the tubule.) U is the concentration of urea (or creatinine) in the urine, P is the concentration in the plasma, and V is the volume of urine in millilitres per minute. UV thus represents the rate of urea excretion which, as we have seen, remains normal in quite advanced cases of renal failure, either natural or experimental. Now, if $\frac{UV}{P}$ is greatly diminished and UV remains normal, clearly P must be much increased, which is exactly what happens.

We have also seen that because of the osmotic diuresis V increases at the expense of U , and the fraction $\frac{U}{P}$, which is related to the osmotic work required to excrete urea or creatinine, is much reduced by a low value for U and a high value for P .

There are, however, three other adaptive processes possibly aiding the excretion of urea or creatinine. The first, which we have already considered, is the increased filtration rate per nephron. The second, which is probably of little significance, is that the slight nocturnal reduction in filtration rate which normally occurs does not take place in renal failure (Brod, 1949).^{*} Thus excretion goes on by day and by night at the same rate. The third adaptation applies to the excretion of urea but not of creatinine. Creatinine is not reabsorbed nor actively excreted by the renal tubule, or not to any significant extent,[†] but urea is reabsorbed, or perhaps we should say it diffuses back into the plasma to the extent of about 30 to 60% at normal rates of urine flow. In other words, the normal urea clearance varies from 40 to 70% of the creatinine clearance. In renal failure reabsorption of urea in the renal tubules is reduced, so that the clearance of urea approaches that of creatinine or inulin (Chasis and Smith, 1938). This may at first sight appear to be an *ad hoc* adaptation or a lucky accident, but in fact it is again explicable as a natural result of an established physiological fact. Möller, McIntosh, and Van Slyke (1929) showed that urea clearance varied with urine flow, and Shannon (1938) has shown that in normal dogs the ratio of urea to creatinine excretion increases with the rate of urine flow, and the same phenomenon has been demonstrated less completely in man (Chasis and Smith, 1938). In chronic renal disease, although total urine flow may not be increased, the rate of flow per tubule is very much greater than normal, as we shall see again in considering water excretion. Thus urea reabsorption will diminish as the rate of urine flow per tubule increases.

To sum up, it may be said that the normal rate of excretion of creatinine and urea is maintained in renal failure even in quite advanced cases, in which probably no more than 10 to 20% of the functioning renal tissue is preserved. This is effected first of all by sustaining a high plasma level of these substances; secondly, by a high rate of filtration per nephron; thirdly, by nocturnal maintenance of maximum possible filtration rate; and, fourthly, by a diminution in the proportion of the urea which the tubules reabsorb.

Conclusion

It may be noted that the requirements of urea excretion may be significantly diminished by reducing the protein intake. Pure physiologists mathematically inclined may doubt whether by doing so we are saving the kidney any significant amount of work, since the total osmotic work of the kidney seems to account for only about 1% of its oxygen consumption. "This," as Homer Smith (1951) remarks, "is not to say that the efficiency of the kidney is only 1%; the kidney's efficiency may be very high indeed—it is the thermodynamic approach in terms of final urine that is only 1% efficient." However this may be, clinicians will be more impressed by the fact that in

^{*}Brod's paper deals with acute nephritis, but his illustration on page 323 showing diurnal fluctuations of creatinine clearance gives data for chronic nephritis ("contracted kidneys").

[†]For consideration of the validity of endogenous creatinine clearance as a measure of glomerular filtration rate see Brod and Sirota (1948).

rats whose renal substance was surgically reduced Addis (1948) found that the survival rate was closely related, though in inverse ratio, to their protein intake. I shall continue to recommend a low-protein diet to my renal-failure patients, however competent their adaptive processes. By so doing it would seem that we may increase their survival, and even if we do not achieve that object we may reduce their blood urea. However non-toxic urea may seem to be, anyone who has tried to write the Lumleian Lectures with a blood urea of 80–90 mg. will know from personal experience that it is an impediment to efficiency. But this experiment will be again referred to in its proper place.

(Figs. A and 1–3 are from the paper by Platt *et al.* (1952), by permission of the editor of *Clinical Science*.)

[The second lecture, with a list of references, will appear in our next issue.]

AN OUTBREAK OF ENCEPHALITIS, POSSIBLY DUE TO POLIOMYELITIS VIRUS

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[WITH SPECIAL PLATE]

An outbreak of encephalitis affecting eight young children is described. Somnolence, extrapyramidal type of rigidity and tremor, and spastic paralyses were the dominant features of the illnesses of most of the children, while flaccid paralyses were conspicuously absent. On clinical grounds the cases thus bore little resemblance to poliomyelitis, and this diagnosis was hardly entertained until poliomyelitis virus was found in the stools of two of the cases. Even so, after study of the histology of the brain and spinal cord of the two fatal cases, we have been unable to reach any certain conclusion on the aetiology of the encephalitis.

