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ACUTE ENCEPHALITIS IN CHILDHOOD*

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In this paper I shall deal with the subject of encephalitis in childhood from the point of view of a neuropathologist interested for more than twenty years in the correlation between clinical presentation and histopathological findings.

Physicians who encounter these cases almost daily must feel with me the vital necessity for their earlier recognition, this being the essential condition for their defeat. From this point of view my experience of clinicopathological correlations affords me little satisfaction. As an exercise in modesty and self-criticism I cannot imagine anything more effective than the preparation of this paper.

If we are honest with ourselves and try to discover what it is we really have in mind when we use the term encephalitis, we would probably say "a morbid process, inflammatory in nature, occurring within the brain," and if we wish to be more precise we would add that the process develops in the presence of a living infective agent, acting locally.

Here we already have our first difficulty. In the course of an infectious disease—for example, German measles or bronchopneumonia—it is a commonplace to observe the features indicating disordered cerebral function—drowsiness, confusion, oneirism, and so on. These features precede the symptoms characteristic of the disease itself, being associated with the invasive stage and making their appearance with the commencement of fever. In these circumstances, even though we are witnessing cerebral manifestations in response to a general infection, it would be unrealistic to envisage a cerebral inflammation, and we do not in fact believe that the infective agent has penetrated the blood-brain barrier.

There can be no doubt that certain functional changes in the cerebral circulation, especially on the venous side, interfere with the distribution of substances essential to the metabolism of the brain, especially oxygen, and that these same disorders of circulation also impede the elimination of products of metabolic activity, so that a combination of anoxia and intoxication is produced.

We assume that these diffuse disorders are easily and commonly reversible, at least in individuals whose brain has not been damaged by a previous affection.

The physician must be on his guard if this state of intoxication is accompanied by constitutional disturbances of greater severity than is characteristic of the

disease, or if focal cerebral or irritative meningeal signs make their appearance, or, again, if the preliminary pyrexial attack is followed by a recrudescence of fever with return of general cerebral disorders of equal or even greater severity. These are the warning signs of an incipient meningo-encephalitis or meningitis.

I shall deal with both these two conditions simultaneously, since, for the pathologist, and perhaps also for the clinician, no encephalitis can be conceived without accompanying involvement of the meninges.

Diagnosis and Significance of Meningo-encephalitis

Repeated vomiting, photophobia, and stiffness of the neck will be present. The optic fundi will show a slight venous engorgement. The cerebrospinal fluid will be clear and normal as regards both cells and protein. There will, however, be an increase in pressure. Clinical examination will show neither a typical nor an atypical pneumonia. The liver will not be enlarged nor will there be a generalized enlargement of lymph nodes. Examination of blood vessels will show no abnormality. We shall be satisfied that we are dealing with an acute serous meningitis, but will be immediately faced with the need to determine its cause.

Leptospirosis cannot be excluded merely because of the absence of jaundice or hepatic enlargement. Leptospire may be isolated from an apparently normal cerebrospinal fluid. To-day it is recognized that leptospirosis is more widespread than had been thought and that a pure meningeal oedema—that is, without change in cell count or albumin content of the cerebrospinal fluid, but with a rise of intracranial pressure, though still moderate in degree—may be the only sign of the penetration of the infective agent into the meningeal spaces. This phase, which we may call "normergic," is no doubt only transient, but it is at this stage that we must act if we are to recover the organism.

Faced with a meningeal reaction without evidence of visceral disease, one must consider also a virus meningo-encephalitis.

It is well known how numerous these viruses are to-day. If we include the rickettsiae, there are more than 60 that are pathogenic for man. Their spread, geographically speaking, is evidence of our inability either to prevent or to treat them. Clinical examination by itself is of little avail in their identification. It is impossible by clinical examination alone to separate an influenza A from an influenza B or a psittacosis from Q fever or primary atypical pneumonia. On the other hand, each of these diseases may be identified by

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a specialized laboratory. This identification, however, is dependent upon one condition: that the physician who suspects involvement of the nervous system should notify such a laboratory of his suspicion and send at the earliest opportunity specimens of blood, faeces, nasopharyngeal mucus, sputum, saliva, or cerebrospinal fluid.

It is not sufficient to seek the virus in the blood. There are diseases in which it is not present in the blood or is extremely difficult to demonstrate. It is now generally recognized that one of the problems of medicine of the future will be the organization of numerous virological laboratories equipped to achieve this early diagnosis. However, we are not here directly concerned with this.

