

was 31%, 9% being attributable to general paresis and a further 22% to other causes. Altogether this was almost four times the death rate to be expected for nonsyphilitic patients of a similar age.

Encephalitis

An encephalitic process can occasionally arise in pyogenic infections such as septicaemia, or develop by direct extension of the inflammatory reaction in diseases such as cerebral abscess or meningitis. But in the more restricted sense to be dealt with here, encephalitis refers to a primary disease in which inflammation of the brain is caused by viral agents.

Meningoencephalitis is the more appropriate term when a marked element of meningeal irritation exists as well. *or bacterial as in ADEM **

Viological studies have gone some way towards isolating and demonstrating the responsible organisms, especially in large epidemics, but a very large number of cases remain in which a viral aetiology is merely presumed to operate on account of the general features of the illness. This applies particularly to sporadic cases where opportunities for extensive viological investigations are not often available, but is also true of some large epidemics, notably the epidemics of encephalitis lethargica in which a specific agent was never conclusively demonstrated.

In some cases of known viral infection it is uncertain whether the virus actually gains access to the central nervous system, or whether the central nervous changes represent an auto-immune or hypersensitivity reaction to the presence of viral infection elsewhere in the body. The latter is thought to be the principal mechanism in many of the forms of encephalitis which follow upon childhood infectious diseases.

A recent development is the increasing evidence that viruses and virus-like agents play some part in sub-acute and chronic degenerative diseases of the brain. These are the so-called chronic, latent or slow viruses, which are now under suspicion in sub-acute sclerosing panencephalitis (p. 305), Creutzfeldt-Jakob disease (p. 400), progressive multifocal leucoencephalopathy (p. 646), and kuru (p. 645).

A comprehensive classification of encephalitis is difficult but Table 13 delineates the main categories for discussion.

Kennard and Swash (1981) illustrate the principal varieties encountered in the UK, by a retrospective review of 60 patients with encephalitis admitted to the London Hospital. Of the 12 where the causative

virus was proven this was herpes simplex in 6, infectious mononucleosis in 3, mumps in 2 and influenza in one. In 29 with similar features to the above no specific virus could be incriminated. Of the 19 post-infectious cases, 15 followed upon upper respiratory tract infections or influenza-like illnesses, 3 followed acute exanthemata, and one vaccination against smallpox.

The clinical picture in most forms of acute encephalitis is of a rapidly developing illness with headache, considerable prostration, and features of central nervous system involvement. Vomiting, irritability and photophobia are common. Some degree of neck stiffness is often detectable, and papilloedema may develop due to cerebral oedema. Pyrexia is variable, but may be low-grade and easily overlooked.

TABLE 13. Varieties of encephalitis (after Robbins, 1958)

Epidemic Virus Infections of the Central Nervous System

Arthropod borne

- Eastern Equine, Western Equine, St. Louis
- Japanese B
- Murray Valley
- Russian Spring-Summer
- Louping Ill.

Enteroviruses

- Poliomyelitis
- Coxsackie group
- Echo group

Encephalitis lethargica

Sporadic Virus Infections of the Central Nervous System

- Herpes simplex
- Mumps
- Infectious mononucleosis
- Herpes zoster
- Infectious hepatitis
- Rabies

Post-Infectious Encephalitis

- Following upper respiratory tract infections *
- Influenza
- Post-vaccination
- Measles
- Rubella
- Chickenpox
- Scarlet fever * bacterial
- Atypical pneumonia

Sub-acute and Chronic Encephalitis

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The dominant feature of cerebral involvement is disturbance of consciousness, ranging from mild somnolence to coma. Delirium figures prominently in some varieties. Epileptic fits are common, especially in children, and can be the opening feature of the illness. Focal neurological signs vary greatly according to the site of major impact of the inflammatory process, and are sometimes remarkably slight or even totally absent. Among the most common are pupillary changes, ocular palsies, nystagmus, ataxia, or affection of the long tracts with alteration of tendon reflexes, upgoing plantar responses and pareses of the limbs. Symptoms of temporal lobe involvement such as dysphasia strongly suggest herpes simplex infection. Sometimes the spinal cord is involved with retention of urine or paraparesis.