The eight cases occurred in a period of four weeks in the summer of 1949. All were in children aged 5 or younger. All except one lived in an isolated row of fourteen houses in a rural part of Cambridgeshire; the remaining child, who was the first affected (Case 1), lived two miles away. Dr. Derek Simpson was in medical charge of the families, and gave us invaluable help.

Case 1

A baby boy aged 13 months became fretful and feverish on June 17, 1949. On the third day he was noticed to have difficulty in pulling himself up to stand in his cot. On the fourth day he began to have "attacks" lasting a few minutes and coming on about every three hours; in these attacks he went rigid and opisthotonic, the arms quivered, but consciousness was retained. Between attacks he slept peacefully. He vomited once. On the fifth day his head was noticed to be turned to the left side. On the sixth day head tremor appeared and he was admitted to hospital.

Examination on June 22 showed a well-nourished child, conscious but with a curiously expressionless face. His

temperature was normal. His neck was slightly stiff. There was a striking slow rhythmic tremor of head and arms, which were held with elbows, wrists, and fingers semiflexed. Tremor of arms, more pronounced on the left side, disappeared with sleep. The arms showed cogwheel rigidity; the tone of the legs was normal. There was no nystagmus. The fundi were normal. Both knee-jerks were exaggerated, the right more so. The left ankle-jerk was absent. The plantar responses were: left extensor, right equivocal. The cerebrospinal fluid showed: 8 polymorphs and 9 lymphocytes per c.mm.; protein, 50 mg. per 100 ml.; sterile.

During the next two weeks the tremor gradually increased; it became accentuated with voluntary movements, and feeding him became difficult on account of the gross tremor of the head. At times the tremor became so violent that his whole cot shook. On July 5 the movements became wilder still and opisthotonos developed, gradually becoming extreme, while his temperature, which had previously been around 99° F. (37.2° C.), rose to 105° F. (40.6° C.). He became comatose, dying on July 12, the twenty-sixth day of his illness.

Necropsy Findings

Central Nervous System.—There was moderate engorgement of the meningeal blood vessels, but otherwise the only macroscopic abnormalities were two small subependymal haemorrhages (the larger 0.75 by 0.3 by 0.2 cm.) in the floor of the left lateral ventricle near the head of the caudate nucleus, and several rather indefinite greyish foci in the white matter of the cervical spinal cord. Histological sections were prepared of the right frontal cortex, right precentral cortex, right occipital cortex, left basal ganglia, mid-brain, pons, cerebellum, medulla, and spinal cord (nine sections at various levels). Only the section of the mid-brain showed severe changes: in it there were large foci of inflammatory cellular infiltration and neuronal degeneration. Microglial cells and lymphocytes were the predominant cells in the infiltration, and some of the former were swollen with lipoid; the picture was, however, unlike that of the myelinoclastic form of encephalitis. Perivascular "cuffing" was seen in the mid-brain and in the medulla; the cells were mainly lymphocytes, but occasional polymorph leucocytes were seen. In the medulla there was also a single focus of cellular infiltration and degeneration in one olivary nucleus. A similar but smaller focus in a cranial-nerve nucleus was the only definite abnormality seen in the pons. The basal ganglia and cerebral cortex showed no abnormality except hyperaemia and occasional small perivascular haemorrhages. None of the nine sections of spinal cord showed any gross abnormality, but in most of them, and especially in those from the cervical and lumbar enlargements, there was very slight cellular infiltration and neuronal degeneration in the grey matter of the anterior horns, with hyperaemia and haemorrhages, the latter mostly not recent. The changes in the spinal cord were everywhere very much less than those usually seen in poliomyelitis; indeed, they were quite inconspicuous (Figs. 1, 2, and 3, Special Plate). There was slight lymphocytic infiltration of the leptomeninges.

Outside the nervous system the following abnormalities were noted: early bronchopneumonia; an apparently mild otitis media (right), which on culture yielded only a few colonies of non-haemolytic streptococci; acute inflammatory changes in the cervical and bronchial lymph nodes, spleen, and a faucial tonsil; and hyperaemia of the skin of the medial side of the left knee, with conspicuous lymphocytic infiltration of the synovial membrane of the joint.

Poliomyelitis Virus Studies.—*Brain:* A suspension of various parts of the brain was inoculated intracerebrally into a rhesus monkey, which remained well. *Stools:* A 10% suspension of faeces taken on the nineteenth day of the illness was inoculated intracerebrally and intraperitoneally into a rhesus monkey, which remained well.

Comment.—On the fourth day of the illness there developed rigidity and tremor, giving a picture charac-

teristic of extrapyramidal disease, with a steady progression to a fatal issue. Lower motor neurone paralysis was absent throughout. The clinical picture was an acute Parkinsonism, presumably due to an encephalitis involving the extrapyramidal motor system. Necropsy showed obvious lesions only in the mid-brain, where there was a predominantly lymphocytic infiltration with neuronal degeneration; lesions in the spinal cord were inconspicuous. The virus of poliomyelitis was not isolated either from the faeces or from the brain at necropsy on the twenty-sixth day of the illness.

