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ENCEPHALITIS *

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The subject of encephalitis is specially suitable for the section of diseases of children because in so many of its forms it is the period of childhood which is principally affected. The term "encephalitis," however, must be interpreted in its broadest sense. It is used to cover a large and heterogeneous variety of conditions, some inflammatory, others toxi-degenerative, and others of a vascular nature—embolic, haemorrhagic, and thrombotic. For the clinician it is often impossible to make a pathological diagnosis with any certainty, as the symptoms presented by the patient can only indicate which parts of the brain are involved, and may be produced by a variety of causes.

In the first place, we recognize two main types of encephalitis—the suppurative and the non-suppurative. About the former, suppurative encephalitis or cerebral abscess, it is sufficient to say that it is due to an invasion of the central nervous system by pyogenic organisms, and is almost invariably secondary to infection of the middle ear and mastoid, or a complication of chronic pulmonary disease.

Non-suppurative encephalitis covers a much wider field, and contains the bulk of our material. The last twelve years, since 1922, have been specially eventful in increasing our knowledge of the clinical and pathological aspects of encephalitis. The stimulus provided has been the wave of prevalence of spontaneous forms of meningo-encephalitis, and of nervous complications following vaccination and some of the exanthemata. Earlier in the present century, starting from about 1916, the world-wide spread of epidemics of encephalitis lethargica constitutes a separate and distinct event. Prior to these two epochs encephalitis occupied comparatively little space in medical literature, and, with the exception of polio-encephalitis, is mainly referred to under purely clinical titles, such as sporadic cases of acute hemiplegia, acute tremor, and acute ataxy.

I propose to review briefly the various types of encephalitis in the following order: encephalitis lethargica and polio-encephalitis; encephalitis as a complication of vaccination, the acute fevers, and exanthemata; and acute disseminated encephalo-myelitis of spontaneous onset.

Encephalitis Lethargica and Polio-encephalitis

Encephalitis lethargica and polio-encephalo-myelitis stand out as distinct and separate entities—diseases of virus causation, with a clear-cut pathology, and without relation to any of the other forms of encephalitis. The neurotropic virus of encephalitis lethargica has a predilection for the grey matter of the brain stem and basal

ganglia, though no part of the nervous system is exempt. In polio-encephalitis, which, compared to the spinal type, poliomyelitis, is undoubtedly a rare disease, the activity of the virus falls focally upon the grey matter of the cortex, less often the brain stem and cerebellum.

The symptoms of "sleepy sickness" are too well known to need much comment. In the epidemics of past years an acute stage was frequently observed, typified by lethargy, disturbance of the sleep rhythm, ocular paralyses, myoclonic and choreiform movements of the limbs. Characteristic symptoms of the chronic stage are lethargy, mental changes, and Parkinsonian rigidity. Mental deterioration in intelligence and behaviour are specially common in cases occurring in early childhood. In recent years, since 1926, the prevalence of the disease has markedly declined, and an acute stage is now rarely witnessed, or is of so mild a nature that its significance escapes recognition. A few cases in the chronic stage still come to light, in children as well as in adults.

To make a diagnosis of polio-encephalitis in the absence of polio-infection in epidemic proportions is probably nearly always inaccurate. The predilection of the polio-virus for the grey matter of the spinal cord has been proved experimentally beyond any doubt. Cerebral lesions, either in man or in animals, are unusual. Even in epidemics of poliomyelitis the cerebral type of case will not account for more than 4 per cent. of the total. The usual syndromes of polio-encephalitis are a sudden onset of fever, vomiting, convulsions, and coma, with a residuum of hemiplegia, sometimes accompanied by mental defect and epilepsy, or the main symptom may be cerebellar ataxy. These syndromes, however, are common to so many types of encephalitis, following acute fevers, the exanthemata, and of spontaneous onset, that in sporadic cases the clinician can seldom be certain of their pathology.