Special interest attaches to the occasional cases which present with psychiatric disorder. This was recognised in the early epidemics of encephalitis lethargica (p. 293) and examples still occur with other varieties. Sometimes impairment of consciousness and neurological signs are entirely absent at the time of presentation, as in the three patients reported by Misra and Hay (1971) who were admitted to a psychiatric unit with a provisional diagnosis of schizophrenia. Virological studies were apparently not performed:

A boy of 18 was admitted with a 2 day history of odd behaviour. He was excited, overactive and aggressive, with thought disorder and catatonic features. Two days after admission one plantar response was equivocal, and 2 days later both plantars were extensor and the left abdominal reflexes diminished. Lumbar puncture revealed no abnormality. He became pyrexial and developed subacute delirium. The electroencephalogram showed a reduction of alpha rhythm and generalised slow activity. He was treated with corticotrophin. Subsequently he developed post-encephalitic parkinsonism.

A woman of 45 was admitted with a 3 week history of depression and irritability and a 2 week history of paranoid delusions. On examination she admitted to thought withdrawal and auditory hallucinations. Three days after admission she became pyrexial and an extensor plantar response was elicited. Lumbar puncture was normal but the electroencephalogram showed a general excess of symmetrical fast activity. She developed auricular fibrillation and congestive heart failure. She was treated for encephalitis and myocarditis and eventually made a complete recovery.

(Misra and Hay, 1971)

Wilson (1976) presents further striking cases of this nature, showing abrupt onset of psychological disturbance and little by way of neurological

dysfunction in the early stages. Crow (1978) reviews other scattered examples which illustrate the potential overlap with schizophrenia. The majority probably represent cases of herpes simplex encephalitis (p. 299).

The course can vary greatly from one patient to another, and from time to time in a single patient no matter what the causative organism. Profound coma may improve dramatically after some days or weeks, or unexpected relapse may follow steady recovery. When the acute phase is over there is generally a long period of physical and mental recuperation which may continue for several months. Occasionally the acute phase is succeeded by a prolonged phase of disturbed behaviour which may outlast all evidence of active infection and closely simulate a psychogenic reaction.

There may be no residua, or these may vary from trivial neurological signs to profound brain damage. Organic personality change may occur. Young children are especially at risk, and the contribution of encephalitis to childhood behaviour disturbance has probably been underestimated. Greenbaum and Lurie (1948) described 78 children referred on account of personality difficulties or behaviour disorder attributable to previous encephalitis, representing almost 3% of their total patients. Boys showed post-encephalitic changes much more often than girls, and the psychiatric sequelae were worse the younger the patient at the time of the attack. Characteristically there was lack of inhibition, restlessness, impulsiveness and extreme distractibility; intellect was often well preserved, but the prognosis was poor in terms of social adjustment.

Further aspects of the clinical picture and after-effects will be described as the varieties of encephalitis are dealt with in turn.

ARTHROPOD-BORNE ENCEPHALITIS

This group contains illnesses broadly similar to one another. They occur in epidemics in different parts of the world and are transmitted to man by the bite of an infected insect, chiefly the mosquito, though in some cases ticks and mites have been suspected. In the USA the main varieties are Eastern and Western encephalitis and St. Louis encephalitis, distinguished mainly by their geographical locations. Louping ill is the only member of the group which is seen in England and this is very rare. It is derived from sheep via sheep ticks. Japanese B encephalitis became well known to the Western world by affecting troops in the Far East during the Second World War.

Recurrent epidemics are a feature of all the diseases listed, often with a seasonal incidence in the warm summer months, and varying somewhat in virulence from one epidemic to another. In some epidemics overt disease is rare in comparison to the number of abortive cases who are found to harbour the viruses without showing signs of illness. This naturally leads to considerable difficulty in reaching a satisfactory laboratory confirmation of the disease when sporadic cases arise, though rising titres of antibodies on repeat examination may help.