Case 2

A boy (brother of Cases 3 and 4) aged 2 years became shivery and looked dazed in the afternoon of June 19, 1949; he vomited once that night. On the second and third days he remained up and about, but seemed drowsy, was off his food, and vomited once. On the fourth day his temperature was found to be 103° F. (39.4° C.); although he did not look ill, he was more sleepy and stayed in bed, remaining there for the next seven days. During these seven days he did not utter one word, but slept continuously except when roused, when he would take small amounts of food or drink, relapsing into sleep immediately afterwards. At such times it was noticed that his right hand shook if he tried to grasp a mug. He was incontinent, which was unusual.

On the eleventh day of the illness, the eighth day from the beginning of the somnolent period, he awoke completely recovered; no tremor was now apparent and he could walk normally. Examined for the first time two days later, no abnormal signs could be found.

Comment.—After a three-day mild illness this boy entered a week of continuous somnolence, during which time tremor of one hand was present. Thereafter recovery was abrupt.

Case 3

This patient was a sister of Cases 2 and 4 aged 3 years. On June 22, 1949, she had a mild cold, was abnormally sleepy, and went to bed, where she remained for the next seven days; during the latter half of this week she scarcely spoke, her somnolence being similar to but less profound than that of her brother (Case 2). On the eighth day she got up, when it was noticed that her right arm was not being moved and that her right hand was tremulous. Three days later, on July 3, a squint of the left eye was first noted by the parents.

On examination on July 13 she looked well. There were a slight tremor of the head, right arm, and right leg, and a left sixth-nerve paresis. The right abdominal reflexes were weak. Two months later all these signs had disappeared.

Comment.—Like her brother (Case 2), the girl was somnolent for a week, by the end of which time tremors of head and right arm and leg were apparent, followed by abducent paresis. Recovery was eventually complete.

Case 4

A brother of Cases 2 and 3 aged 9 months was "rather shaky" on the evening of June 25, 1949. Next day coarse tremors of both hands were more pronounced, although he was otherwise well. By the third day the tremor had disappeared.

Virus Studies.—The pooled stools of Cases 2, 3, and 4, collected on July 14, were inoculated intracerebrally, intranasally, and intraperitoneally into a rhesus monkey and caused typical clinical and histological poliomyelitis.

Comment.—The infant had a mild two-day illness with a coarse tremor as the sole symptom. No notice would have been taken of this had it not been that the parents had witnessed the illnesses of the two older children.

Case 5

A baby girl (sister of Case 6) aged 18 months became abnormally sleepy on June 22, 1949. Next day she

remained lying down all day, sleeping continuously except when roused to take food. This somnolence persisted over the next seven days, during the whole of which time she uttered no word. She was incontinent, which ordinarily she was not. On the fifth day it was seen that when she was roused she could not use her left hand, and that her left arm and left leg shook if she tried to use them. Her head was bent towards the left shoulder.

When admitted to hospital on June 30 she was afebrile and consciousness was normal. Slight neck stiffness and spastic hemiplegia with hyperreflexia of left arm and leg were present, and a coarse tremor developed in these limbs if she was disturbed. The plantar reflexes were: right extensor, left normal. The cell and protein content of the cerebrospinal fluid were normal.

Recovery of movement of left limbs was gradual. By July 18 she was moving all limbs fairly well, but slight intention tremor was present in both hands. At six weeks from the onset she had recovered completely.

Virus Studies.—A 10% suspension of a stool collected on the fifteenth day of illness was inoculated intracerebrally, intranasally, and intraperitoneally into two rhesus monkeys; both developed clinical and histological poliomyelitis.

Comment.—The illness began with somnolence, which lasted for a week. On the fifth day there developed a spastic hemiplegia and tremor affecting the left side, with transient pyramidal signs (extensor plantar reflex) on the right side. Recovery was complete. Poliomyelitis virus was isolated from faeces.

Case 6

This patient, a sister of Case 5, aged 5 years, became feverish on the evening of July 1, 1949, and refused to eat. Next day she was well and remained so until the 4th, when she complained of headache and went to bed.

On admission to hospital on July 5 her temperature was 103° F. (39.4° C.), and consciousness was normal. There was no neck stiffness. Slight tremor of head and of outstretched hands was present, increased by intention. Tendon reflexes were normal. The cerebrospinal fluid showed: 6 polymorphs and 9 lymphocytes per c.mm.; protein, 20 mg. per 100 ml.

The patient became afebrile by July 7, and thereafter the tremor gradually disappeared; by the end of the third week it was only just discernible, and at seven weeks recovery was complete.

Comment.—This was a mild febrile illness of biphasic type, the only neurological sign being tremor. Virus studies were not made.

Case 7

A girl aged 5 had a headache and was feverish on the evening of July 3, 1949. On the 4th she slept all day, ate nothing, and continued to complain of headache and feeling sick. By the third day she had recovered completely.