The physician's responsibility is to know in what circumstances he should suspect a viral infection. We must admit straightaway that he will have only presumptive clues to go on; but these, nevertheless, are worth retaining, for indeed there is nothing better. Of course, in addition to the classical virus infections (influenza, smallpox, poliomyelitis, epidemic encephalitis, and the acute specific fevers) we now have new entities such as psittacosis, epidemic hepatitis, lymphocytic choriomeningitis, and infective mononucleosis.

For the physician, an infectious disease comprises in general one or several initial rigors, a cycle during which the temperature rises and then falls by lysis, a crisis or turning-point, a leucocytosis in the blood with shift to the left and leucocytes with toxic granulations, and a tendency to suppurative lesions.

These signs are often absent in viral diseases. Indeed, should they be present one must suspect an intercurrent infection.

Positive Signs of Viral Disease

As for the positive signs of viral disease, these comprise a biphasic development of fever, bradycardia, a relative leucopenia with lymphocytosis, prominent initial constitutional disorders followed by symptoms of disordered function of the organs—for example, the brain, lungs, liver, intestines, etc.—a tendency to show epidemicity, and, finally, with certain exceptions, resistance to sulphonamides and antibiotics. We may, in passing, point out that the biphasic character of the fever has a certain general biological significance. Its first period (of four or five days) usually corresponds to the phase of viraemia, the second period to the phase of localization of the infection to a particular system of the body (nervous system, viscera, skin, etc.). The first phase is made manifest by non-specific constitutional disorders which vary little in form; this makes them so much more difficult to recognize. It is therefore not surprising that certain infections can be diagnosed only when they have attacked a particular body system; that is, when the first signs of localization within the system become manifest.

I need hardly mention that each of the viral infections of the nervous system has its sites of predilection: posterior root ganglion, anterior horns, substantia nigra, and so on.

It is the association of the focal signs with a history of contact with particular animals (the horse in equine encephalomyelitis, mice in lymphocytic choriomeningitis, pigs in leptospirosis, sheep in louping ill, and so on) which suggest the aetiological diagnosis to the clinician.

However, things are not always straightforward. As already pointed out, the involvement of a particular body system in the second febrile phase is an expression of localization of the viraemia, and the foci within the affected system are an expression of the degree of selectivity shown by the virus. One cannot be sure, however, that this second febrile phase is not due to the superimposition of a second and different viral infection on the first, this second infection deciding the site of the foci. Indeed, it seems probable that this is a fairly common situation. We have only to think of buccal herpes (a cutaneous localization) superimposed upon one of a wide variety of meningitides; the types of tonsillitis and pharyngitis which accompany primary atypical pneumonia; the types of enteritis without demonstrable bacterial causes which accompany smallpox; or poliomyelitis and epidemic hepatitis.

One last example seems particularly important to me. Recently, diarrhoea affecting infants and young children has been recognized from which an agent has been isolated that can be inoculated upon the cornea of a rabbit in the same way as can herpes virus. Until recently this virus has been confused with that of herpes because it also causes a contagious stomatitis. The same virus has been isolated from the genitourinary tract of adults. Just as in the case of herpes, one may conceive in the case of this new virus that the newborn infant becomes infected as it traverses the birth passages of the mother. However, one cannot exclude the possibility of a member of the nursing staff acting as a healthy carrier, which would explain the occurrence of epidemics in crèches and children's homes.

These features that I have just outlined are not—and this should be emphasized—specific for viral infections. They are equally characteristic of the infections that one used to call pseudoviral, the best-known varieties of which are the leptospiral and rickettsial infections.

These positive and negative features have, nevertheless, a real diagnostic value.

Allergic Reactions

The second febrile phase comprises, apart from the signs of involvement of particular organs or body systems which I have just mentioned, a reaction reflected in the composition of the cerebrospinal fluid—that is, an increase in cells or protein—while specific agglutinins appear in the blood. These changes in the cerebrospinal fluid are a manifestation of the interaction of viral antigen and antibodies—that is, they represent an allergic defensive reaction. In the late stages of the infection, in proportion as sensitization develops, a phase sets in characterized by cyto-albuminological dissociation associated with an abnormal colloidal reaction. This last phase is an indication that the antigenic and pathogenic agent has not been eliminated.

