken at a different time, and only six were definitely negative. A large number of sera from patients, the clinical diagnosis of whom did not suggest that they were suffering from virus meningo-encephalitis, were negative in all the tests.

The results of our investigations agreed well with those of Verlinde et al. and Vesenjak et al. (see pages 513 and 565). The latter also examined some of the sera for lymphocytic choriomeningitis and Q fever, but with negative results. Verlinde et al. carried out complement-fixation tests with several sera against the RSSE antigen with mainly positive results, although with distinctly lower titres. This positivity is readily understandable in view of the relation of the two viruses within the arthropod-borne group.

The virological results thus provided generally satisfactory confirmation of the clinical diagnosis. Of the cases investigated, only 8% were definitely negative and 76% were definitely positive. Clinically, therefore, we are justified in concluding that the large majority of the 304 cases were cases of virus meningo-encephalitis involving the central nervous system. It is possible that some of the negative cases may have been cases of different diseases, particularly poliomyelitis. This view is supported by the fact that the negative cases were on the average considerably younger than the positive—some were children—and that most of the paretic cases among them were affected in the legs.

As we have already said, a differential diagnosis is very difficult to make on purely clinical grounds, and is practically impossible in certain cases. However, on the basis of the large number of patients studied, we may draw attention to certain points of difference from and similarity to other virus infections which follow a similar course. With their shorter and benign course, lymphocytic choriomeningitis and Coxsackie meningitis do not affect the differential diagnosis, but louping-ill, RSSE, and Czech tick encephalitis—all arthropod-borne encephalitides—must be considered, as must poliomyelitis.[8]

In western countries louping-ill has so far given rise to no human epidemics, the disease in man being restricted to sporadic cases. The course of the disease is usually diphasic,[3, 25, 26] but there are no severe paralytic symptoms. Sheep are considered the primary reservoir of the virus, and the disease is unlikely to occur where there is no sheep-farming. However, Russian workers [27, 28] have reported severe and even fatal cases in Byelorussia, although it is not yet clear whether a different virus, possibly that of RSSE, is involved. The post-mortem findings in the Byelorussian cases revealed, as in the Austrian epidemic, considerable destruction of the cerebellar neurons.

With its meningitic, encephalitic, spinal paralytic, and radiculitic and transverse myelitic forms, RSSE greatly resembles the virus meningoencephalitis of the Austrian epidemic: in both the paralysis primarily affects the shoulder girdle and upper extremities. However, the case-fatality rate in RSSE seems to be appreciably higher and the meningeal cases do not predominate; the post-mortem findings are similar. RSSE has been exhaustively described by Smorodintsev,[31] Margulis et al.,[21] and other Russian authors, and has been studied virologically by Casals & Olitsky.[2]

Czech tick encephalitis was first observed in Bohemia and Moravia in 1948 by Krejci [18-20] and Hloucal.[10-12] The course of the disease and its various forms show a great similarity to RSSE, but the case-fatality rate is appreciably lower than that in either RSSE or the virus meningoencephalitis described here. It is interesting to note that in Czech tick encephalitis and in RSSE the encephalitic aspect is usually more pronounced than it was in the Austrian epidemic. Virological investigations of Czech tick encephalitis have been carried out by Gallia, Rampas & Hollender [6] and by Edward.[4]

It is with respect to poliomyelitis that the differential diagnosis is of particular importance, especially in Central Europe, where poliomyelitis has repeatedly given rise to widespread epidemics. It is impossible in individual cases to differentiate the two diseases from clinical and post-mortem findings alone, but the following characteristics, derived from analysis of our clinical data, may help in making a differential diagnosis during an epidemic. An initial feverish episode—Fanconi's [5] " spezifische Vorkrankheit " (minor illness)—is observed even more frequently in virus