Comment.—This was a transient febrile illness, with headache as the dominant symptom. Virus studies were not made.

Case 8

A boy aged 5 awoke on the morning of July 14, 1949, complaining of headache. He lay about all day, ate little, and vomited once. On the next day he remained up at first, but in the afternoon went to lie down, where shortly afterwards his mother discovered him completely unresponsive, though still just capable of swallowing a little water.

He was admitted to hospital on July 16. His temperature was 104.8° F. (40.5° C.). He was in deep coma. His trunk was opisthotonic, and his limbs were rigid and extended, with wrists flexed. His eyes deviated upwards and inwards; the left pupil was larger than the right; the fundi were normal. Tendon reflexes and abdominal reflexes were absent; plantar reflexes were extensor. The cerebrospinal fluid showed: 20 polymorphs and 61 lymphocytes per

c.mm.; protein, 20 mg. per 100 ml. Twitchings of limbs developed and he died in hyperpyrexia on the third day of his illness, a few hours after admission.

Necropsy

Central Nervous System.—There was general hyperaemia of the grey matter throughout the brain and cord, and of the leptomeninges (especially over the temporal lobe). The mid-brain was soft and bulged abnormally on section, as also did the spinal cord at all levels. The claustrum appeared abnormally large, especially on the right side. These were the only macroscopic abnormalities in the central nervous system. Histological sections included 11 sections from various parts of the cerebral hemispheres, 6 from the basal ganglia, 10 from the spinal cord; 3 from the cerebellum, 2 from the medulla, and 1 each from the hypothalamic region, mid-brain, and pons. A Gasserian ganglion and a dorsal root ganglion were also sectioned. Microscopical examination showed an encephalomyelitis with maximal involvement of the mid-brain (especially the substantia nigra) and the hypothalamus. Conspicuous changes were also seen in the olivary nuclei of the medulla and slight but definite changes in the reticular formation of the pons. Except for a few foci of inflammation and neuronal degeneration in the optic thalami and lenticulate nuclei, especially near to the lateral ventricles, the basal ganglia had escaped. No definite lesion other than one petechial haemorrhage was seen in the cerebral hemispheres. In the spinal cord one section of the cervical enlargement showed severe involvement of an anterior horn; in this one section the histological picture was characteristic of poliomyelitis (Figs. 4 and 5), but none of the nine other sections at various levels down to the lumbo-sacral region showed any conspicuous abnormality. There appeared, however, to be slight cellular infiltration in the anterior horns of the upper cervical region and lumbar enlargement. In the posterior root ganglion and the Gasserian ganglion there was considerable cellular infiltration (apparently lymphocytic) with focal degeneration of neurones.

In the affected parts of the central nervous system there were two main features: first, infiltration of the grey matter with microglia cells and polymorphonuclear leucocytes, and perivascular cuffing due to the presence of numerous lymphocytes and macrophages—together with a variable number of polymorphonuclear leucocytes—in the Virchow-Robin spaces; and, secondly, degeneration of neurones, with neuronophagia. The meninges of the brain and spinal cord showed a slight degree of infiltration with lymphocytes and macrophages.

The only definite abnormalities outside the nervous system were as follows: one small focus of cellular infiltration in the myocardium of the interventricular septum; partial collapse, congestion, some oedema, and intra-alveolar haemorrhage in the lungs; a considerable excess of neutrophil leucocytes in the spleen; pus in one tonsillar crypt, with leucocytic infiltration in the adjacent lymphoid tissue; reactive hyperplasia in the rather large cervical lymph nodes; petechial haemorrhages in the thymus; congestion of thyroid, pituitary, and pancreas; threadworms in appendix; inequality in the size of the pupils, the left being decidedly larger than the right.

Virus Studies.—A suspension of various parts of the brain was inoculated intracerebrally into two rhesus monkeys; both remained well.

Comment.—This was a fulminating infection leading to the picture of decerebrate rigidity and death on the third day. Poliomyelitis virus was not isolated from the brain.

The Table on page 1320 summarizes these case records. Additional virus studies were carried out by Dr. N. B. Finter, of the Department of Pathology, Cambridge. Specimens of blood and/or cerebrospinal fluid from Cases 1, 5, 6, and 8 were inoculated both intracerebrally and intraperitoneally into mice, rabbits, guinea-pigs, and hamsters,

Clinical Features and Virus Findings in Eight Children with Encephalitis

Case No.	Sex	Age in Years	Date of Onset	Main Clinical Features	C.S.F.: Cells per c.mm.	Outcome	Poliomyelitis Virus Findings
1	M	1 1/2	17/6/49	Acute Parkinsonism	8 polys. 9 lymphs.	Death 26th day	Brain and stool—negative
2	M	2	19/6/49	Somnolence; tremor	—	Recovery	Pooled stools—positive
3	F	3	22/6/49	Somnolence; tremor; sixth-nerve paresis	—	"	
4	M	9/12	25/6/49	Tremor	—	"	
5	F	1 1/2	22/6/49	Somnolence; tremor; spastic hemiplegia	None	"	Stool—positive
6	F	5	1/7/49	Tremor	6 polys. 9 lymphs.	"	—
7	F	5	3/7/49	Headache; vomiting	—	"	—
8	M	5	14/7/49	Decerebrate rigidity	20 polys. 61 lymphs.	Death 3rd day	Brain—negative

and into the amnions and yolk sacs of eggs. Samples of both brain and spinal cord tissue from Case 8 were similarly treated. No viral agent was isolated.