So long as an infection of the nervous system is unaccompanied by focal signs, and the cerebrospinal fluid remains normal, it is not customary to speak of an encephalitis. This is, of course, a convention rather than an absolute truth. If a child succumbs during this initial phase we speak of a toxic encephalopathy—that is, a diffuse toxic affection of the cerebrospinal axis—because anatomical studies fail to reveal the presence within the cerebral parenchyma of inflammation in the general pathological sense—that is, a process characterized by exudation and cellular proliferation.

In actual fact there are cases that are extremely difficult to analyse, which perhaps it would be wrong to exclude from the domain of true inflammation, so much the more so since the introduction into general pathology of the concept of serous inflammation. One observes from time to time, both in infants and in young children, cerebral disorders with an acute and fatal course, which reproduce exactly in their clinical development and anatomical substrate what is seen in the endogenous and exogenous intoxications.

It is worth while pausing for a few moments over this picture of an acute serous inflammation of the brain, which may or may not be accompanied by an acute involvement of the myocardium or liver. This condition is encountered in young children suffering from an acute gastro-enteritis. The only premonitory signs are repeated vomiting and diarrhoea, with or without colic. At this point a sudden circulatory collapse supervenes, with coldness of the extremities, cold sweating, and anxiety. Death follows within two to five days, sometimes without fever developing. Bacteriological examination is negative and necropsy equally disappointing; the liver is oedematous, its parenchyma slightly dissociated with focal fatty degeneration; the brain is swollen, with engagement of the cerebellar tonsils; the myocardium shows stasis, with slight hyaline swelling of the walls of the vessels; the lungs are the site of a slight oedema; and the kidneys show epithelial desquamation of the tubules. One is forced to conclude that a toxic agent has severely disturbed the permeability of the capillaries, resulting in an infiltration of the interstitial tissues with diapedesis of red cells and plasma, and disturbance of tissue respiration. In the brain the disturbed equilibrium of permeability results in cerebral oedema, such as we are familiar with in uraemia, eclampsia, and epilepsy.

In the cases we have been able to observe there always have been, at the onset, intestinal upsets sometimes accompanied by fever. Intestinal infection by micro-organisms of high toxicity or even viruses may cause an increased permeability of the intestinal mucosa. This breakdown of the filtering mechanism of the intestines allows the passage of colloidal substances (albumin or breakdown products) to which the tissues of the bowel wall may become sensitized. Their further absorption will result in an allergic reaction culminating in an acute serous inflammation.

From a personal point of view, it seems difficult to reject such cases of acute serous inflammation of the brain from the encephalitis group merely on the grounds that the exudation is serous rather than cellular. On the other hand, one can well understand the uneasiness many feel when asked to consider as inflammatory a process which is morphologically identical with that resulting from an exogenous intoxication and perhaps developing, like the latter, without fever.

Bickerstaff and Cloake (1951), in England, have described an encephalitis of the brain stem. In this condition there is a severe affection of the third and other cranial nerves, of the supranuclear oculomotor pathways, disorders of deep sensation, and of the pyramidal tracts. The symptoms develop and then recede over a period of weeks or months. Cure is the rule and sequelae are exceptional. According to the authors, the most remarkable feature of the illness is the contrast between the extreme severity of the patient's condition at its worst and the favourable outcome which

is the rule. The only case which was subjected by Woolf to post-mortem examination was that of a boy aged 14 years in whom the only lesions were those of oedema, a few very localized perivascular infiltrations in the frontal region, and periportal round-cell infiltration. The authors regarded the malady as the central equivalent of an infectious viral polyneuritis. The cerebrospinal fluid showed a pleocytosis with cyto-albuminological dissociation suggesting a still active infection rather than an allergic state. The presence of inflammatory hepatic lesions would support this interpretation.

Acute Haemorrhagic Encephalitis

In considering those cases where involvement of the capillary system results in diapedesis of red blood cells, we enter the domain of acute haemorrhagic encephalitis or encephalopathy, in which we shall, no doubt, run into the same difficulties in classification.