meningo-encephalitis than in poliomyelitis, and the latent period between the first and second phases is generally longer, varying from three days to three weeks. Of our cases under clinical observation, 74% were of the purely meningeal form as against an average of about 50% in poliomyelitis. The course of virus meningo-encephalitis is thus milder, with a preponderance of non-paralytic forms. On the other hand, we observed predominantly encephalitic symptoms in 7% of our cases, and these are relatively rare in poliomyelitis. We also observed a few radiculitic or transverse myelitic cases; these are also seen in Czech tick encephalitis and RSSE, but it is uncertain whether they exist in poliomyelitis. A particularly marked difference from the clinical picture of poliomyelitis is in the site of the paralysis; in the majority of virus meningo-encephalitis cases the paralysis involved the shoulder girdle and the proximal segments of the upper extremities, whereas in poliomyelitis the legs and pelvic muscles tend to be preferentially affected. Another small difference from poliomyelitis is that it is not uncommon for the paralytic stage to last a week or more in virus meningo-encephalitis. We feel, however, that so far as recovery from paralysis is concerned the prognosis is more favourable in virus meningo-encephalitis. The case-fatality rate—4.6% in our clinical cases—is somewhat lower than in poliomyelitis, in which it varies between 6% and 8%. In our cases spinal fluid cell counts of 350 cells to 1,500 cells per mm^3 and over were not uncommon, initial leucocytosis in the spinal fluid was relatively rare, and the cell count took an average of four to seven weeks to fall to normal. In poliomyelitis, cell counts above 350 per mm^3 are extremely rare, there is almost always an initial leucocytosis, and the cell count takes an average of only three to four weeks to fall to normal. Pyramidal signs, retention of urine, and herpes labialis were occasionally seen in our cases, but occur very rarely in poliomyelitis. The sedimentation rate in our cases was almost always greatly increased, in striking contrast to poliomyelitis.

The problems involved in the clinical differential diagnosis of inflammatory diseases of the central nervous system have recently been considered by Hoff.[13] It would exceed the scope of this article to study in detail all the problems arising from considering the classification of the viral meningo-encephalitides from the pathogenetic, clinical and immunological, serological, or epidemiological aspects. The author has already done so for this epidemic at the symposium of the Croatian Neurological Society, held at Zagreb in December 1953; the proceedings of this symposium have not yet been published.

Treatment

Since there is no specific treatment or serotherapy, only symptomatic and supporting treatment could be given. In all cases, strict rest in bed was prescribed, the patient lying in a comfortable position with the extrem-

ities protected. In the acute stage, glucose was administered intravenously, sometimes several times a day, for dehydrating in order to combat oedema in nervous tissue. Patients were also given Pyramidon, aminophylline, vitamin C, and vitamin B complex. In certain cases, strophanthin or digitalis and other tonics were given to strengthen the heart and improve the circulation. With the meningeal cases especially, we formed the impression that the rate of improvement in the general condition and of the fall in the spinal fluid counts was the same whether these various forms of treatment were given or not. We feel, however, that frequent spinal puncture is by no means contra-indicated, and that it results, particularly in the acute meningeal stage, in an alleviation of symptoms for which patients are grateful. Disturbances following spinal puncture were practically never reported, even when the puncture was done after the meningitis had largely subsided; indeed, the temperature frequently fell a day or two after the first puncture. During the first week of illness we made two or three punctures, one or two during each of the next two weeks, and one approximately every 10-14 days during the remainder of the illness. Cases with a particularly protracted meningitic course and persistent changes in the spinal fluid were given fever treatment and mercurial inunction.

In the paralytic cases we began—as for poliomyelitis—with hot, damp packs applied to the paralysed extremities, which were maintained in a position of moderate flexion; the same treatment as for purely meningeal forms was also given. For cases in which ascending paralysis and paralysis of the peripheral respiratory muscles developed, a respirator was used. Immediately after the acute febrile stage, physiotherapy was begun, with massage, exercises, galvanic stimulation and treatment under water; good results were obtained with intraspinal electrotherapy[7] as developed by Grinschgl, Eichhorn & Moschik.[9] For paralytic cases fever therapy and similar non-specific treatment was given. With the encephalitic cases, particularly those with serious excitation states, restlessness, and epileptic fits, we made successful use on several occasions of artificial hibernation induced by Largactil, Phenergan, pethidine, or the barbiturates.

In a number of cases we also gave infusions of Periston N and administered gamma-globulin for several days in succession; however, this treatment proved unsuccessful. Antibiotics had no effect.