Pathological changes are similar in the different varieties. There is diffuse rather than focal cerebral involvement, affecting the grey matter particularly. Microscopy shows infiltration of lymphocytes and polymorphs, congregated especially around the blood vessels, ('perivascular cuffing'), scattered small focal haemorrhages, necrosis of neurones, and areas of neuroglial proliferation. Various forms of inclusion body may be found in the neurones and neuroglia. Demyelination is rarely seen, in contrast to the post-infectious encephalitis (Casals, 1958).

The clinical picture is similarly uniform, though varying in intensity and prognosis according to the virulence of the epidemic. There is usually a predilection with regard to age, the very young and the old being especially affected. The onset is with fever, headache and gastrointestinal disturbance, often with signs of meningeal irritation. Fits are common, likewise progression to coma or semi-coma, but marked delirium is rarely a feature (Drachman and Adams, 1962). Focal signs include cranial nerve palsies, especially of the oculomotor nerve, and paresis in the limbs of upper motor neurone type. Eastern equine encephalitis is among the most severe, with early onset of profound neurological deficits and death in approximately 70% of cases (Feemster, 1957).

The blood usually shows a polymorphonuclear leucocytosis. The cerebrospinal fluid shows some increase of pressure, a moderate rise of protein, and 200–1000 cells of which polymorphs predominate early and mononuclears late. The cerebrospinal fluid sugar is normal. Serological tests may allow the identification of the causative organism by neutralization or complement fixation tests (Robbins, 1958).

The incidence of enduring sequelae is related to the length of coma in the acute stage and to the age at which infection occurs. Follow-up of a large Californian series showed residual defects in some 50% of infants under one year and in 20% of adults, the former being much the more severe and including mental deficiency, spastic paralysis, athetosis and

fits (Finley, 1958). Among adults, transient depression and exhaustion are common during convalescence but serious organic residua are rare. Occasionally some degree of dementia or personality change becomes apparent in the year that follows, and a very small number show ataxia, dysarthria or hemiparesis. Post-encephalitic parkinsonism is very rare indeed. Subjective complaints are much more frequent—depression, irritability, insomnia and nervousness—and can persist for a year or two in a manner which simulates neurosis. These may be accompanied by forgetfulness, difficulty in concentration, tremors or ataxia which suggest a basis in minor cerebral damage. Zeifert *et al.* (1962) found that the electroencephalographic findings on follow-up were often at variance with the objective evidence of neurological damage, and abnormal recordings proved to correlate more closely with emotional disturbances than with motor or intellectual defects.

ENTERO-VIRUS ENCEPHALITIS

The enteroviruses are more prone to produce the picture of aseptic meningitis than encephalitis (p. 309). The poliomyelitis virus is distinguished by its effects on the spinal cord and the accompanying encephalitis is usually very slight in degree, but the related Cocksackie and Echo viruses can occasionally produce definite encephalitic manifestations.

Outbreaks are commonest in summer and autumn. The Cocksackie and Echo illnesses usually run a benign course, accompanied by other systemic symptoms characteristic of the virus concerned—maculopapular rashes, muscular pains, or pleurodynia. The changes in the cerebrospinal fluid resemble those of poliomyelitis, with a moderate elevation of protein, normal sugar, and 50–100 cells (polymorphs early and mononuclears later). The virus may be isolated from the stools, but is of more significance if found in the cerebrospinal fluid. A rise in serum antibodies may be demonstrated during the course of the disease by neutralisation or complement fixation tests, though many asymptomatic infections evoke the same response. Serological testing is also made difficult on account of the large number of antigenically distinct viruses in this group.

Children affected before one year of age may occasionally be left with neurological impairment and seizures (Sells *et al.*, 1975). Otherwise serious sequelae are uncommon with Cocksackie and Echo virus infections. Muscular weakness may be marked and persist for some time during convalescence, but

true paralysis is rare. Poser *et al.* (1969) have reported the occasional development of post encephalitic parkinsonism after such infections, but this is usually a transient and mild disability unlike that following encephalitis lethargica (p. 295).