These serous or serohaemorrhagic encephalitides in the guise of acute oedema can be observed in the types of gastro-enteritis just discussed. They may also occur in the acute exanthemata, in influenzal states, and in anaphylactic shock. The symptomatology is always the same: nausea, malaise with a tendency to circulatory collapse, profuse sweating, hyperpyrexia, convulsions, coma, and death. The cerebrospinal fluid is clear or blood-stained, or, much more rarely, xanthochromic. The treatment is again that of severe medical shock. Should there be added to such a picture a simple ascending or descending hemiplegia or a hemiplegia with a tendency to bilaterality, it is more likely that we are dealing with another syndrome: that of acute infantile encephalopathy due to venous thrombosis or thrombophlebitis, the anatomical substrate of which is haemorrhagic infarction with oedema. In some cases there is also a meningeal haemorrhage.

This complication can supervene in the course of any cranio-facial infection, in many general infections, especially measles, scarlet fever, typhoid fever, and whooping-cough, but also, without obvious cause, in marasmic infants or young children. In an important work, Woolf (1955) stressed the significance of thrombosis of the superior longitudinal sinus in acute infantile cerebral diplegia. The condition to which he has drawn attention may develop without convulsions and in children who have previously been normal.

It is obvious that the field of phlebitis and marasmic thrombosis will shrink in proportion as we recognize earlier and more accurately these cryptic infections and realize that they are responsible for the thrombosis, and not the anaemia and dehydration which are usually blamed.

While one may hesitate in the case of the acute infectious or fulminant post-infectious encephalitides to dogmatize on the inflammatory or degenerative nature of the cerebral lesions, the situation is different in regard to the thrombophlebitic encephalopathies. There can be no doubt that the thrombosis results from a change in the walls of the veins or a disturbance of the blood, but it is by the intermediary of necrosis that the focal neurological signs are produced, the necrotic component being out of all proportion to the inflammatory component of the lesion. We are therefore dealing with a post-infectious encephalopathy.

Not all so-called idiopathic cerebral venous thromboses occur in the circumstances we have just outlined.

A few cases arise from the venous counterpart of an obliterative endarteritis of Winiwarter-Buerger, a migrating manifestation of thrombosis elsewhere, or a polyarteritis nodosa. All these conditions are, however, rare in childhood.

One should not only take stock of the paralytic features but look for evidence of cranio-facial venous stasis such as oedema of the soft parts or retinal venous thrombosis. This is scarcely the place to elaborate the picture, for these syndromes of cerebral venous thrombosis are classic, at least in Britain, where for the school of neurology they are a matter of everyday experience. It will suffice for me to add that the persistence of gross paralysis or the appearance of a purulent meningitis demands the rejection of the diagnosis of encephalitis, and puts the physician on his guard lest a cerebral abscess develops subsequently, especially if there has not been a prompt administration of antibiotics.

On the other hand, the presence of a cerebral tumour or abscess may be stimulated by otitic hydrocephalus. In this condition a child first presents with an acute otitis or, more often, a recrudescence of old otitis, especially on the right side. This may be followed, with or without accompanying headache, by a third-nerve paralysis on the side of the infected ear together with papilloedema. The patient's general condition remains very good or only slightly affected; the cerebrospinal fluid remains normal or its tension may be increased. The ventricles are of normal size or smaller than normal. The picture suggests an excess of cerebrospinal fluid. Whether this results from hypersecretion of the choroid plexuses or defective absorption is still a matter for discussion, but there can be no question of explaining the raised intracranial pressure in terms of mechanical obstruction to the cerebrospinal fluid pathways. In order to avoid any suggestion of an inflammatory origin or dogmatic postulation of the site of the accumulation of fluid, Sir Charles Symonds proposed the name "otitic hydrocephalus." We shall not pause to consider the mechanism by which this disorder is produced, preferring to abide by the name suggested by Sir Charles because it characterizes so well the clinical features even though there are some who find it too narrow in its implications.

Encephalopathy or Encephalitis?

In acute cases the choice of diagnosis between encephalopathy and encephalitis to a considerable extent depends upon the orientation of the neuropathologist. If he is particularly conscious of the diffuse neuronal changes he will regard the case as an encephalitis; if, on the other hand, the vascular stasis and oedema make the deeper impression upon him, he will favour a diagnosis of encephalopathy in the course of a fulminant post-infection encephalitis. One can sense the hesitation of neurologists and neuropathologists to commit themselves in the names commonly employed to describe these conditions—malignant state, acute neurotoxicosis, dysmetabolism of infants, diffuse toxic encephalitis or encephalopathy, and so on. This uneasiness results, of course, from the minimal lesions which must form the basis for our diagnosis.