The frequency with which a diagnosis of polio-encephalitis is made in cases of acute hemiplegia in young children dates back to 1884. In that year Strümpell published a paper, based on twenty-four cases, in only two of which was the condition a complication of measles and of scarlet fever. He cited the uniformity of the symptoms with motor paralysis, the healthy type of child affected, the early age of onset (nineteen out of twenty-four cases in the first three years of life), and claimed that the condition was a specific disease, infective in origin, closely analogous to spinal paralysis or poliomyelitis. His opinion was supported by Marie and others, but queried by Wallenberg, who remarked that, although the symptomatology of acute hemiplegia in children was sharply defined, its morbid anatomy possessed no characteristic lesion. Gowers also opposed the theory, and stated that encephalitis of the Strümpell type was a "theoretical disease."

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Encephalitis Associated with Vaccination and Acute Fevers

The group of encephalopathies associated with the acute fevers, exanthemata, and vaccination has been intensively studied within recent years. These nervous complications have long been recognized as rare occurrences, but actually since 1922 the cases following vaccination, measles, small-pox, and chicken-pox have been more numerous.

The clinical syndromes of the encephalopathies following vaccination, the acute fevers, and exanthems are of several types, but some types tend to be more often associated with certain fevers than with others. A meningeal syndrome, or state of meningismus or serous meningitis, with headache, vomiting, cervical rigidity, Kernig's sign, and sometimes convulsions, may be observed in any of the fevers. Other syndromes are: (1) a combined cerebral and spinal type; (2) a mainly spinal type; (3) a cerebellar or ataxic form; and (4) a focal cerebral hemiplegic type.

After vaccination, measles, and small-pox the combined encephalo-myelitic and the mainly myelitic syndromes are most common. Cerebellar ataxy, less often spinal symptoms, are seen following chicken-pox. In the much rarer cases following German measles, cerebral, cerebellar, and spinal symptoms have been recorded. The focal hemiplegic syndrome is the commonest complication of whooping-cough, scarlet fever, and mumps.

The nervous complications of vaccination, measles, small-pox, chicken-pox, and German measles have many features in common. This family likeness is noticeable in the symptomatology, the uniformity of the time interval, or period of incubation, separating the primary exanthem and the nervous symptoms. Further, the occurrence of nervous symptoms seldom bears any relation to the severity of the primary exanthem, or to the size of the epidemic.

The sequence of events is generally as follows. Usually after an incubation period of about seven days, and therefore in the period of decline of the primary exanthem when the patient is afebrile, the nervous symptoms appear abruptly with a renewal of pyrexia. Meningeal symptoms are commonly present, and drowsiness is a prominent symptom, often deepening to coma, which may last for several days. On the return of consciousness the character of the paralysis becomes more obvious. In the encephalo-myelitic type multiple focal signs of involvement of the brain and spinal cord are observed, including diplegia, hemiplegia, and aphasia, choreiform movements, rigidity, tremor, difficulty in speech and in swallowing, absence of the knee- and ankle-jerks, with extensor plantar responses. Trismus is often observed. Ocular paralyses and nystagmus are uncommon, but some swelling of the optic disks is frequently present. In the cerebellar type the predominant feature is ataxia. The character of the spinal type is that of a transverse or an ascending myelitis, with sensory disturbances and retention of urine.

Some reference must be made to the relative frequency of these complications. The case records, prior to the last twelve years, have been very few in number, and the instances of post-varicellar complications still rarer. Dagnelie, van Bogaert, and others have estimated from the literature a total of sixty-nine cases following chicken-pox, of which fifty have occurred since 1920, with thirteen in the year 1930 alone. In measles the figures have shown a striking rise since 1924. In England for the four years 1927 to 1930 of fatal cases alone there have been twenty-five. Post-vaccinal encephalitis began to be more frequent in 1922. From 1922 to 1927 the total of cases in Holland was 170, in England and Wales ninety-three, of which nine were in infants under 1 year. A raised incidence has been reported in nearly all European countries and in America. This prevalence, however, must not be exaggerated,

for, as Rolleston states, "the proportion of cases with nervous sequels was 1 to every 33,000 vaccinations, and of deaths, 1 to every 66,000 vaccinations." Since 1929 the number of cases following vaccination has markedly diminished. Following small-pox, mostly of the modified type, a slight increase of nervous complications has occurred. Marsden and Hurst described ten cases out of 40,313 cases of small-pox notified in England and Wales between 1928 and 1931. With one exception the ages in the group were all below 15 years.