Epidemiological Findings

An infecting agent common to the cases was inferred on the following grounds: (1) all eight cases occurred in a period of four weeks; (2) with the exception of Case 1 all the affected children came from four families living in an isolated row of houses; and (3) there was an obvious similarity between the illnesses—for instance, tremor was a prominent symptom of Cases 1; 2, 3, 4, 5, and 6, while the histology of the brains of the two fatal cases (Nos. 1 and 8) was essentially similar. Only in Case 7 is there some doubt; this 5-year-old girl had a mild two-day illness with fever, headache, and vomiting—symptoms which in the circumstances were suspicious but not conclusive of a mild encephalitis.

Age Distribution.—All eight children were aged between 9 months and 5 years. This represented a high incidence among the children living in the row of houses, where seven children (Cases 2 to 8) of the total of 21 below the age of 6 years were affected; adults were not affected. A house-to-house call was made to find out whether there had been any unexplained minor illnesses. The only cases discovered were on the farm where Case 1 lived. His two brothers had suffered from fever and sore throats, clinically a follicular tonsillitis, at the time of onset of their brother's illness. A lad who worked on the farm had fever, severe headache, and backache on July 15 but recovered on the next day. This illness might have been due to the agent responsible for the encephalitis.

Mode of Spread.—There was ample opportunity for contact among the seven children (Cases 2 to 8) living in adjacent houses, and the pattern of the epidemic (see Diagram) is compatible with a case-to-case spread, with a

Diagram showing dates of onset of encephalitis in Cases 1-8.

suggestion of groups of cases occurring at intervals of about 7 to 10 days—Cases 2, 3, 4, and 5, followed by Cases 6 and 7, followed by Case 8. Case 1 was the son of a farm worker living on a farm two miles from the homes of the other cases, with whom he had no direct contact. Three possible connexions existed, however: first, this farm supplied milk to the homes of all the cases; secondly, the milk roundsman himself was a contact of all the cases;

and, thirdly, the father of Cases 5 and 6 worked on this farm, occasionally saw Case 1, and sometimes milked the cows. Although neither of these men had any recent illness, in view of the other evidence pointing to a case-to-case spread it is conceivable that one of them was a symptomless carrier of the encephalitogenic agent.

Suspicion naturally fell on milk as the vehicle of infection when it was found that the common milk supply came from the farm where Case 1 lived, that it was prepared under bad hygienic conditions, and that it was not pasteurized. However, this milk was supplied to several hundred people, including 200 schoolchildren, in the district, amongst whom only this localized outbreak occurred, so that a milk-borne agent was improbable.

Spread of infection from faeces could not be excluded; the households concerned used pail privies and buried the contents in the garden. At the time flies were not numerous.

These and many other lines of inquiry were pursued, but no conclusion was reached regarding the primary source of infection, and it remained doubtful whether infection was first introduced to the farm and spread from there, or whether it was introduced simultaneously to the farm and to the families living in the isolated row of houses. Spread by contact was the likeliest explanation of the later cases in families in these houses.

Discussion

The nature of the encephalitis rests upon evidence of four kinds—the pattern of the clinical illness, the epidemiological pattern, the virus findings, and the neurohistological findings. Of the known forms of encephalitis three must be considered—poliomyelitis, lethargic encephalitis, and that group comprising Japanese B, Australian X, St. Louis, and equine encephalitis.

Poliomyelitis

Since the clinical signs in the affected children were predominantly those of somnolence, extrapyramidal type of rigidity, and tremor, with pyramidal signs such as spastic paralyzes, and since there was a conspicuous absence of cranial, bulbar, or spinal paralyzes (save for a single example of an abducent paresis), poliomyelitis was not seriously considered until this virus was found in the stools

LEGENDS TO PLATE**S. MARSHALL AND K. S. MILLINGEN**

FIG. 1.—Hilar gland. Note pigment-containing macrophages, stromal oedema, diffuse and focal infiltration with abnormal "monocytic" cells. (H. and E. $\times 500$.)

FIG. 2.—Liver. Necrosis and fatty change in liver cells; loss of normal architecture; abnormal "monocytes," some with hyperchromatic nuclei. (H. and E. $\times 400$.)