It must be stressed that the encephalitides are in reality far less common than is suggested by the number of cases sent to us with this diagnosis; in fact, they are

much less common than the encephalopathies. It is therefore not without interest to recall briefly which encephalitides are most often encountered in Belgium.

Since acute encephalitis is most frequently an episode in the course of a more generalized disease one bases one's diagnosis on the symptomatology of the generalized disease—for example, mumps, primary atypical pneumonia, and glandular fever. Theoretically, at least, one may also encounter acute encephalitides complicating psittacosis or shingles. Acute herpetic encephalitis in the infant has, on the other hand, a very characteristic picture, but should be diagnosed only after careful consideration.

The acute post-infectious encephalitides can occur in exceptional cases in the course of an unobtrusive basal pulmonary infection or may even precede the clinical signs of the latter. The diagnosis is extremely difficult, especially when the encephalitis is fulminant. The child passes from normality to coma with hyperthermia, with or without convulsions and with or without cardio-respiratory collapse. If it develops a hemiplegia the chances of there being an encephalopathy are obviously greater. Such fulminant post-infectious encephalitides preceding the clinical manifestations of basal infection are, however, exceptional. Faced with a case of "comatose encephalitis" one will be right nine times out of ten in diagnosing an encephalopathy. No doubt one does see in whooping-cough, measles, and scarlet fever exceptional cases with a fulminant course, where the picture is that of a diffuse haemorrhagic encephalitis with blood-stained cerebrospinal fluid. These cases cannot be separated from the encephalopathies described in the course of these diseases, when they appear in the invasive phase, at the beginning of the phase of focal symptoms, or during a flare-up with return of fever.

Cerebral Herpes

I must now deal briefly with two types of encephalitis that may be encountered. The first is herpetic encephalitis. Here we may distinguish two forms. In the first, an infant, especially a premature infant, after an alarming phase of rigidity becomes irritable or stuporous, its temperature rises, there is cyanosis with extreme dyspnoea, and the conjunctivae appear jaundiced or subicteric. The infant has diarrhoea, vomiting, and, most characteristically, epistaxis, melaena, haematomas at injection sites, and cutaneous herpetic lesions becoming unrecognizable because of their tendency to ulceration, necrosis, confluence, and haemorrhage. The liver and spleen are enlarged. Myoclonus and convulsions ensue, and death occurs, ushered in by severe shock and subnormal temperature.

What is seen is in essence a fulminant polyvisceral disease with a predilection for the liver and brain. At necropsy, the liver, suprarenal cortex, lungs, spleen, and bone marrow are peppered with necroses containing acidophil inclusions. The focal cerebral lesions are those of an acute post-infectious disseminated encephalitis and are not the result of direct damage to the brain by the herpes virus.

In the other form of cerebral herpes the onset is cerebral. Usually the patient is an infant several weeks old. The onset is abrupt, with delirium, convulsive seizures, and opisthotonos; sometimes there are paralytic and spontaneous movements of the extra-pyramidal type, together with cutaneous or mucosal

herpes, with death following in eight to ten days. The cerebrospinal fluid is often clear, but may be haemorrhagic, with an increasing number of white cells up to 1,000 per c.mm. accompanied by an increase in the protein. At necropsy there is severe necrotic encephalitis, usually with an asymmetrical bilateral temporal-hippocampal distribution, causing the affected brain to have a creamy consistency. This is the picture of acute herpetic encephalitis with direct damage to the brain by the herpes virus.

Acute Necrotizing Encephalitis

Closely related to herpes encephalitis is the condition termed by Greenfield (1950) "acute polioclastic encephalitis," and by van Bogaert *et al.* (1955) as acute necrotizing encephalitis. Exceptionally it occurs in childhood. The onset is usually hepatointestinal, pharyngeal, pulmonary, or simply general and indeterminate. Severe disturbances of consciousness rapidly supervene—for example, mental confusion with agitation, olfactory or visual hallucinations, and Jacksonian or generalized convulsions. There may be a hemiplegia with signs of cranial-nerve involvement. The cerebrospinal fluid shows a lymphocytic pleocytosis with a normal or moderately increased protein content. Death usually follows within 5 to 15 days, but may be delayed beyond this time. At necropsy there is a violent inflammatory necrosis of the superficial layers of the brain, with large neighbouring areas of paling in the hippocampus, temporal lobe, insula, and callosal-marginal regions. Inoculations are negative, but inclusions of type A are seen as in herpes. The autonomy of this condition is doubtful and further studies are indicated. In this condition, also, the differential diagnosis is from thrombophlebitis of the posterior cerebral veins or temporal lobe abscess.