The mortality rate in the cases following these fevers is unequal. It is least in the post-varicellar cases—about 6 per cent. In the cases following measles Ford estimates the mortality at about 10 per cent., and in post-vaccinal cases the average mortality has been 30 to 40 per cent. Otherwise the prognosis is good, and recovery usually complete, though some form of paralysis, or a psychosis, such as a speech disturbance, aphasia, or abnormal behaviour, may linger for a while. A permanent incapacity of some form has apparently been more common in the cases following measles than after vaccination or chicken-pox.

In scarlet fever, encephalitis, usually of the hemiplegic type, may occur early in the fever or not until later in the period of desquamation. The nervous symptoms in whooping-cough are often delayed until after the period of paroxysmal coughing has practically ceased. Usually the syndrome consists of multiple convulsions, or whooping-cough eclampsia, in some cases accompanied by hemiplegia, diplegia, idiocy, and blindness (Baginsky, Schmitt, Turnowsky). Most cases of pertussis eclampsia are fatal, but in a few instances recovery has occurred, even with return of vision and disappearance of hemiplegia. Symptoms of meningitis or of meningo-encephalitis, with hemiplegia, may occur in mumps, but are extremely rare. Meningeal and meningo-encephalitic complications may also occur in many other acute infections, such as pneumonia, erysipelas (Eckel), streptococcal pharyngeal and otitic inflammation. I have seen complete recovery occur in a case of this type following a streptococcal infection of the throat and middle ear in a boy of 7 years. It is interesting to note that Freud, in 1897, stated that hemiplegia in children occurred after infective conditions in the following order of frequency: measles, scarlet fever, small-pox, German measles, whooping-cough, diphtheria, follicular tonsillitis, gastro-enteritis, pneumonia, typhoid, mumps, and vaccination.

Broadly speaking, the pathological features of the encephalopathies following vaccination, the exanthemata, and other fevers are of two main types. In one the principal points are congestion, oedema, vascular endothelial proliferation, and ganglion cell degeneration. This type is known as acute toxic encephalitis, and sometimes as acute haemorrhagic encephalitis with the presence of microscopical extravasation of red cells in relation to the vessels. The distinctive feature of the other type is the presence of areas of demyelination around the small veins, chiefly in the white matter—demyelinating encephalitis.

Toxic encephalitis is the form usually associated with whooping-cough and acute infections, such as pneumonia and streptococcal tonsillitis and otitis media. Some cases of scarlatinal meningo-encephalitis are of this kind, and it has also occurred in association with measles and small-pox. The onset of symptoms, however, in cases of this nature complicating measles and small-pox shows no typical incubation period, but may even precede the appearance of the rash. Toxic encephalitis is almost certainly a reaction to bacterial toxins rather than the result of a microbic invasion. Grinker and Stone have drawn attention to the fact that the characteristic cerebral, vascular, endothelial proliferation, and ganglion cell degeneration has also been observed in cases of food poison-

ing, and can be produced experimentally by inorganic poisons. A purely meningeal syndrome, or serous meningitis, can also be produced by a toxæmia. Blühdorn describes ten such cases in children, three complicating pneumonia, two whooping-cough, and five of spontaneous onset.

The endotoxin of whooping-cough has been shown experimentally in guinea-pigs by Fonteyne and Dagnelie to have a highly toxic action in minute doses injected intracerebrally. An intense convulsive state was provoked with a rapidly fatal meningo-encephalitis. Dubois, Ley, and Dagnelie, in eight fatal cases of whooping eclampsia, found fairly distinctive anatomical changes, consisting of small-celled meningeal infiltration and toxic degenerative changes of the ganglion cells. In none of these cases had hæmorrhage occurred.

Vascular lesions as a cause of hemiplegia in whooping-cough and scarlet fever have in the past acquired an importance which cannot be justified. It is possible in whooping-cough in the early stages, during a particularly severe bout of coughing, that asphyxia may lead to vascular stasis, cerebral oedema, and even hæmorrhage, resulting in a temporary or permanent hemiplegia. I have seen cases of hemiplegia, presumably of asphyxial origin, both in whooping-cough and in asthma, and in each instance the paralysis entirely cleared up.