ENCEPHALITIS LETHARGICA

('Epidemic Encephalitis') *viral attack of basal ganglia

An earlier generation of neurologists and psychiatrists was much concerned with this disease on account of the devastating epidemics of 1918 to 1920 and the chronic sequelae that occurred. From the 1930s onwards it largely disappeared, at least in its original form, though champions exist for the view that variants still occur sporadically and often go unrecognised (p. 297). Strangely no causative organism was isolated despite extensive researches, and laboratory proof has never been available to uphold the diagnosis in disputed cases.

Whether or not the disease may be relegated to history, it remains an exceptionally important disorder. The thousands of cases available for observation displayed a wealth of psychopathological phenomena which could be clearly ascribed to pathological changes in the brain. This had an important influence on psychiatric thinking at a time when psychodynamic explanations for mental pathology were gaining perhaps too much ground. Certainly it focused attention on the relation between mental symptoms and brain structure in a way which few affections of the nervous system had done before. The sequelae of the disease demonstrated that an organic basis could sometimes exist for 'functional' disturbances, including tics, psychotic developments, far-reaching disturbances of personality, and particularly compulsions and other profound disturbances of will. Hendrick (1928) reviews the attempts which were made by psychiatrists of every school to capitalise on the lessons to be learned from encephalitis lethargica for understanding the neuroses and psychoses, and von Economo (1929) wrote: '... just as we find it hard today to follow up the trend of thought of our scientific predecessors for whom bacteriology and the lore of brain-localization did not exist, future generations will hardly be able to appreciate our pre-encephalitic neurological and psychiatric conceptions, particularly with regard to so-called functional disturbances'. There is, of course, a danger that these important lessons will be forgotten with the passage of time. The clinical features of the disease will therefore be described in some detail.

Encephalitis lethargica was first reported by von Economo in 1917, after a small local epidemic had led to numerous patients being seen in the Vienna Psychiatric Clinic with a strange variety of symptoms that did not fit into any known diagnostic category. The shared features were slight influenza-like prodromata followed by a variety of nervous manifestations, marked lethargy, disturbance of sleep and disturbance of ocular movement. At autopsy the picture of microscopic foci of inflammation, particularly in the grey matter of the mid-brain and basal ganglia, was sufficiently constant to suggest a common cause despite the variety of neurological and psychiatric phenomena which occurred. Complete recognition followed in the great pandemic which started in London in 1918 and spread throughout Europe during the next two years, approximately coincident with the influenza pandemic of that time. The polymorphic forms of the disease continued to be a striking feature, fresh epidemics often running close to type and differing from those nearby both in the acute phases and in the incidence of sequelae.

There was a seasonal pattern, most epidemics beginning in early winter. The peak incidence was in early adult life from age 15-45, though no age group was spared. At one time a toxic agent was suspected, but the general pattern combined to suggest an airborne infective agent, gaining access via the nasopharynx and transferred by carriers or those in the pre-symptomatic stages of infection. The agent was shown to be filter-passable and the disease was transmissible to monkeys by injection of brain tissue from infected patients, but the virus itself continued to elude attempts at isolation. It was a matter of controversy whether the coincident influenza epidemics had predisposed the host to react abnormally to some relatively innocuous organism, and some evidence suggested that the herpes virus might itself be responsible. These questions were not decisively settled, but the great majority of epidemiological evidence suggested that an independent virus was responsible.

In retrospect it appeared that this was not entirely a new disease, and similar widespread epidemics could be traced in history. In England a second peak occurred in 1924, but thereafter there was a striking fall off of new cases throughout the 1930s, though sporadic cases continued to be seen and small local epidemics appeared from time to time.

The following description is largely taken from von Economo's (1929) classical account.

*The evidence of bacterial enceph lethargical-like illness has not yet been discussed by medical doctors. Pathogenesis of PANDAS is similar to enceph-letharg but Not deadly.

Acute Clinical Picture

A prodromal stage lasting several days consisted of malaise, mild pharyngitis, headache, lassitude and low pyrexia, all symptoms being slight and resembling the prodromata of influenza. A great variety of decisive nervous symptoms then appeared, depending on the localisation of the virus within the central nervous system. The polymorphic forms of the disease were much documented at the time, varying somewhat between epidemics and to a rather less extent in different patients during the same epidemic. Often there was change from day to day in a given patient.