FIG. 3.—Spleen. Many pigment cells; diffuse infiltration with abnormal "monocytes," one in top left corner showing nuclear fenestration. (H. and E. $\times 500$.)

FIG. 4.—Kidney. Note tubular degeneration; granular debris within tubules; monocytic cells in capillaries and stroma. (H. and E. $\times 500$.)

H. J. RICHARDS

FIG. 1.—Young cellular fibrous tissue of painful tender nodules. (H. and E. $\times 105$.)

FIG. 2.—More mature tissue of the contracture, which is less cellular; increased intercellular tissue and laying down of collagen. (H. and E. $\times 105$.)

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FIG. 1

FIG. 2

FIG. 3

FIG. 1.—Case 1. Most affected part of spinal cord (cervical). Part of an anterior horn shown at top right. Neurones relatively well preserved; very little cellular reaction. Blood vessels at bottom left surrounded by wide but empty Virchow-Robin spaces. (Ehrlich's H. and E. $\times 65$.) FIG. 2.—Case 1. High-power view Fig. 1. Slight cellular infiltration in anterior horn, with well-preserved neurones. (Ehrlich's H. and E. $\times 640$.) FIG. 3.—Case 1. High-power view Fig. 1. Many neurones shrunk and deep-staining; little cellular infiltration. Circular pale focus possibly petechial haemorrhage in which erythrocytes mostly disintegrated. (Ehrlich's H. and E. $\times 640$.)

FIG. 4.—Case 8. The most affected part of spinal cord. Greater part of an anterior horn included at top right. Note degree of cellular infiltration and disappearance of most of the neurones. (Ehrlich's H. and E. $\times 65$.)

FIG. 5.—Case 8. High-power view of part of the anterior horn seen in Fig. 4. Most cells are microglial. Irregular darkly stained object at top middle is a degenerating neurone showing neuronophagia. (Ehrlich's H. and E. $\times 640$.)

D. R. C. WILLCOX: HAEMOLYTIC ANAEMIA AND RETICULOSES

FIG. 1.—Case 4. Section of spleen. Edge of lymph follicle below. Pulp vascular, contains many histiocytic and some giant cells. (H. and E. $\times 200$.)

FIG. 2.—Case 4. Section of spleen showing details of the unusual type of giant cell. (H. and E. $\times 800$.)

of two of the cases. The idea of poliomyelitis existing in an encephalitic form dates back to Strümpell (1885), who first used the term polio-encephalitis to describe the acute febrile illness of infancy associated with convulsions and followed by spastic hemiplegia. This is now known to have nothing to do with poliomyelitis (Wyllie, 1948). Excluding such cases, occasional cases have been reported (for example, Case 57 of Medin, 1898) in which a patient had suffered an acute illness with somnolence, coma, convulsions, ataxia, or pyramidal effects as prominent features, and in which poliomyelitis has either been surmised on account of the existence at the time of a poliomyelitis epidemic (Peabody, Draper, and Dochez, 1912) or, less frequently, has been proved at necropsy (Jennings, Hamilton-Paterson, and MacCallum, 1949; Kelleher, Bratton, and MacCallum, 1949). Such cases are rare, and no record has been found of any consecutive series of cases presenting a purely encephalitic picture. Two minor clinical points are worth comment. The absence of any pleocytosis in the cerebrospinal fluid of Case 5 on the eighth day of the illness would be unusual in poliomyelitis. On the other hand, the biphasic illness of Case 6 was suggestive of poliomyelitis.

Epidemiologically the course of the outbreak was compatible with, though not typical of, poliomyelitis: it occurred in summer, only children of 5 or under were affected, and 7 out of 21, or one-third of one group of children, were ill—a heavier incidence than has been usual in recent poliomyelitis outbreaks in Britain.

The significance to be attached to the finding of poliomyelitis virus in the faeces of one patient and the pooled faeces of three others is difficult to assess, since we do not know the incidence of poliomyelitis virus in the faeces of the general population at the time of the outbreak. That the incidence in Cambridgeshire was probably low may be surmised from the fact that there was a low incidence of poliomyelitis in Cambridgeshire in 1949 and in previous years. Up to the time of the outbreak of encephalitis no case of poliomyelitis had occurred in the vicinity, but on July 17 a typical case occurred in a 20-year-old woman who lived a mile from the farm where Case 1 lived and who visited this farm once a week to pay for the milk she obtained there. The failure to demonstrate virus in brain tissues from the two fatal cases is not of great significance, since in the experience of Dr. F. O. MacCallum (personal communication) successful isolation is achieved in only about 50% of fatal cases.