Leucoencephalitis

Between the cases of acute haemorrhagic encephalitis occurring at the onset or first phase of an infectious disease and the later neurological complications mentioned below is a small group of cases which will show either a serohaemorrhagic pattern or, if they survive longer, a pattern of perivenous glial encephalitis. I mention these cases because they have been first described in Australia by a graduate of Birmingham University—Hurst (1941)—under the title of "acute haemorrhagic leucoencephalitis." These cases can hardly be diagnosed during life, but can be identified with certainty by post-mortem examination.

The acute encephalitides which I mentioned earlier are contemporaneous with the first or second febrile phase of viral disease—that is, with the viraemic or normergic phase of the illness. Cerebral complications may, however, supervene at a later or much later stage.

The physician should think of the allergic type of post-infectious encephalitis whenever an exanthematic fever, whooping-cough, influenza A or B, or even a banal respiratory infection is followed after a certain delay, with or without return of fever, by the slow, insidious, and progressive development of neurological symptoms and signs. In other cases there is a fresh spike of temperature and rapid development of coma. In the less severe cases the clinical picture is made up of a mixture of successive cerebellar, choreiform, and

pyramidal symptoms together with cranial nerve signs. Because of the predilection of the lesions for the white matter, these cases are often called post-infectious leucoencephalitides. They are nowadays well recognized and in most cases the prognosis is very favourable.

When no primary disease is discovered, one refers to a primary leucoencephalitis. Those favouring this term believe that the leucoencephalitides result from the activities of a virus which in most cases is activated by vaccination or by an insidious primary disease. Others believe that the primary disease has passed unnoticed and is only made manifest by the late—"allergic"—neurological complications.

At this stage the cerebrospinal fluid usually shows the albuminocytological dissociation and abnormal colloidal reactions that I mentioned earlier.

Late Encephalitides

The late post-infectious or allergic encephalitides can last for weeks or even months. Their progress often remains good in spite of the severity of the clinical picture, which may go as far as decortication or decerebration, reducing the child for weeks to a purely vegetative existence and necessitating the most skilled nursing. The clinical picture of the late encephalitides is well known. Many studies have been published on those that follow chicken-pox, measles, and vaccination. Each of these primary diseases has a tendency to produce cerebral complications with a particular profile. This profile is, no doubt, not exclusive; it is merely that one finds a neurological picture of one particular profile more commonly after one primary disease than after the others. The late encephalitides remain an admirable field for those who study encephalitic phenomena in their general biological context, together with other articular, serous, or muscular manifestations of these infections. They may even provide a means of access to the as yet unknown mechanisms which underlie the genesis of the demyelinating diseases.

It is highly probable that a very small part of the allergic encephalitides, occurring without obvious primary disease, represents the initial stages of disseminated sclerosis. This eventuality, so ominous for the subject concerned, is certainly exceptional, and if an encephalitis should leave a child with a certain number of sequelae (epilepsy, disturbance of character, etc.) the inference should rather be one of multifocal healed lesions due to the encephalitis.

Treatment

I have attempted to deal only with the acute encephalitides of childhood, because it is these which pose to the physician the most delicate diagnostic and therapeutic problems. If their diagnosis brings home to us our ignorance, how much more so does the question of treatment.

The physician must, of course, deal with the primary disease of which the encephalitis is only a localized feature. The cerebral complication will, however, also engage his attention, as it affects both immediate and remote prognosis.

The affection of the nervous centres may result in disturbances of ionic balance in the blood, exhaustion of the cerebral and the peripheral autonomic control which participates in the general defence mechanisms of

the individual, changes in coagulation of the blood, and disturbances of the blood-brain barrier. This constellation of factors has its effect upon the symptomatology. Coma or convulsions may develop, or hypothermia or hyperthermia require our therapeutic intervention.