The 'basic' form, and that most usual in sporadic cases, was the *somnolent-ophthalmoplegic variety*. Somnolence developed after the prodromal phase, with slight signs of meningeal irritation. Initially there was merely a tendency to drowsiness from which the patient could easily be roused, sometimes with evidence of confusion or mild delirium but rarely with marked motor unrest. If recovery did not occur at this stage it progressed further to more or less permanent sleep for weeks or sometimes months, often deepening to coma. On recovery disturbances of sleep function might persist for many months during convalescence.

Paresis of cranial nerves set in early, especially of the 3rd and 6th, with ptosis, paralysis of ocular movements, and less commonly pupillary abnormalities or nystagmus. Such signs were usually persistent, but sometimes fugitive and fleeting. Facial palsy or bulbar palsy occasionally developed. In the limbs isolated pareses and reflex abnormalities were seen, with spasticity, hypotonia or ataxia. An admixture of other phenomena appeared in some cases—parkinsonism, chorea, athetosis, and catatonic phenomena. Rarely there were fits, transient aphasias, or cerebellar symptoms.

In other cases the picture was dominated after the prodromal stage by signs of motor unrest. This was the *hyperkinetic form*, with myoclonic twitches, severe jerking chorea, wild jactitations and anxious excited behaviour. Sometimes compulsive tic-like movements, torticollis and torsion spasm appeared. Oculomotor signs and epileptic fits were common. Delirium could be marked with constant urgent unrest by day and night, sometimes closely resembling delirium tremens with anxiety amounting to terror in response to vivid hallucinations. Typically the acute disturbance lasted a few days only, but insomnia or reversal of sleep rhythm then usually persisted for weeks or months after recovery. Other

cases passed on to the typical somnolent-ophthalmoplegic form or to the parkinsonian form.

The *parkinsonian form* was characterised by rigidity and akinesia from the outset. Movements were remarkably slowed and sparse, the patient lying still for hours at a time or responding with profound psychomotor retardation. Speech, like motor movements, was greatly delayed, yet the patient could be shown to be mentally intact despite a superficial appearance of gross dementia. The limbs showed increased tone of extrapyramidal type and often a coarse tremor. The gait was festinant, and salivation occurred as in paralysis agitans. Catatonic phenomena could be seen, including classical *flexibilitas cerea*. Along with these features somnolence, sleep inversion and oculomotor signs might be in evidence. Many progressed thereafter to the chronic parkinsonian phase of the disease.

The *psychotic forms* were rare, but presented with acute psychiatric disturbance as the initial feature. Here mistakes in diagnosis frequently occurred until neurological signs declared themselves. The usual picture was of an acute organic reaction, but stupor, depression, hypomania and catatonia were also reported. Sometimes impulsive and bizarre behaviour was the sole manifestation for several days, accompanied by bewildered and fearful affect. Or mental conflicts were brought to the fore, adding a psychogenic colouring to the presenting symptoms. Several examples were reported by Sands (1928):

A woman of 28 developed a sore throat lasting for a week. A few days later she became excited, rambling and impulsive and was diagnosed as suffering from manic-depressive psychosis. No neurological abnormalities were found. She became extremely fearful, asking whether she was about to die or if something terrible was going to happen to her family. She spoke irrelevantly and was very tense. The pupils were later found to be irregular with sluggish reactions, and the tendon reflexes were diminished. In the following week she developed choreiform and athetoid movements and a left facial weakness. She died a few days later after a period of disorientation, high pyrexia and noisy disturbed behaviour.

A woman of 32 suddenly became restless and noisy, sang and screamed, and claimed to be the daughter of Christ and impregnated by him. She lay in bed in a strained attitude, and was markedly deluded and uncooperative. The pupils were widely dilated and reacted sluggishly to light, and the tendon reflexes were diminished. She continued in a state of excitement for three days then became drowsy, with diplopia and irregularity of the pupils. Three weeks later she recovered completely.