The histological differentiation of the various types of encephalomyelitis is based upon the *distribution* and the *character* of the histological changes in the central nervous system. In poliomyelitis the lesions are restricted to the grey matter, and they are found (Bodian, 1949) in the spinal cord, especially in the anterior horns; in the brain stem, especially around the fourth ventricle, but not in the ventral part of the pons or in the inferior olive; in the mid-brain and hypothalamus; and sometimes in the precentral gyrus but not elsewhere in the cerebral cortex. Except for focal lesions in the inferior olivary nuclei, all of the lesions in the two fatal cases described above fall within the normal territory of poliomyelitis as thus defined. Involvement of the posterior root ganglion and Gasserian ganglion as in Case 8 is also seen in poliomyelitis. Thus it is seen that if no regard be paid to the relative severity of involvement of different parts of the affected territory, the *distribution* of the lesions in the two fatal cases closely resembles that in poliomyelitis. The slightness of the changes in the spinal cord compared with those in the brain is, however, a serious objection to the diagnosis of poliomyelitis. Even in cases of poliomyelitis which show little or no clinical evidence of cord involvement it seems invariable to find conspicuous histological changes in the cord (Jennings *et al.*, 1949; Kelleher *et al.*, 1949); yet none of the nine sections from various levels of the cord in Case 1, and only one of the ten sections in Case 8, showed more than very slight changes.

In *character* as distinct from *distribution*, the lesions in the two fatal cases are identical with those usually seen in

poliomyelitis: neuronal degeneration is conspicuous, neuronophagia is present; the most severely affected foci of grey matter are heavily infiltrated with microglia cells, which in some places have taken up fairly large amounts of lipid matter; and the perivascular cuffs of cells include lymphocytes and a small number of polymorphonuclear leucocytes but very few, if any, plasma cells.

From the histological point of view, therefore, the only findings which are opposed to the diagnosis of poliomyelitis are, first, the slightness of involvement of the spinal cords; and, secondly, the presence of focal lesions in the inferior olivary nuclei. Since these features were present in both of the only two cases examined, and since they are both very unusual in poliomyelitis, if the epidemic is attributed to infection with poliomyelitis virus, it appears necessary to assume either that the virus was possessed of unusual properties or that some unusual environmental factor was affecting the response of the children to infection.

Lethargic Encephalitis

Although the remarkable somnolence shown by three of the cases at once brought this disease to mind, the clinical picture as a whole differed in many respects from the descriptions of this disease. Thus the onset was sudden rather than insidious, the sole example of a cranial nerve palsy was an abducent palsy, and the cells in the cerebrospinal fluid were 25 to 50% polymorphonuclears, whereas the pleocytosis is lymphocytic in lethargic encephalitis even in acute cases (Perdrau, 1922). Finally there were no sequelae in the six patients who survived.

Epidemiologically also the facts are against this diagnosis. It occurred in summer and affected children only, with multiple cases in two families, whereas outbreaks of lethargic encephalitis have been confined to winter or spring, young children are less often affected than adults, and multiple cases in a family are rare.

The histological lesions of encephalitis lethargica as seen in the outbreaks which followed the first world war were usually maximal in the mid-brain, the upper part of the pons, and the basal ganglia; slighter changes were commonly seen in the medulla (MacNalty, 1921). Changes were rarely seen in the spinal cord, and at most were slight. Involvement of the cerebral cortex has been described (Buzzard and Greenfield, 1919; Watson, 1920), but is not characteristic; nor were the degenerative changes in the Purkinje cells of the cerebellum seen once by Marinesco (1918). This distribution of lesions is closely similar to that seen in our two fatal cases; in both of the latter, however, changes were present in the spinal cord, and although these cord changes were slight compared with those usually seen in poliomyelitis, yet they were apparently more extensive in Case 1, and more severe in Case 8 than was normal in encephalitis lethargica. The distribution of the lesions in our cases is nevertheless consistent with the diagnosis of encephalitis lethargica.

However, when the histological characteristics of the lesions are considered as well as their distributions, it seems unlikely on histological grounds that our cases were due to encephalitis lethargica. The appearance of the foci of microglial infiltration in the grey matter with severe degeneration of neurones and conspicuous neuronophagia; the presence of polymorphonuclear leucocytes and the absence of plasma cells amongst the inflammatory cells; the degree of cellular infiltration in the meninges—all these speak for an inflammatory reaction more intense than that usually seen in encephalitis lethargica. The character of the lesions is undoubtedly more like poliomyelitis than encephalitis lethargica.

St. Louis, Equine, Japanese B, and Australian X Encephalitis

It is generally agreed that these four epidemic types of encephalitis due to neurotropic viruses are closely related, there is much similarity in their symptomatology and neuro-

histology, and, in addition, the viruses of some members of this group have antigens in common. Epidemics caused by this group of virus agents have occurred in hot weather, have sometimes chiefly affected young children, and have been associated with a clinical picture quite similar to our cases. In this group of encephalitis the histological lesions are often widely scattered throughout the central nervous system. Although the brain stem is perhaps the favourite location, the cerebral hemispheres, cerebellum, and spinal cord may all be involved; the white matter as well as the grey matter is affected; and there is more meningeal reaction than in encephalitis lethargica. In Japanese B encephalitis destruction of Purkinje cells in the cerebellum is a striking feature. In view of the restriction of the lesions to the grey matter in our two fatal cases, and of the absence of involvement of the cerebral cortex or cerebellum, it is impossible to regard the distribution of the lesions as at all characteristic of this group of infections; nevertheless, on histological grounds it is not impossible that our cases might belong to that group. The character of the lesions also is consistent with such a diagnosis, but again there is nothing distinctive about it. The Purkinje cells in our cases did not appear to be reduced in number, and although some of them showed apparent degenerative changes, similar changes can be seen in control sections of the cerebellum of children who did not die of encephalitis.