RÉSUMÉ

Du 1er avril au 1er décembre 1953, 304 cas de méningo-encéphalite à virus ont été hospitalisés dans la Clinique neurologique de Graz (Autriche). Parmi ces cas, 225 (74%) étaient méningés, 57 (19%) paralytiques et 22 (7%) encéphalitiques. Les formes les plus graves, comprises dans les deux derniers groupes, représentaient 26% du total.

Comme la poliomyélite, la maladie est le plus souvent diphasique. La période prodromique dure 2-8 jours, avec des symptômes rappelant ceux de la grippe. La seconde phase, séparée de la première par une période de quiescence de 8-12 jours, est caractérisée par l'invasion du système nerveux par le virus.

Durant l'épidémie, on a observé fréquemment des cas ne présentant que des symptômes de grippe, avec liquide céphalo-rachidien normal et sans atteinte du système nerveux. La réaction de fixation du complément a montré que le sérum de certains de ces malades contenait des anticorps anti-méningo-encéphalite. Il faut donc supposer que, comme dans la poliomyélite, il existe des formes inapparentes ou abortives, dans lesquelles le virus ne devient pas neurotrope, mais reste pantrope. L'évolution grave de la maladie est déterminée probablement par l'impossibilité pour le sujet de développer des anticorps en assez grande quantité et assez rapidement, ainsi que par des facteurs prédisposants et aggravants.

L'examen post-mortem montre une encéphalite aiguë, avec lésions de la substance grise plus spécialement. Les modifications pathologiques sont particulièrement graves dans la moelle cervicale et la couche de Purkinje du cervelet, dans laquelle on observe parfois des destructions cellulaires totales. L'atteinte du cervelet est caractéristique du louping-ill et de l'encéphalite verno-estivale russe. Elle est beaucoup moins marquée dans la poliomyélite. Toutefois, ce caractère ne peut servir de critère différentiel.

Le diagnostic sérologique ne peut être fondé que sur la virologie et la sérologie, c'est-à-dire sur des tests tels que l'isolement du virus et la mise en évidence des anticorps par les épreuves de fixation du complément et de neutralisation. 8% des cas analysés du point de vue virologique se sont montrés nettement négatifs et 76% nettement positifs. On peut conclure que la grande majorité des cas étudiés étaient des méningo-encéphalites avec atteinte du système nerveux central. Il est possible que quelques-uns des cas négatifs aient été des cas de poliomyélites. Cette supposition est appuyée par le fait que les cas négatifs étaient des sujets beaucoup plus jeunes que les cas positifs et que leurs paralysies affectaient surtout les jambes.

Il est extrêmement difficile, dans les cas isolés, d'établir un diagnostic différentiel d'après les seuls caractères cliniques et anatomo-pathologiques. Toutefois, le nombre élevé des cas étudiés durant l'épidémie qui a sévi en Autriche autorise certaines conclusions valables en temps d'épidémie. La méningo-encéphalite avec ses formes de paralysie spinale, de radiculite et de myélite transverse ressemble beaucoup à l'encéphalite verno-estivale russe, sans en avoir cependant la gravité. Dans les deux maladies, l'épaule et les membres supérieurs sont les parties atteintes de préférence par la paralysie. Comparée à la poliomyélite, d'autre part, la méningo-encéphalite présente plus souvent une période prodromique et sa période de quiescence est en général plus longue. Dans l'épidémie en cause, 74% des cas étaient exclusivement méningés. Cette proportion ne dépasse guère 50% dans la poliomyélite. L'évolution de la méningo-encéphalite est moins grave. Les formes non paralytiques prédominent. Un critère différentiel particulièrement important est la localisation des paralysies. Dans la plupart des cas de méningo-encéphalite, la ceinture scapulaire et les parties proximales des membres supérieurs ont été paralysées. Dans la poliomyélite au contraire, ce sont les jambes et les muscles pelviens qui sont atteints le plus souvent. La guérison des cas paralytiques est plus fréquente et la létalité (4,6%) èst plus faible que dans la poliomyélite, où elle atteint 6,8%. La vitesse de sédimentation est fortement accrue dans la méningo-encéphalite, au contraire de ce que l'on observe dans la poliomyélite.

Aucun traitement spécifique de la méningo-encéphalite à virus n'a pu être préconisé. L'auteur énumère et discute les divers traitements symptomatiques appliqués durant l'épidémie.

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