A woman of 30 developed headache for two days then

became excitable, restless and uncooperative. She was admitted to hospital with a diagnosis of manic-depressive psychosis. She proved to be deluded and occasionally hallucinated, and claimed at times to be a physician or a great singer. Her temperature was found to be 102°F, and the cerebrospinal fluid was under increased pressure with six cells per millilitre. Many weeks later she developed ocular palsies and other neurological signs typical of encephalitis lethargica.

It was disputed whether some cases might run their course as a psychotic illness alone without somatic symptoms at any stage. This could neither be proved nor disproved owing to the lack of specific tests for the disease. But in 1924 the Board of Control reported that many patients had been admitted to mental hospitals with diagnoses of non-specific confusional, delusional and hallucinatory states, yet in later years proved to show the classical sequelae of encephalitis lethargica (*Lancet*, 1966a). The psychiatric literature abounded with case reports, and arguments centred on whether the cases had been missed because the neurological signs had been mild and fleeting, or whether the disease could present as a 'cerebral' form without localised manifestations.

Other forms presented with acute bulbar palsy, or monosymptomatically with intense chorea, persistent hiccough or neuritis. Abortive types were common in most epidemics, with symptoms capable of arousing suspicion during the epidemic but easily overlooked at other times. There might be little more than headache and sleeplessness, with perhaps diplopia as the suggestive feature. Hysterical symptoms or mild confusion might be all that was noted in the mental state.

During the acute phase there was usually rapid debility and loss of weight. Fever might accompany the prodromal phase or persist throughout, while other cases ran their whole course without pyrexia at any stage. A moderate leucocytosis was often present but was not invariable. Examination of the cerebrospinal fluid was not in any way decisive, though most cases showed some abnormalities—moderate increase in pressure, 5–20 lymphocytes, a slight rise in protein, or a weakly luetic Lange curve. In other well-marked cases, however, the fluid was entirely normal. Many abortive cases developed only the prodromata, while others recovered early after definitive symptoms and signs had appeared. Some ran a fulminating course with death after a few days or weeks. Usually, however, the acute disturbances lasted for several weeks, with some months more before ocular palsies, lethargy and sleep disturbances resolved.

A protracted convalescence was not uncommon, with repeated relapses and fresh exacerbations. Convalescence also brought prolonged asthenic states, incapacitating depressive illnesses and a variety of sleep disturbances—insomnia, sleep reversal, and narcoleptic phenomena.

Upon recovery focal neurological abnormalities might persist. Paralysis of external ocular movements or of isolated eye muscles were frequently permanent, also pupillary abnormalities, difficulty with accommodation and inability to converge the eyes. Hemiparesis, aphasia, or other focal cerebral symptoms might remain, likewise chorea, tics, torticollis, torsion spasm or epilepsy. Hypothalamic damage was seen in adiposity, menstrual disturbance, impotence, or precocious puberty. The outstanding sequelae, however, were parkinsonism and changes of personality as considered below.

Altogether in clinically well-marked acute cases, some 40% ended fatally, 40% were left with residual defect, and 20% recovered completely. Approximately half of those with residual defects were permanently disabled from working, mostly on account of progressive parkinsonian symptoms (von Economo, 1929).

Chronic Sequelae

The most seriously disabling sequelae consisted of parkinsonian developments, change of personality, and mental defect. Severe psychiatric illnesses were also seen. The incidence of each varied in different epidemics, but a definite relationship emerged with regard to the age at which the acute infection had occurred. Adults tended to develop parkinsonism, children personality disturbances, and infants were left with mental defect. Generalised dementia did not appear to occur when the mature brain had been affected.

Parkinsonism sometimes developed gradually out of the acute stage, or could set in unexpectedly after full recovery. In the interval the patient may have shown persistent symptoms such as headache, irritability and sleep disturbance but this was by no means invariable. Indeed as time went by it became apparent that sequelae could develop after many months or years of completely normal health. By contrast personality change and mental defect were usually evident immediately after the acute infection.

Sometimes typical sequelae were seen without any clear history of acute disturbance, perhaps because the latter had been exceptionally mild, or perhaps because the causative agent could produce chronic