The second pathological type, or demyelinating encephalitis, is characteristic of the cases of encephalomyelitis following vaccination, measles, small-pox, chicken-pox, and German measles. The origin of this demyelinating reaction has yet to be solved—whether it is due to the action of the virus of the primary exanthem itself, or due to toxins, or to a latent hypothetical virus stirred into activity by any of these fevers. In vaccination experimental research has failed to reproduce lesions analogous to the demyelinating encephalitis seen in man. Hurst states that the lesions produced in the nervous system by vaccine virus are of a totally different type.

Spontaneous Acute Disseminated Encephalo-myelitis

Under this title several conditions are grouped which present cerebral, spinal, and meningeal symptoms, either combined or separately. They arise independently of the acute fevers or exanthems, or of any known cause. One form is clinically and pathologically indistinguishable from the cases of encephalo-myelitis following vaccination and measles. It shows the same demyelinating feature. Hurst considers that it should be regarded as an independent clinical and pathological entity, whether following one of the fevers or arising spontaneously. The spontaneous cases within recent years have occurred in children and young adults, and if the condition existed formerly it was either unrecognized or excited little interest.

Another form resembles in both clinical and pathological features the toxic encephalitis complicating acute infections—pneumonia, tonsillitis, and scarlet fever. It has been described under several titles: acute meningo-encephalo-myelitis of childhood, acute toxic or serous encephalitis (Brain and Hunter, Brown and Symmers). Both sporadic and epidemic cases have been recorded. Recovery is often complete in non-fatal cases, but the mortality has varied in different epidemics. In Brown and Symmers's ten cases of "acute serous encephalitis," aged 2 years and 2 months to 7 years, all died.

Cases of a mainly meningeal type have been described as "epidemic serous meningitis," or "epidemic meningitis minor" (Schlesinger, Braithwaite and Innes). In Braithwaite and Innes's series of thirteen cases in children between 9 weeks and 6 years old, five were spontaneous and six secondary to mild bronchopneumonia.

It is difficult to know where to fit in the spontaneous cases in young children of acute tremor, acute ataxy, and acute hemiplegia, of which there are a large number of records in the literature (Poynton, Miller). Very little is known of the pathology of these conditions, as they are seldom fatal, and their causation is obscure, though they are possibly of toxic origin. In the cases of acute ataxy, and of acute tremor with hypertonus, nystagmus, and scanning speech, recovery is usually complete. In the cases of acute hemiplegia the paralysis is permanent, and often accompanied by amentia and epilepsy. This condition occurs chiefly in healthy young children, most often in the first three years of life (Taylor, Osler), and early symptoms are fever and a convulsive state, lasting for several days or longer. In such a case, which succumbed to bronchopneumonia, I had the opportunity of making a post-mortem examination, and found a thrombosis of one anterior cerebral artery, with no evidence of arterial disease elsewhere.

The Cerebro-spinal Fluid.—In all those forms of non-suppurative encephalitis the state of the cerebro-spinal fluid is fairly uniform. It may be normal, or show a slight rise in the protein percentage and a small or moderate increase of cells, which are mainly lymphocytes. Occasionally a turbid fluid is encountered, especially in the cases following measles, and polymorphs may predominate. A diagnosis of tuberculous meningitis is apt to be made in the early stages, but on subsequent lumbar punctures the persistence of normal percentages for the chlorides and glucose excludes this possibility.

Treatment.—Besides its diagnostic use, lumbar puncture is of value in alleviating the symptoms, and should be performed daily in the acute stage. Convalescent sera in the cases following vaccination (Horder, Hekman), and after measles and chicken-pox, have been used with apparent success, but the use of these sera must be empirical until more is known of the causation of these nervous complications.

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Major G. D. Jameson, R.A.M.C., in his annual report to the Gibraltar City Council, states that the general health of Gibraltar was good in 1933, when the zymotic death rate was the lowest recorded during the past decade. The infantile mortality rate was lower than in any previously recorded year. During a short period in the autumn, water for drinking purposes was supplied from wells at North Front to supplement the existing rain-water supply. This water was chlorinated before distribution, and the scheme worked successfully.