Within the group of cases probably, or possibly, due to cerebral thrombosis or thrombophlebitis, otitic hydrocephalus has a tendency towards spontaneous cure except in cachectic infants or children. Indeed, one may say that it is the only variety of cerebral thrombosis or thrombophlebitis in childhood in which the prognosis is not very gloomy. Palliative measures (repeated lumbar punctures, limitation of fluid intake, and anticonvulsive medication) are in other thromboses of little avail. The advisability of anticoagulant therapy is still under discussion. It certainly carries with it a serious danger if the cerebrospinal fluid is blood-stained. Our own view, however, is that, having regard to the severity of the illness before us, especially if the cerebral signs are progressive and the seizures show a tendency to become generalized, it is better to make use of the chance of success which the anticoagulant remedies offer. We would say that these remedies are particularly indicated where (though this is rare in childhood) the cerebral event is accompanied by thrombosis of the vessels of the limbs.

In the fulminant encephalopathies without hemiplegic signs and where there is no suggestion of thrombosis, the essential aim is the restoration of the ionic equilibrium of the blood. One must attempt to block the autonomic system by chemical insulation and should not, therefore, hesitate in the presence of convulsions to give barbiturates by transfusion.

Let us suppose a diagnosis of encephalitis, and probably a virus encephalitis, suggests itself; most of the viral encephalitides are, with rare exceptions, insensitive to both the antibiotics and the sulphonamides. We shall therefore reserve these two groups of substances for the treatment of the accompanying secondary infections. On the other hand, we will, of course, employ salicylates and iodine in high dosage as we did during the European encephalitis epidemics in 1920-5. Recently a place has been given to cortisone and corticotrophin in the treatment of these acute forms as well as the late forms of post-infectious encephalitis. In the acute forms we have not had the impression that these substances are of undoubted value. In regard to the late forms it is difficult to evaluate a therapy in a condition where the natural outcome is in any case so favourable.

In the presence of coma, and especially in the presence of those prolonged states of disturbed consciousness which are seen in late post-measles encephalitis, the treatment will be that usually given in the state of common shock.

I have mentioned the serous encephalitides; their treatment will also be that of states of severe shock.

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THE ELECTROENCEPHALOGRAM IN MYXOEDEMA COMA

CLINICAL AND ELECTROENCEPHALOGRAPHIC STUDY OF THREE CASES*

BY

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Myxoedema as a cause of death was first described by Hadden in 1879, when a patient under the care of Ord (1878) died in coma. That myxoedema might be other than an easily remediable condition, however, was largely ignored until recent reports made it clear that myxoedema coma was not in fact a rarity, and that it was almost invariably fatal. During the past four years at least 20 cases have been reported in this country alone—all these patients died except one in the series reported by Malden (1955). Summers (1953) reported five cases in which the patients died in hypothermic coma, the initial temperatures varying from 23.9 to 35° C. Treatment by immersion in a warm bath, thyroxine, and cortisone had no effect. Dyson and Wood's (1956) patient died after 100 µg. of triiodothyronine had been given intravenously. Malden (1955) reported three cases of hypothermic coma; two patients died but one recovered after treatment with electric blankets and intravenous corticotrophin and thyroxine. He noted that hypothermia was present in all three cases, the blood sugar was normal, and there was absence of shivering (due, he supposed, to failure of the thermo-regulatory centre).

Reports of recovery have been remarkably few. Apart from the case of Malden (1955) only two other survivals have been described; one a very early case which recovered spontaneously in 24 hours (Brotmacher and Coghill, 1953), the other a condition of deep coma in a woman of 83 who recovered with thyroid extract, but in whom the temperature was not noted (Martin and Whittle, 1953). That it is an extremely dangerous condition, however, is evident, and Summers (1953) thought that the changes produced by extremely low body temperatures are apparently irreversible or that the body reaches a state in which it can no longer respond to thyroxine.

Coma in myxoedema patients presents a clinical picture similar in many respects to coma in hypopituitarism (Sheehan and Summers, 1952). Caughey and Garrod (1954), in discussing factors which could precipitate coma in hypopituitarism, mentioned infection, hypoglycaemia, hypersensitivity to drugs and anaesthesia, sodium depletion, water retention, cerebral anoxia, and hypothermia as possible factors. It is possible that some of these factors may also operate in the production of myxoedema coma and that adrenocortical failure or even some degree of pituitary failure (Hubble, 1955) may be concerned.

It is interesting to note the effect of artificially induced hypothermia in man and animals. Dundee, Scott, and Mesham (1953) found that cardiac arrest occurred in three dogs at temperatures of 23° C., 25° C., and 26.5° C. Swan *et al.* (1953), however, described temperatures ranging from 21.5 to 26° C. in 15 patients

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