In this group of encephalitis the virus can often be isolated with relative ease by intracerebral inoculation of mice; the negative findings in this respect therefore are worth noting.

Summary and Conclusions

An outbreak of encephalitis is described; eight children were affected, with two deaths.

Clinically the pyramidal and extrapyramidal motor systems were predominantly affected, and lower motor neurone lesions (with one minor exception) did not occur.

The histology of the brains of the two fatal cases was consistent with poliomyelitis; on the other hand, the lesions in the spinal cords were not nearly so prominent as is the rule in poliomyelitis.

Poliomyelitis virus was recovered from the stools of one case, and from a pool of the faeces of three others.

In comparing the clinical, epidemiological, viral, and neurohistological findings in our cases with those of other known encephalitis, we conclude that this outbreak was either one of poliomyelitis with several most unusual features or was an example of some hitherto undescribed type of encephalitis. We slightly favour the former view.

Our thanks are due to Dr. F. O. MacCallum, Director of the Virus Research Laboratory of the Public Health Laboratory Service, and to Dr. N. B. Finter, of the Department of Pathology, Cambridge, for the virus studies; and to Mr. S. W. Patman for the photomicrographs.

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HAEMOLYTIC ANAEMIA AND RETICULOSES

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[WITH SPECIAL PLATE]

Haemolytic anaemia associated with various neoplastic processes is a recognized but not a common clinical entity (Davidson, 1932; Waugh, 1936; Singer, 1940; Stats, Rosenthal, and Wasserman, 1947). In many of these cases the haemolytic picture is merely incidental to the malignant process. Lucey (1939) and Pollard (1948) have recorded single cases in which haemolytic anaemia presented, apparently of idiopathic type, and the neoplastic association was found only at necropsy. Both these were cases of carcinomatosis.

Four cases of haemolytic anaemia are recorded here. In two of them clinical evidence of malignant disease (lymphosarcoma and reticulum-cell sarcoma) first appeared several months after the onset of haemolytic anaemia. In another case reticulo-endothelial changes were found only at post-mortem examination. These cases appeared to illustrate some points of interest in the clinico-pathological picture, and also in the possible mechanism of production of this type of anaemia.

Case 1

An unmarried woman aged 40 had lived a healthy and active life. Menstruation had ceased 18 months previously. She complained of lassitude for five weeks, and of dyspnoea and palpitations for two weeks. The severity of her symptoms had increased rapidly up to the time of her admission to hospital.

On admission on June 14, 1949, she was slightly dyspnoeic at rest. The skin and mucous membranes were very pale and slightly icteric, as were the sclerae. The apex beat was just beyond the mid-clavicular line, and a blowing systolic murmur was heard in this area. Her temperature was 99.8° F. (37.7° C.), pulse 100, and respirations 22. There were no other abnormalities on physical examination. The spleen was not palpable.

Investigations.—Urine: excess of urobilin, no bilirubin, no haemoglobin. Blood: haemoglobin, 33% (5.15 g.); red cells, 1,200,000; colour index, 1.3; M.C.D., 8 μ ; P.C.V., 18%; M.C.V., 150 μ^2 ; M.C.H.C., 29%; M.C.A.T., 3.3 μ ; reticulocytes, 24%; late normoblasts 3 per 100 white cells: the red cells showed anisocytosis and slight anisochromia with numerous polychromatic cells and macrocytes; white cells, 9,800 (polymorphs 70%, eosinophils 1%, basophils 1%, lymphocytes 21%, monocytes 1%, myelocytes 4%, metamyelocytes 2%); the polymorphs showed a left shift. The red-cell fragility was slightly increased: haemolysis started at 0.55% saline, and was complete in 0.30% saline. The direct Coombs test was positive. Chemical: serum bilirubin, 2.25 mg. per 100 ml.; van den Bergh direct test, delayed response; empirical liver tests (thymol turbidity and flocculation and colloidal gold) were negative; test meal, histamine-fast achlorhydria.

A diagnosis of acute haemolytic anaemia of unknown cause was made. The patient was transfused on three occasions without incident. A course of penicillin was given to combat any possible infective cause of the haemolysis. She continued pyrexial and jaundiced for some time, but was sufficiently improved by August 2 to be discharged, her haemoglobin then being 13.26 g. per 100 ml.

When seen at the out-patient department on September 28 and October 8 and 26 her haemoglobin was falling. In